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Role of Extracellular Matrix in Adaptation of Tendon and Skeletal Muscle to Mechanical Loading

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Kjær, Michael. Role of Extracellular Matrix in Adaptation of Tendon and Skeletal Muscle to Mechanical Loading. *Physiol Rev* 84: 649–698, 2004; 10.1152/physrev.00031.2003.—The extracellular matrix (ECM), and especially the connective tissue with its collagen, links tissues of the body together and plays an important role in the force transmission and tissue structure maintenance especially in tendons, ligaments, bone, and muscle. The ECM turnover is influenced by physical activity, and both collagen synthesis and degrading metalloprotease enzymes increase with mechanical loading. Both transcription and posttranslational modifications, as well as local and systemic release of growth factors, are enhanced following exercise. For tendons, metabolic activity, circulatory responses, and collagen turnover are demonstrated to be more pronounced in humans than hitherto thought. Conversely, inactivity markedly decreases collagen turnover in both tendon and muscle. Chronic loading in the form of physical training leads both to increased collagen turnover as well as, dependent on the type of collagen in question, some degree of net collagen synthesis. These changes will modify the mechanical properties and the viscoelastic characteristics of the tissue, decrease its stress, and likely make it more load resistant. Cross-linking in connective tissue involves an intimate, enzymatical interplay between collagen synthesis and ECM proteoglycan components during growth and maturation and influences the collagen-derived functional properties of the tissue. With aging, glycation contributes to additional cross-linking which modifies tissue stiffness. Physiological signaling pathways from mechanical loading to changes in ECM most likely involve feedback signaling that results in rapid alterations in the mechanical properties of the ECM. In developing skeletal muscle, an important interplay between muscle cells and the ECM is present, and some evidence from adult human muscle suggests common signaling pathways to stimulate contractile and ECM components. Unaccostumed overloading responses suggest an important role of ECM in the adaptation of myofibrillar structures in adult muscle. Development of overuse injury in tendons involve morphological and biochemical changes including altered collagen typing and fibril size, hypervascularization zones, accumulation of nociceptive substances, and impaired collagen degradation activity. Counteracting these phenomena requires adjusted loading rather than absence of loading in the form of immobilization. Full understanding of these physiological processes will provide the physiological basis for understanding of tissue overloading and injury seen in both tendons and muscle with repetitive work and leisure time physical activity.

I. INTRODUCTION

Extracellular matrix (ECM) placed in tendon tissue as well as peri- and intramuscularly ensures a functional link between the skeletal muscle cell and the bone. Despite this important role, it is surprising how little is known about ECM compared with the insight into the biology of both skeletal muscle and bone. The role of contractile filaments in skeletal muscle is well appreciated in relation to force development (286, 319, 415, 445), as is the role of the adjacent tendon tissue functioning as a passive structure in transforming this developed force from the muscle to the bone with mechanical loading (459, 525, 532), thereby allowing for joint movement of the body (16, 69, 70, 116, 282, 283, 459, 550). Signals from mechanical loading will initiate a cascade leading from gene expression, transcription, translation, and posttranslational process modification to the integration of events to provide protein synthesis in the ECM (699). These mechanisms are however only partly understood. Furthermore, to what extent the connective tissue and the muscular tissue share signaling pathways that ensure an optimal coordinated transformation of loading activity (both tissue stretching and contractile activity) into structural and functional adaptation of both muscle fibers and extramuscular tissue is not very well described (163, 417, 654).

The ECM consists of a variety of substances, of which collagen fibrils and proteoglycans are truly ubiquitous (153). In addition to the proteoglycans (PG), the hydrophilic ECM includes (164, 339, 581) a variety of other proteins such as noncollagen glycoproteins (582, 583). It is known that the force transmission of the muscle-tendon complex is dependent on the structural integrity between individual muscle fibers and the ECM (48) as well as the fibrillar arrangement of the tendon and its allowance for absorption and loading of energy (15, 16). Furthermore, it is well described that the tensile strength of the matrix is based on intra- and intermolecular cross-links, the orientation, density, and length of both the collagen fibrils and fibers (57, 447, 496, 497, 630–632, 640). However, the signals triggering the connective tissue cells in response to mechanical loading, and the subsequent expression and synthesis of specific extracellular matrix proteins, as well as its coupling to the mechanical function of the tissue are only partly described (51–53, 173, 181).

This review focuses on the physiological role of the ECM, especially collagen, for the tendon-muscle interaction and the adaptation to mechanical loading. Somewhat in contrast to the classical view of the ECM tissue being relatively static and inert, evidence is evolving that tendons and intracellular connective tissue are more dynamic structures that adapt to the variety of functional demands that the musculoskeletal system is subjected to, and that this tissue adapts both in a structural and functional way to mechanical loading (53, 173, 386, 630). Recent development of refined in vivo techniques have underlined that connective tissue of skeletal muscle and tendon is a lively structure with a dynamic protein turnover and that it possesses the capacity to adapt greatly to

changes in the external environment such as mechanical loading or inactivity and disuse.

II. CONVERSION OF MECHANICAL LOADING INTO TISSUE ADAPTATION OF TENDON AND EXTRACELLULAR MATRIX OF SKELETAL MUSCLE: THE GENERAL CONCEPT

Mechanotransduction is an important mechanism by which mechanical stress acts upon a cell and initiates intracellular signaling, promotes cell growth and survival (222, 530, 544, 556, 625), governs morphology and architecture in several cell types (125, 197, 589, 639, 697), and influences metabolic responses (287). Various cells respond differently to mechanical challenges, and the molecular basis for mechanotransduction, especially related to the cell membrane, has been a topic for a recent review and will not be dealt with further here (254). It is however clear that with regard to ECM of tendon and skeletal muscle, any mechanical stimulus is suspected to initiate an adaptation that would make the tissue more damage resistant to ensure an optimal force transmission with muscular contractions.

The ECM is a conglomerate of substances in which biochemical and biophysical properties allow for the construction of a flexible network that integrates information from loading and converts it into mechanical capacities (152, 494, 690). It serves as a scaffold for adhesion of cells mediated by integrins, dystroglycan, and proteoglycans at the cell surface and of tyrosine kinase receptors (98, 290). The interaction between the ECM and the adhesion molecules leads to activation of intracellular signaling pathways and cytoskeletal rearrangement (52, 82, 114). In combination with this, the PGs with their glycosaminoglycan side chains are able to bind and present growth factors to their relevant receptors, and furthermore, the ECM can release growth factors upon relevant mechanical stimulation. The complete signaling pathways responsible for mechanotransduction responses are yet to be described, but several candidates have been suggested from investigations on a variety of fibroblasts in dermis, vasculature, and cardiac muscle (166, 396, 667). Integrin molecules are major structural components of adhesion complexes at the cell membrane linking the ECM to the cytoskeleton (108, 128, 541). In this way integrins establish a mechanical continuum along which forces can be transmitted from the outside to the inside of the cell, and vice versa (238, 290, 291, 667, 668). It is believed that integrins are the sensors of tensile strain at the cell surface (290). Ingber et al. (291) have suggested that integrins together with the cytoskeleton form a mechanically sensitive organelle. At the myotendinous junction, lack of integrin expression will lead to structural damage during muscle contraction (442). Integrins are important structural components of the adhesion complexes at the cell membrane, and they play a crucial role in linking the ECM to the cytoskeleton (227, 412, 418, 419, 579). Thereby they provide a bridge through which forces can be transmitted between inside and outside of the cells in a two-way street principle. Further evidence for this is provided by the fact that integrins can convert mechanical signals to adaptive responses in the cell (115, 591). In addition to integrins, also the dystrophin-glycoprotein complex plays an important role in mechanotransduction of muscle and tendon tissue (107, 130, 288). The β-subunit cytoplasmic domain of integrin is interacting with the cytoskeleton, and the demonstration of $\alpha_7\beta_1$-integrin linked to laminin in the ECM is important for signal transduction (81, 309a, 309b), and lack of the α_2-laminin leads to muscle dystrophy. Interestingly, overexpression of $\alpha_7\beta_1$-integrin in dystrophin-deficient mice leads to reduction in dystrophic symptoms, indicating that some substitution effects exist between integrin and laminin (107). Extracellular matrix ligands for integrins are known to be collagens, fibronectin, tenascin, and laminin (412). Several studies have demonstrated that the expression of several other ECM components are controlled by the level of mechanical loading. For example, collagen XII and tenascin-C, which are present in both tendon and other connective tissue structures like ligaments, have been shown to increase their expression and synthesis when fibroblasts are stretched in vitro and are suppressed in cells that are left in a relaxed state (127, 129). Although not yet confirmed, integrins are likely candidates for sensing tensile stress at the cell surface (290, 683, 694, 698). Thus some evidence indicates that integrin-associated proteins are involved in the signaling adaptive cellular responses to mechanical loading of the tissue, and it is likely that this takes also place in tendon and skeletal muscle ECM-related fibroblasts (531).

Several intracellular pathways for mechanotransduction signaling have been suggested, including focal adhesion kinase (FAK), paxillin, integrin-linked kinase (ILK-1), and mitogen-activated protein kinase (MAPK) (127, 206, 207, 241, 451, 618). MAPK is crucial for the conversion of mechanical load to tissue adaptation inducing signaling from the cytosol to the nucleus. It is well described that several cell types and subsets of MAPKs such as extracellular signal-regulated kinase 1 and 2 (MAPK-erk1+2, p44), stress-activated protein kinases p38 (MAPK-p38), c-*jun* NH_2-terminal kinase (MAPK-jnk, p54), and extracellular signal-regulated kinase 5 (MAPK-erk5) can be activated by mechanical stress, as well as by lowered pH, growth factors, hormones, and reactive oxygen species (250, 414, 678, 693, 696). In regard to mechanical loading, it has been shown in muscle that MAPK can be activated both as a result of active muscle contraction (36, 37, 559) and after passive stretch (161, 439). The activation of

MAPK results not only in a production of transcription factors, thus mediating gene expression, but also in an activation of the protein synthesis on the translational level through eukaryotic initiation and elongation factors (229). It has furthermore been suggested that the mode of mechanical load is coupled to a certain type of MAPK activation. In line with this, it has recently been shown in rat skeletal muscle cells that concentric activation of muscle associated with metabolic and ionic changes resulted in a preferential increase in MAPK-erk1+2, whereas intense eccentric tensile loading with barely any metabolic changes resulted in a marked increase in MAPK-p38 (as well as in MAPK-erk 1+2) (693). In another study that also used rat skeletal muscle, a strong relationship was found between peak tension (whether active and/or passive) and MAPK-jnk (439). This falls in line with the demonstration of MAPK-jnk activation and the induction of immediate early genes by mechanical stress in smooth muscle cells (253). Whether any marked increase in MAPK-p38 is found in skeletal muscle is still debatable. Whereas one study could not find any increase in MAPK-p38 in rat muscle during concentric, stretch, or eccentric muscle activity (439), another study found a marginal and late increase in MAPK-p38 (37, 241) while a third study found MAPK-p38 activation in exercised human skeletal muscle (674). It has been shown that activation in skeletal muscle of MAPK-p38 is fiber-type specific (243). Somewhat in contrast to muscle, it seems very clear that in connective tissue MAPK-p38 is mainly activated with mechanical stretching of the tissue (127). Findings on regulation of matrix metalloproteinase (MMP) activation in fibroblasts point toward a differentiated interplay between MAPKs, in which MAPK-p38 is important for induction of MMP, while MAPK-erk1+2 mediates the repression (534). Although not conclusive, these findings are compatible with stress pattern-dependent MAPK pathways in both the muscle cell and the fibroblast and suggest an intimate interplay between the muscle cell and intramuscular connective tissue in response to mechanical loading. Evidently, such pathways do not in any way rule out other mechanistic pathways (e.g., calcium-dependent pathways) to be involved in mechanotransduction also (36).

Taken together, it is likely that separate modes of tissue loading and thereby of physical training will differentially stimulate the subtypes of MAPK in both myocytes and fibroblasts. Most likely, endurance like oxidative loading of tissue stimulates MAPK-erk, whereas strength type of exercise is more likely to use the MAPK-jnk pathway (693). Furthermore, passive stretch both in muscle and connective tissue preferentially gives rise to stimulation of MAPK-p38 (89). In human models, stretch does not cause any increased muscle protein synthesis, and thus does not result in any hypertrophic effect on the muscle (211). The fact that the stretch of muscle cells and of fibroblast shows parallel MAPK activation suggests that adaptive processes in intramuscular connective tissue interact closely with those of skeletal muscle tissue when subjected to mechanical loading.

III. TENDON AND SKELETAL MUSCLE EXTRACELLULAR MATRIX CONTENT: ORGANIZATION AND PHYSIOLOGICAL FUNCTION

A. Tendon Components

Tendons consist of a systematic and densely packed organization of connective tissue dominated by collagen organized into fibrils, fibers, fiber bundles, and fascicles, as well as by the presence of other ECM proteins. The nature of the individual components of the tendon is equipped to withstand high tensile forces (224, 627, 632). The division of tendons into fibrils ensures that minor damage does not necessarily spread to the entire tendon, and also provides a high total structural strength (Fig. 1). Tendon consists of 55–70% water, and a substantial part of this is associated with proteoglycans in the ECM (187, 307, 546, 659, 660). Of the tendon dry weight, 60–85% is collagen. This collagen is predominantly type I (~60%) arranged in tensile-resistant fibers, and composed of two α_1- and one α_2-chains. These are products of separate genes rather than a posttranslational modification of a single molecule. Also, collagen types III (reported between 0 and 10%), IV (~2%) (12, 260), V, and VI are present (72, 74, 307, 324, 652, 653). In addition to this, a small amount of elastin fibers are present (~2% of dry weight) (194, 195, 307). Apart from a very small amount of inorganic substance (<0.2%), the remaining substance consists of different proteins (accounting for ~4.5%) (660), but very little information is present as to the relative contribution of these (10b). It has been shown that the inorganic substance is dominated by PGs, especially small leucine-rich proteins of which decorin (up to 1%) (164, 307, 660) and cartilage oligomeric matrix protein (COMP, up to 1%) (465, 601, 604) are probably the most abundant. In addition, other small leucine-rich PGs such as fibromodulin, biglycan (up to 0.5%), and lumican, together with osteoadherin, tenascin-C, proline arginine-rich end leucine-rich repeat protein, optican, keratocan, epiphycan, syndican, perlecan, agrin, fibronectin, laminin, vercican, and aggrecan are present in tendon tissue (300, 307, 537). The PGs and water are thought to have a spacing and lubricating role for the tendon, whereas the role for several of the small and nonaggregating leucine-rich PGs is more unclear. The proteoglycans also seem to play an important role in fibril fusion, as do fibrillin molecules aligning along fibrils (50). Tendons vary markedly in design, most likely coupled to their function. In the

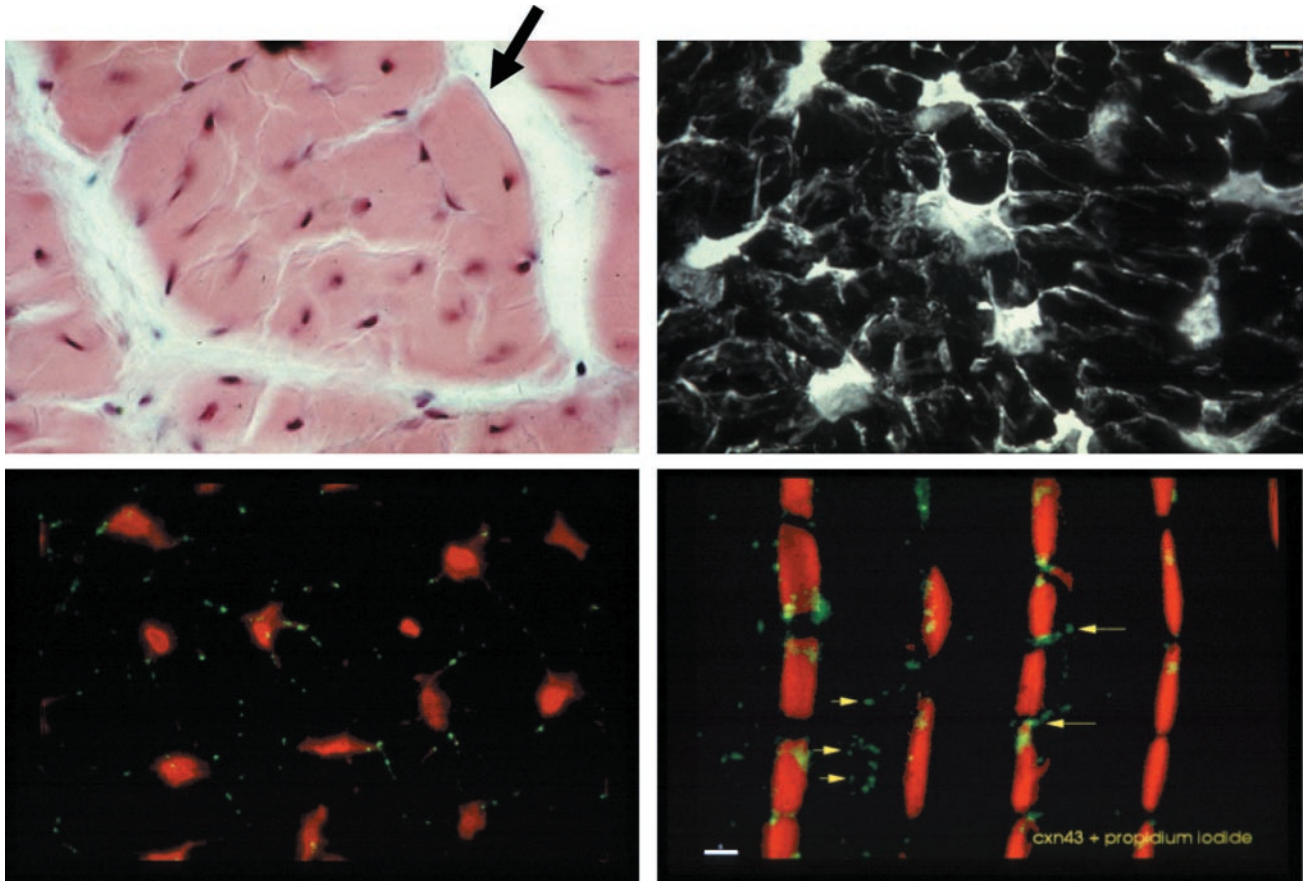

FIG. 1. Structure of tendon tissue. Sections of tendon tissue. *Top left*: a transverse section of a tendon stained with hematoxylin and eosin. In the center of the section a fascicle with fibroblasts is seen surrounded by loose connective tissue endotenon (arrow). *Top right*: a confocal laser-scanning microscopy image of a transverse tendon section. High power view of a three-dimensional reconstruction shows adjacent fibroblasts within a fascicle. It is notable that the cells have sheetlike processes toward each other. *Bottom left* and *right*: transverse and longitudinal section, respectively, of a tendon stained with immunnofluorescence labeling for the gap junction protein, connexin43 (green, indicated by yellow arrows on the longitudinal view, *bottom right*). Sections are counterstained with propidium iodide (red) to indilsecate fibroblast nuclei. This indicates the gap junction coupling between tendon fibroblasts and supports the view of a communicative network of tendon cells. [Modified from Benjamin and co-workers (62, 447, 528) and personal communication with M. Benjamin.]

quadriceps the tendon can be found to be short and thick, whereas several of the tendons to the fingers or toes are long and thin. Furthermore, tendons may vary in thickness along its length and are often surrounded by loose connective tissue lined with synovial cells, the paratenon, to allow for large movements of the tendon. The epitenon is the connective tissue sheet that immediately surrounds the tendon, and it consists of loose, fatty, areolar tissue that allows for the tendon together with the tendon sheet, the peritendon, to glide against adjacent tissue (574).

B. Tendon Fibroblast Signaling

Tendons are dominated by fibroblasts. In addition, also other cell types like endothelial cells and mast cells as well as axons are, together with the ECM, also present in tendons. It has been demonstrated that tendon fibroblasts lie in longitudinal rows and have numerous sheetlike cell extensions that extend far into the ECM (447) (Fig. 1). Isolated tendon fibroblasts respond to mechanically induced loading with expression of several ECM components (53). In the intact tendon, cells are linked to each other via gap junctions as evidenced by immunolabeling for connexin32 and connexin43 (447, 528). Where the latter represents the meeting of cell processes as well as where cell bodies meet, the former only represents contact between cell bodies. In total, the architecture of the fibroblasts of the tendon and their interconnection provides a three-dimensional network that surrounds the collagen fibrils and provides a basis for cell-to-cell interaction. In vitro, tendon cells upregulate collagen and gap junction production under mechanical cyclic loading, and pharmacological inhibition of the gap junction leads to loss of this response (52, 662). Gap junctions must

under loading be able to withstand high loads and have been shown to be coupled to the actin cytoskeleton (394, 395, 695).

In articular chondrocytes and compressed tendon regions, a compression-sensitive organization of intermediate filaments has been shown (179, 528, 529). As well actin filaments and fibers have been shown in developing intervertebral discs and in scar connective tissue (194). However, the demonstration of these has not been put into a functional perspective (331, 469). It has been demonstrated that in knockout mice for the intermediate filament vimentin, α-smooth muscle actin organization is abnormal in dermal fibroblasts and that their contractile ability is impaired (180). Recently, it has been shown that tendons have actin-based cell-cell interaction (515) and that actin stress fibers run along the rows of fibroblasts (529). When mechanically loaded, junctional components n-cadherin and vinculin rose together with tropomyosin, without any change in actin levels. The rise in cadherin and vinculin suggests an increased cell-cell adhesion or cell-matrix adhesion. This suggests that mechanical load transforms fibers into partly contractile components that may contribute to an active mechanism in the recovery after stretch and that these structures can maintain the integrity of the longitudinal tendon rows and to monitor tensile load and contribute in the mechanotransduction during exercise (529).

C. Tendon Vasculature and Blood Flow Regulation

Compared with muscle, tendons have relatively limited vasculature, and the area occupied by vessels represents ~1–2% of the entire ECM (373, 374). The vessels mainly emanate from the epitenon where longitudinal vessels run into the endotenon (10c, 341, 373, 374). Supplying arteries and arterioles may come from the perimysium at the musculotendinous junction and vessels from the tendon bone junction (113, 137, 574). Long tendons are supplied by several vessels along their length (271, 341). Due to the large excursion (up to 6 cm) that some tendons experience during movement, the vessels to such tendons need to be long and often winding in nature.

The ECM in relation to both muscle and tendon is extensively filled with blood vessels (508, 509), to provide the contracting muscle with oxygen and substrate for energy production, and to ensure an efflux from musculature of combustion products. It remains, however, unsolved to what extent the blood flow to connective tissue alters with mechanical loading of the tissue. In the resting state, rabbit tendons have been shown to have tendon flow of around one-third of that in muscle, and it is known that blood flow in both tendons and ligaments increase with exercise and during healing in animals (46). Both with the use of radiolabeled xenon washout technique from peritendon tissue as well as with application of near-infrared spectroscopy and simultaneous infusion of contrast substance (95), it has been possible to demonstrate in human models that blood flow within and around tendon connective tissue increases up to sevenfold during exercise, both in young, middle-aged, and elderly individuals (93, 94, 377, 378, 381). This increase is by far smaller that the 20-fold increase in adjacent skeletal muscle blood flow under similar exercise conditions (93, 94). However, compared with the metabolic activity of the tendon during exercise, it might be adequate. Furthermore, it can be shown that skeletal muscle blood flow during maximal exercise is close to what is possible to achieve with postocclusion reactive hyperemia, while the flow in tendon is still only 20% of that during maximal exercise (93, 94). This implies that tendon flow is not simply a function of skeletal muscle blood flow and that its regulation represents a separate regulatory system.

Vasodilatory agents have been measured simultaneously in skeletal muscle and its adjacent tendon during mechanical loading in vivo, and it has been found that adenosine concentrations rise in an intensity-dependent fashion in muscle, whereas the changes in tendon were less marked and unrelated to intensity (375). Furthermore, bradykinin concentrations rose in parallel in the two tissues during exercise, and already elicited its maximal response at low exercise loads (375). The changes in tissue bradykinin concentrations are in the range that has been found to cause a vasodilatory effect on endothelium (554). These findings indicate that these two substances are involved in blood flow regulation in skeletal muscle and tendon with exercise and that bradykinin is involved in the blood flow increase during lower work loads both in tendon and muscle. Whether bradykinin exerted its vasodilatory effect directly on the vasculature (109) or more indirectly via release of other substances as nitric oxide (NO) (490), prostaglandins (58), or endothelium-derived hyperpolarizing factor (EDHF) (279, 458) is yet to be established.

Interestingly, it has been shown that prostaglandin concentrations rise both in muscle (214, 317) and in connective peritendinous tissue (385) with exercise. Whereas inhibition of prostaglandin synthesis by itself did not inhibit total flow during exercise in skeletal muscle, but did so only if simultaneous blockade also of NO synthesis was performed (96), the peritendinous and tendinous blood flow during exercise was diminished by 40–50% compared with control exercise without blockade (376). This differentiated regulation of blood flow regulation in skeletal muscle and tendon tissue, respectively, can be hypothesized to imply also a differentiated regulation of blood flow within the skeletal muscle itself. This would be so if parts of the vasculature in muscle is located in regions with abundance of ECM, i.e., aponeurosis and perimysial tissue. The finding of flow heterogeneity within

skeletal muscle as well as the demonstration of nutritive and nonnutritive vessels in skeletal muscle (94, 95, 137) are certainly supporting evidence for such an idea. It would also explain a separate role during exercise for vessels that were very responsive to vasodilation dependent on work load and thus providing maximal supplementation of substrate and oxygen to the muscle, and on the other hand vasculature located in connective tissue, both within the muscle and in relation to tendon tissue, where flow is coupled to inflammatory activity in repair processes for the ECM. The latter would also serve as a kind of shunt with the potential of partly limiting its vasodilation to share blood with the nutritive vessels during exercise.

With regard to the ECM, the main question remains whether the increase in flow is sufficient to meet the oxidative needs of the tendon and its cells during exercise. Determination of oxygen saturation and content of the Achilles tendon region in humans has been performed using near-infrared spectroscopy with the addition of a dye dilution method (94–96). When simultaneous recording of tissue oxygenation and blood flow of human tendon regions was performed both at rest and during muscular contractions, it can be demonstrated that a tight correlation exists between increasing blood flow and declining oxygen tissue saturation (334) (Fig. 2). This correlation could indicate a coupling and fits very well with what is found in skeletal muscle during exercise (96). This illustrates that during exercise the estimated oxygen uptake in humans tendon regions rises severalfold compared with the resting state and that even during intense mechanical loading of tendons, there is no indication of any tissue ischemia.

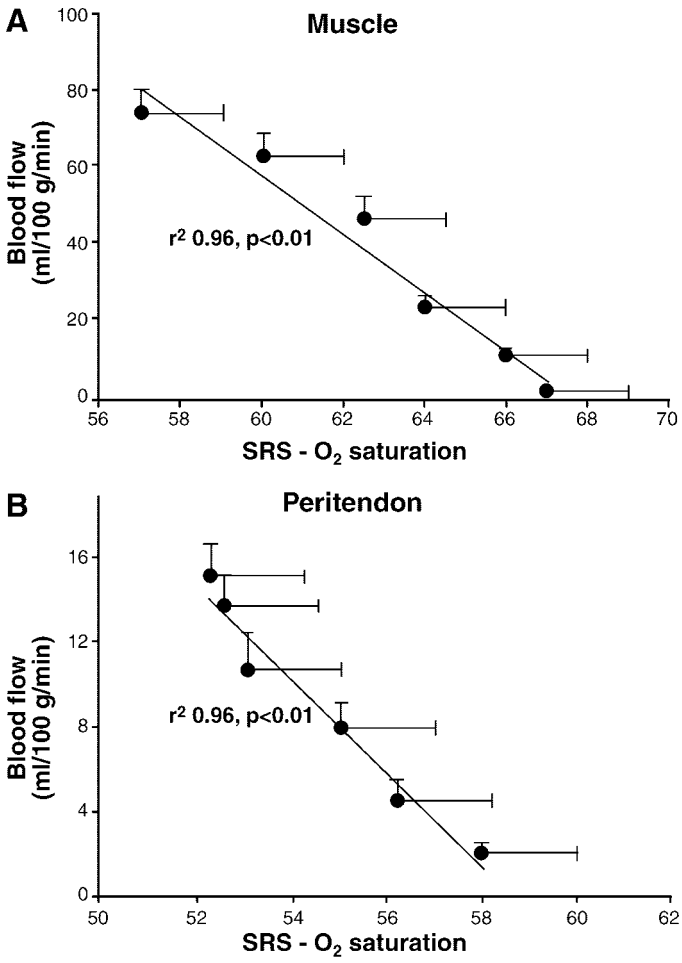

FIG. 2. Blood flow during rest and exercise in human tendon and muscle. The correlation between spatially resolved near infrared spectroscopy (SRS) oxygen saturation and blood flow either in leg gastrocnemius muscle or in the Achilles tendon region. Regional tissue flow was determined with use of indocyanine green dye infusion in combination with SRS, and values during rest (~2 ml·100 g^{-1}·min^{-1} in tendon) and during graded increasing plantar flexion exercise with the calf muscle until exhaustion. The correlation was tested for significance by the use of the Spearmann test. Note that even during intense exercise the average tissue O_2 saturation did not decrease below 57% for skeletal muscle and 52% for tendon tissue. [From Boushel and co-workers (93, 94) and Kjær et al. (334) with permission.]

D. ECM Components in Skeletal Muscle

Intramuscular connective tissue has multiple functions (301a, 407) (Fig. 3). First it provides a basic mechanical support for vessels and nerves. Second, the connective tissue ensures the passive elastic response of muscle. Third, it is now clear that force transmission from the muscle fibers not only is transformed to tendon and subsequent bone via the myotendinous junctions but also via lateral transmission between neighboring fibers and fascicles within a muscle (228, 338, 415, 626). It has been shown that tension developed in one muscle part can be transmitted via shear links to other parts of the muscle, and that even the cutting of an aponeurosis in a pennate muscle still maintains much of the force transmission (401). The perimysium is especially capable of transmitting tensile force (631). Although studies have also demonstrated a potential of the endomysium for force transmission, the orientation and curvilinearity of the collagen fibers provide high amounts of elasticity and thus not sufficient stiffness to function optimally as a force transmitter.

Intramuscular connective tissue accounts for 1–10% of the skeletal muscle and varies quite substantially between muscles (208, 301, 391, 628) (Fig. 3). Whereas the endomysium encloses each individual muscle fiber with random arrangement of collagen fibrils to allow for movement during contraction, the multisheet-layered perimysium runs transversely to fibers and holds groups of fibers in place, while the epimysium is formed of two layers of wavy collagen fibrils to form a sheetlike structure at the surface of the tendon. It has been demonstrated in bovine muscles that the endomysial content can vary between ~0.5 and 1.2% of the muscle dry weight, whereas the

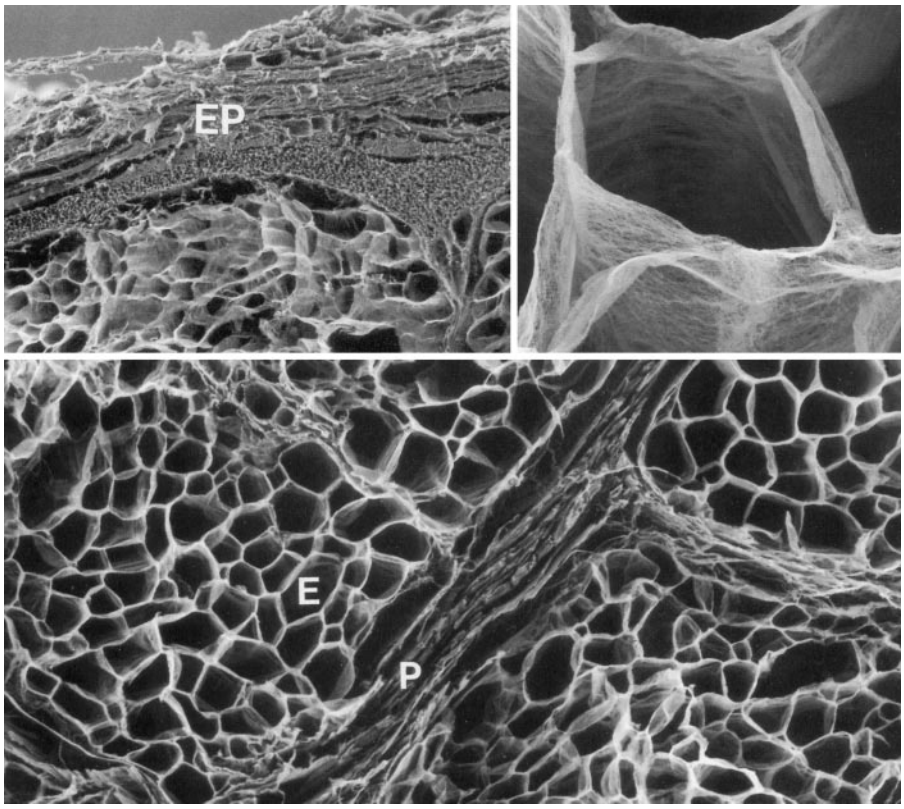

FIG. 3. Structure of intramuscular connective tissue. Skeletal muscle (bovine semitendinosus muscle) extracellular network shown by scanning electron micrographs after removal of skeletal muscle protein. *Top left* shows the epimysium (EP), and the *bottom* illustrates the perimysium (P) as well as the endomysium (E). On the *top right*, the endomysium surrounding one individual skeletal muscle fiber is shown. [Modified from Nishimura et al. (483).]

perimysium accounts for between 0.4 and 4.8% (520). This relatively small variation in the endomysial compared with perimysial connective tissue content between muscles could indicate that at least some functional differences between muscle groups related to connective tissue content are mainly defined by perimysial characteristics. The intramuscular connective tissue is dominated by collagen and ensures not only an organization into fasicles and fibers, but contributes importantly to the force transmission (39). Several collagen types have been identified in intramuscular connective tissue (up to 7) (174, 410, 411), and whereas type IV dominates the basement membrane adjacent to the plasma membrane of the sarcolemma (12, 342), the fibrillar collagen type I and III (and to some extent type V) dominates the epi-, peri-, and endomysium (the reticular layer). By far type I collagen dominates the intramuscular collagen content (reported from ~30% and up to 97% of total collagen) (47, 48, 257, 407). At the other end of the scale, collagen types II, VI, IX, XI-XVI, and XVIII-XIX represent only very minor amounts (88a, 167, 252a, 410, 411, 440, 471, 486). It is likely that the difference in relative content of connective tissue in specific muscles is coupled to function and the role of connective tissue (247, 248). Differences between muscles with regard to their relative content and type of collagen is already present early in development (483, 485), and in cattle, the concentration of hydroxyproline as well as of collagen type I and III achieve their highest levels two-thirds through gestation (411). Interestingly, the highest collagen concentrations are achieved at the time when myotubes undergo their first phase of morphological and contractile differentiation (411). Furthermore, small leucine-rich proteoglycans of intramuscular connective tissue are expressed in parallel with development of skeletal muscle (506). Decorin and fibromodulin mRNA were markedly elevated for a few days, and biglycan and lumican for 1 wk postnatally (485). Interestingly, during this period the structure of the intramuscular connective tissue changes markedly, thereby the neonatal structure is less organized than that seen just 2–3 wk later (672). The increases in PG expression are paralleled by increases in myostatin expression and transforming growth factor-β (TGF-β) and could suggest an interplay between the development of skeletal muscle and intramuscular connective tissue (485, 672).

E. Functional Implications of ECM in Tendon and Muscle

It is important to accept that both tendon and intramuscular connective tissue interact closely with the contractile elements of the skeletal muscle to transmit force (521, 562, 566, 567, 573, 610, 675, 691). The dimensions of tendons will influence the ability to stretch, and the ability of the tendon and the intramuscular connective tissue to

store and release elastic energy during movement reduces the overall energy need during walking or running (15, 71). Some of the evidence for the functional importance of ECM components stems from studies of mutant knockout models. Given its important role in basal membrane formation, it might be obvious that mice lacking laminin will result in growth retardation and muscle dystrophy. Furthermore, mutations of integrins will also lead to muscle dystrophy and in collagen type VI to myopathy (303, 442). In mice lacking collagen type IX or XI, abnormal collagen fibrils will be found especially in relation to joints (199, 397), while in animals lacking type X collagen chondrodysplasia will develop (666). Furthermore, a defect in types IV, IX, XIII, and type XV collagen will cause myopathy symptomatology (87, 88a, 185, 367). Knockout models for collagen type I, especially when accompanied by mechanical loading, have been difficult to study, in that these animals develop severe osteogenesis imperfecta (126). Finally, somewhat interestingly, in models for proteoglycan defects in the form of a fibromodulin-null mouse, irregular collagen fibrils in tendon structure was observed, whereas no changes were detected in bone or cartilage (615). Mice lacking biglycan and fibromodulin will experience ectopic tendon ossification (27). In line with this, in mice lacking COMP, no clear musculotendinous abnormalities could be found, whereas in humans without COMP, skeletal dysplasias are observed (267). The limitation of these models is the concept of redundance, a phenomenon that is likely to be present also in the ECM, as it can be demonstrated for regulation of circulation and release of hormones in relation to exercise (333, 334).

An important role in linking together the fibrous elements of the ECM whether in muscle or tendon are the proteoglycans (111, 572, 581, 583, 584, 673). Within muscle, it has been demonstrated that PGs in the perimysium are rich in chondroitin and dermatan sulfate. In contrast, those PGs that are present in the endomysium and the basal membrane are dominated by heparan sulfates (484). In addition, decorin has been demonstrated to be present in at least bovine muscle closely associated with chondroitin sulfate (183, 480), and this is dominant in muscles during the early embryonic and postnatal state (644, 645), whereas heparan sulfate is dominant in the late embryonic state. Although several of the ECM substances in addition to collagen have been located in tendon (and muscle), little information on its functional role has been provided. One of the leucine-rich small proteoglycans that envelopes the collagen fibrils is decorin (583). Knockout of decorin suggests the involvement of decorin in the formation of collagen fibrils and to some extent controls the diameter of the fibril and prevents any lateral fusion of collagen fibrils (111, 156). Furthermore, inhibition of decorin results in larger collagen fibrils and increased mechanical properties in healing ligaments (478, 479). The clear role of decorin, or any coordinated effect of either fibromodulin or lumican situated in the same region as decorin, but having different binding sites (268, 616), is not definitively clear (119, 196, 616). More recently, it has been shown in chick embryonic tendon that small leucine-rich PGs like decorin are bound to collagen even before collagen fibril assembly, and this suggests a much earlier involvement of decorin and other PGs than thought so far (245). Even though PGs and glycosaminoglycans are important for tendon function, it has been suggested that neither these nor the collagen fibril size in itself can explain the biomechanical capacities of tendon tissue, therefore suggesting a more complex interplay involving factors and component of tendon tissue yet to be described.

One of the large chondroitin sulfate PGs, aggrecan, is largely upregulated upon compressive loading of the tendon tissue, whereas decorin only responds to tensile loading (548, 549), and is likely to be involved in the preference to synthesize type II collagen in regions of tendons that are subjected to compressive forces (61, 62, 528). Compressed areas of tendon are found to have increased amounts of larger weight PGs (200, 557). This illustrates the differentiated response to tensile and compressive loading, respectively, on collagen and ECM proteoglycans (663, 664).

IV. REGULATION OF COLLAGEN AND OTHER EXTRACELLULAR MATRIX PROTEIN SYNTHESIS: INFLUENCE OF CHANGES IN MECHANICAL LOADING

A. Steps of Collagen Synthesis: Methodological Considerations

The major component of the ECM, collagen, is produced in principal by fibroblasts either on the membrane-bound ribosomes of the rough endoplasmic reticulum (ER) or placed within the ECM, respectively. Collagen biosynthesis is characterized by the presence of an extensive number of co- and posttranslational modifications of the polypeptide chains, which contribute to the quality and stability of the collagen molecule (Fig. 4). Intracellularly, translation of preprocollagen mRNA occurs in ribosomes and procollagen assembly in the endoplasmatic reticulum (437, 443, 661). C-propeptide domains of polypeptide α-chains fold, and trimerization initiates the triple helix formation in fibrillar collagen types. These events depend on a well-matched interaction of ER enzymes like prolyl-4-hydroxylase (P-4-H), galactosylhydroxy-lysyl-glucosyltransferase (GGT), lysyl hydroxylase, prolyl-3-hydroxylase, hydroxylysylgalactosyltransferase as well as on heat shock protein 47, glucose regulating protein 94, and protein disulfide isomerase (201, 202, 368,

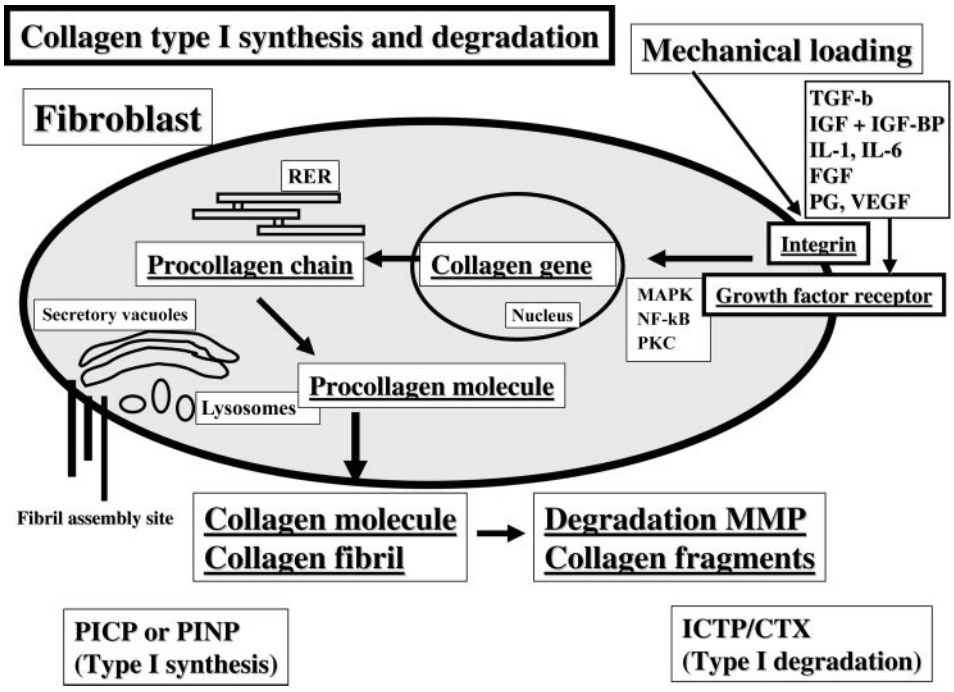

FIG. 4. Collagen type I synthesis and degradation. Schematic representation of pathways involved in collagen synthesis. Potential growth factor candidates that function as important regulators of gene avtivation are indicated. TGF-b, transforming growth factor-β; IGF/IGF-BP, insulin-like growth factor and its binding proteins; IL, interleukin; FGF, fibroblast growth factor; PG, prostaglandin; VEGF, vasoactive endothelial growth factor. Mitogen-activated protein kinase (MAPK) plays an important regulatory role for initiation of gene signaling, and matrix metalloproteinases (MMP) are major regulators of collagen degradation in relation to mechanical loading.

473, 539, 561, 568, 604). Genetic information for procollagen chain formation is divided into several exons in the DNA separated by relatively large intron areas and thus demands extensive processing of RNA prior to that mature mRNA being available for protein synthesis (661). Procollagens are transferred from ER to the extracellular space through the Golgi apparatus and contain NH_2-terminal and COOH-terminal extension peptides at the respective ends of the collagen molecule (264). The fact that procollagen is larger that the conventional transport vesicles necessitates transport within the Golgi apparatus (88).

After secretion into the extracellular space, the amino-propeptides are cleaved by specific proteinases and the collagens self-assemble into fibrils or other supramolecular structures (516) (Fig. 3). The synthesis of collagen fibrils occurs first as an intracellular step with assembling and secretion of procollagen, followed by an extracellular step converting the procollagen into collagen and subsequent incorporation into stable cross-linked collagen fibrils (Fig. 3). The synthesis of type I collagen is used here to illustrate the fibrillar collagen formation, due to its dominance in the connective tissue of tendon and muscle, but synthesis of other collagen types shares many similarities with that of collagen type I, but is described further in this review. Following the transcription of genes coding for the formation of collagen type I, the pro-α-chains initially synthesized undergo marked post-translational reactions. First, hydroxylation converts residues to 4-hydroxyproline or 3-hydroxyproline by three different hydroxylases (473). Interestingly, the hydroxylases only act on nonhelical substrates and do not act on collagen or collagen-like peptides that are triple helical. Newly synthesized collagen polypeptides are glycosylated, and this process ends before the folding of collagen into a triple helix structure. Finally, the intracellular processing completes with the synthesis of both intrachain and interchain disulfide bonds (170). This last process is not started before the translation is completed and probably not before the chains are released from ribosome. The procollagen is then secreted from the cell, and it is well described that the rate of secretion depends on the intracellular processing of the protein. If folding of the pro-α-chains into the triple helical confirmation is prevented, secretion of the protein is delayed. The three polypeptide chains form a triple-helical structure. The α-chains forming the structure are composed of repeating amino acid sequences Gly-X-Y, where the glycine residue enables the three α-chains to coil around one another. Proline and 4-hydroxyproline residues appear frequently at the X- and Y-positions, respectively, and promote the formation of intermolecular cross-links. The stability and quality of the collagen molecule is largely based on the intra- and intermolecular cross-links. The 4-hydroxyproline formation is catalyzed by P-4-H and is a unique feature of collagen. Thus its assay is suitable for evaluating collagen content. Levels of P-4-H activity generally increase and decrease with the rates of collagen biosynthesis, and assays of the enzyme activity have been used for estimating changes in the rate of collagen biosynthesis in various experimental and physiological conditions (256–258, 318, 474, 569–571, 619, 620).

The exact location of the processing of procollagen to collagen might however be more complex than that (533). Procollagen N-proteinase (called ADAMTS-2) has

recently been cloned (142, 143), and procollagen C-proteinase has been documented to be identical to bone morphometric protein (BMP-1) (327, 398) in which, at least in mouse embryonic tendon, all three protein variants of BMP-1 are expressed (541, 580). Recent experiments in embryonic chicken tendon using pulse-chase followed by sequential extraction have revealed that both intra- and extracellular pools of active procollagen C-proteinase (BMP-1) are present in fibroblasts, whereas the N-proteinase is located in close proximity or within the plasma membrane (91, 111). Conversion of extracellular procollagen to collagen was prevented when procollagen C-proteinase was blocked, whereas on the other hand, collagen fibrils were seen in post-Golgi vesicles and tubules (111). Therefore, despite demonstrated procollagen to collagen conversion being completed extracellularly, some collagen formation may be completed intracellularly and the sequence of C- and N-proteinase in converting procollagen into collagen appears to be more random than so far thought (111).

Fibril segments are prerequisites for fibril formation (496, 497) and have been shown to increase in length from a few microns to ~100 μm (76–78), and gradually develop increasing diameter (203, 204). It is likely that fibrils develop into different mass profiles, where some are regular linear ones, some are very short and spindle-shaped, and some are intermediary fusing fibers (245, 492). The collagen molecules are arranged either unipolar or bipolar (245, 312, 313) and fuse end to end (77, 78). Most likely as a result of MMP activity from the fibroblasts, this end-to-end fusion is followed by increased decorin formation (77, 78) and removal of collagen type XIV from fibril surfaces (703). The fibrillar structure and the tissue's resistance toward loading is yet to be clarified (135, 231), but it is known that the cross-link-deficient tendons are less resistant to loading (680) and that the elongation of the tendon depends on molecular gliding within the collagen fibrils (215, 519). Proteoglycans are important for fibrillogenesis (156, 164, 702), and when decorin/fibronectrin binding is inhibited, tendon length is increased (112). Determination of pyridinoline (Pyr), which represents important components of cross-links of mature collagen fibers within the ECM, has shown that the content of Pyr is especially high in tendon and ligaments, and interestingly also that the Pyr-to-collagen ratio appears to be high in tendon and ligament compared with, e.g., bone (237). This underlines the likely importance of cross-links in these structures (339) and stresses the complexity in studying structure-function relationship with regard to connective tissue as tendon, ligaments, and to some extent skeletal muscle (194).

B. Determination of Collagen Turnover in Humans

To determine turnover rates for collagen, radiolabeled amino acids have been introduced (387–389). These allow for labeling of substances such as proline, which are incorporated into the collagen. If infused they will result in an increase in the specific activity of a certain tissue removed from the experimental species at a selected time point. The calculation of turnover rates initially however was based on first-order decay curves that rely on the prerequisite that all collagen molecules are equally likely to be degraded. If, which has been shown, the collagen pool is subdivided into a more fast and a more slow exchanging pool, this method likely gave a pessimistic picture of the capability to turnover collagen (387). More recently, the use of techniques "flooding" the precursor pool to reduce or eliminate reutilization and using infusion over a relatively short time has been performed successfully (44).

Microdialysis of both muscle and connective tissue has been performed with the intention to mimic the function of a capillary blood vessel by perfusing a thin dialysis tube with a physiological fluid implanted into the tissue (384–386). This allows for collection of extracellular fluid both in animals and in humans in vivo, both with the organism in a basal state as well as during conditions where physiological perturbations are performed, whether these are chemical or mechanical. The collection of dialysate allows for calculation of interstitial concentration of unbound substances that are able to cross the membrane of the catheter, provided the technique is supplemented by calibration methods that allow for quantitation of this. Using microdialysis fibers along the peritendon also provides the possibility to study during exercise. For several metabolic parameters it has been shown that determinations peritendinously reflect the changes that occur intratendinously (379).

C. Responses to Increased Loading: Acute and Chronic Exercise

Muscular and tendinous collagen and the connective tissue network are known to respond to altered levels of physical activity (347–350, 507, 612, 613, 623, 658, 682, 688, 706). The specific activities and content of collagen components are known to be greater in the antigravity soleus muscle than in the dorsiflexor tibialis anterior, which is not tonically active (349, 569). Furthermore, ECM in skeletal muscle is known to respond to increased loading caused by endurance training (348, 349, 619, 711), acute exercise (474), or experimental compensatory hypertrophy (676) by increased collagen expression, synthesis, and collagen accumulation in the muscle. Strenuous exercise, especially acute weight-bearing exercise that contains eccentric components, is known to cause muscle damage (33). Upregulation of collagen synthesis may be a part of the repair process but may also occur without any evidence of muscle damage (256). Acceleration of colla-

gen biosynthesis after exercise may thus reflect both physiological adaptation and repair of damage.

It has been found in mice that acute exercise increases activities of enzymes of collagen turnover 48 h after exercise. Enzymes responsible for collagen synthesis were increased, and the most in muscles dominated by red rather than white muscle fibers (474, 650, 651). This fits with the demonstration of higher content of collagen, as measured by amount of hydroxyproline, in red versus white muscle fiber dominated muscles, and with a high recruitment of red fiber muscles during the specific exercise protocol (349). Interestingly, the changes in collagen enzyme activities were accompanied by a rise in both hydroxyproline and collagen content of the exercised muscle, which persisted up to 3 wk after exercise (474, 650, 651). Later studies have demonstrated that expression of types I and III collagen was increased at the mRNA level within 1 day (257, 345) and that of type IV collagen as early as 6 h after acute exercise (344).

Extracellular conversion of procollagen to collagen requires at least two enzymes: a procollagen aminoprotease that removes the aminopeptides and a procollagen carboxyprotease that removes the carboxy propeptides. The cleavage of the carboxypeptide allows for indirect determination of collagen type I formation. Development of assays for such markers of type I collagen synthesis [the COOH-terminal propeptide of type I collagen (PICP)] and degradation [the COOH-terminal telopeptide region of type I collagen (ICTP)] has made it possible to study the effect of exercise on collagen type I turnover (99). When determined in circulating blood, these markers have been shown to be relatively insensitive to a single bout of exercise, whereas prolonged exercise or weeks of training were shown to result in increased type I collagen turnover and net formation (383). However, as bone is the main overall contributor of procollagen markers for collagen type I turnover in the blood, and as serum levels of PICP and ICTP do not allow for detection of the location of the specific type of region or tissue in which changes in turnover are taking place, from these studies it cannot be concluded whether changes in collagen turnover of tendon-related tissue or intramuscular connective tissue occur. The use of the microdialysis technique has recently been applied to the peritendinous space of the Achilles tendon in runners before, immediately after, and 72 h after 36 km of running (386) (Fig. 5). With this technique it was demonstrated that acute exercise induces changes in metabolic and inflammatory activity of the peritendinous region (386). In addition, acute exercise caused increased formation of type I collagen in the recovery process, suggesting that acute physical loading leads to adaptations in non-bone-related collagen in humans.

Furthermore, when type I collagen synthesis and degradation in connective tissue of the Achilles peritendinous space was studied before and after 4 and 11 wk of intense physical training, an adaptive response of the collagen type I metabolism of the peritendinous tissue around human Achilles tendon was found in response to physical training (382) (Fig. 5). The increase in interstitial concentrations of PICP rose within 4 wk of training and

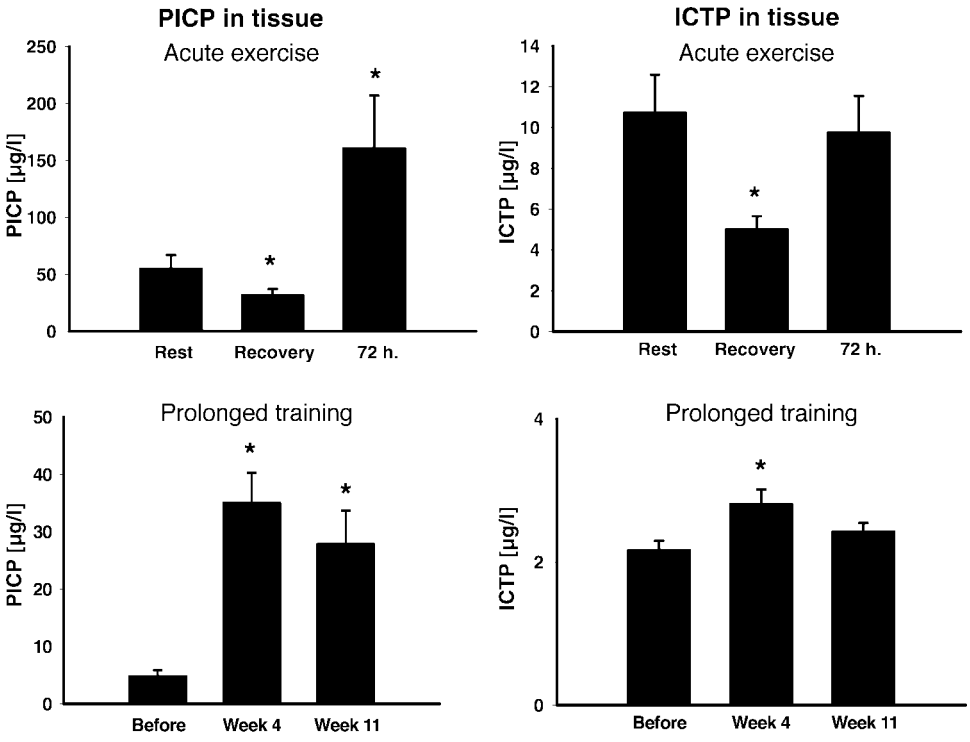

FIG. 5. Collagen type I synthesis and degradation in response to acute and chronic exercise. Interstitial concentrations of carboxy-terminal propeptide (PICP) and telopeptide region (ICTP) of type I collagen in peritendinous tissue of human Achilles tendon. Microdialysis was used to obtain tissue concentrations, and PICP was used as an indicator for collagen type I synthesis, while ICTP was a marker for degradation of type I collagen. The *top panels* show values obtained in highly trained individuals before (rest), immediately after 36 km of running (recovery), as well as 72 h after termination of exercise (72 h). Both PICP and ICTP decreased initially after exercise, and a marked increase in collagen synthesis was detected 72 h after exercise. The *bottom panels* show values obtained in healthy humans before, as well as 4 and 11 wk into daily physical training. Both synthesis and degradation increased after 4 wk of physical training, whereas after 11 wk only the collagen synthesis, and not the collagen degradation, was chronically elevated. *Values significantly ($P < 0.05$) different from basal levels (rest). [Adapted from Langberg and co-workers (382, 386).]

remained thereafter elevated for the entire training period, indicating that collagen type I synthesis was chronically elevated in response to training. As blood values for PICP did not change significantly over the training period, it is reasonable to suspect that the increased collagen type I formation occurs locally in non-bone tendon connective tissue rather than reflecting a general rise in formation of collagen type I throughout the body (382). Also, tissue ICTP concentrations rose in response to training, but this rise was transient, and interstitial levels of ICTP returned to basal levels with more prolonged training. Taken together, the findings indicate that the initial response to training is an increase in turnover of collagen I, and that this is followed by a predomination of anabolic processes resulting in an increased net synthesis of collagen type I in non-bone connective tissue such as tendons (382). The pattern of stimulation of both synthesis and degradation with the anabolic process dominating in response to exercise in tendon-related connective tissue is a pattern that is in accordance with events occurring with muscle proteins in response to loading (540). As individuals in the training study (382) were training on a daily basis, it can be difficult to differentiate effects of each bout of acute exercise from the chronic training adaptation. Previous acute bouts of exercise will influence the outcome of each subsequent one. This probably explains why highly trained runners (training up to 12 h/wk) in one study had high basal levels of interstitial levels of PICP (386). Thus it cannot be excluded that the effect on collagen metabolism found during a program with daily training simply reflects an effect on collagen formation from the last training bout, rather than chronic effect of training.

On the basis of these findings it can be concluded that both an increased collagen turnover is observed in response to training and that with prolonged training a net synthesis of collagen type I is to be expected. Whether a net synthesis of collagen type I is transformed into morphologically detectable increases in tendon size is far from clear. However, in accordance with this view, it has been demonstated in animal models that training results in enlargement of tendon diameter (74, 605, 689). Furthermore, recent cross-sectional observations in trained runners versus sedentary humans have shown that magnetic resonance imaging (MRI)-determined Achilles tendon cross-sectional area was enlarged in trained individuals compared with untrained controls (553). It can also be speculated that training initially results in an increased turnover of collagen type I to allow for reorganization of the tissue and that more prolonged training results in a net increase in tendon tissue and probably alterations in tissue strength.

No clear dose-response relationship between type and amount of training and adaptive responses of collagen formation exists, but in equine tendon it has interestingly been found that in tendon subjected to low-level repetitive stress (extensor tendon) the collagen level is higher that in flexor tendons subjected to high stress (497). This indicates that intensity and loading pattern including recovery periods between training bouts likely play an important role in adaptation of ECM. Stretch-induced hypertrophy of chicken skeletal muscle has been shown to increase muscle collagen turnover using tracer methods (389), which is in accordance with the present findings on humans in which collagen synthesis increased markedly at the beginning of training. From studies by Laurent and co-workers (387–389), it was concluded that a large amount of newly synthesized collagen was wasted, resulting in disproportionate high collagen turnover rate compared with the magnitude of net synthesis of collagen. Likewise, in human muscle, type IV collagen degradation, as indicated by an increased MMP-2, increased over a period of 1 year with electrical stimulation of spinal cord injured individuals, without any detectable change in type IV content, indicating an increased collagen turnover rate with no or very little net synthesis (342). Measuring the racemization and isomerization of its C-telopeptide (CTx) has been used to determine collagen type I turnover. As these processes are coupled to protein turnover it is likely that they reflect an index of collagen turnover (237). With this method it has been shown in human cadaver tissue that tissues like tendon and ligament have a turnover rate comparable to that in bone, and that the turnover of collagen type I is in fact quite pronounced in skeletal muscle (237). These data agree with studies using radiolabeled proline/hydroxyproline in animals showing a relative turnover (3%) of collagen per day in skeletal muscle (389).

The present studies in humans and animals support the idea of a simultaneous activation of both formation and degradation in collagen of both muscle and tendon tissue in response to loading. Interestingly, for type I collagen in tendon, timewise this is followed by a more pronounced imbalance in favor of formation and resulting in a net collagen synthesis, whereas in muscle, type IV collagen does not seem to reveal any net synthesis. In addition to an increased turnover of collagen, indirect evidence for loading increased both synthesis and degradation rates has been demonstrated also for non-collagen components of the ECM (53, 537, 549).

An important step in collagen type I formation is the enzymatic regulation by procollagen C-proteinase (PCP) of the cleavage of PICP and PINP of procollagen to form insoluble collagen (311). It has been demonstrated that mechanical load can enhance the expression of the PCP gene, but not of the procollagen C-proteinase enhancer protein (PCPE) in dermal fibroblasts (498). In addition to this, it was shown that both the synthesis and the processing of procollagen were enhanced by loading in vitro. This effect was demonstrated to be specific as non-collagen protein synthesis in that study was not elevated (498).

Furthermore, an enhanced processing of procollagen to insoluble collagen was found, as evident by a larger increase in the actual amount of insoluble collagen produced compared with the increase in procollagen synthesis. Interestingly, in that study it was demonstrated that the above-described changes only occurred if cells were in tissue cultures containing TGF-β or serum (498), indicating that mechanical loading by itself is not able to cause changes unless certain growth factors were present.

D. Immobilization and Collagen Turnover

In contrast to physical loading, immobilization of rat hindlimb leads to a decrease in the enzyme activities of collagen biosynthesis in both skeletal muscle and tendon (569, 570), which suggests that the biosynthesis of the collagen network decreases as a result of reduced muscular and tendinous activity (181). The rate of the total collagen synthesis depends mostly on the overall protein balance of the tissue, but it seems to be positively affected by stretch in both muscle and tendon (569, 570). Changes in the total collagen content of muscle, measured as hydroxyproline content, are usually small or absent during immobilization lasting for a few weeks, which is probably due to the turnover rate of collagen (257). Collagen expression during immobilization has been shown to be at least partially downregulated at the pretranslational level (11). The mRNAs for type I and III collagens were already decreased after 3 days of immobilization, whereas stretch seemed to counteract this decrease (11). The content of type IV collagen was also reduced as a result of immobilization (12).

In other studies of rats, amounts of collagen in skeletal muscle were studied in response to immobilization at increasing muscle length to cause either atrophy or hypertrophy (569). Whereas P-4-H decreased and proteolytic enzyme activity increased in shortened muscle, no increase in P-4-H or GGT could be detected in lengthened muscle (569). Electrical stimulation could, at least in some muscles, counteract the immobilization-induced drop in muscle mass together with the decrease in content of hydroxyproline and collagen-related enzyme activities (571). To some surprise, it was found that denervation of muscles in rats resulted in an elevation of hydroxyproline content and in P-4-H and GGT activities of muscle (571). Although non-collagen proteins of the atrophying muscle were degraded at a high rate during denervation, this could not solely explain the rise in collagen content and enzyme activity with denervation. In tendons of immobilized and denervated muscle, activities of collagen-synthesizing enzymes fell during immobilization in the shortened position but were unaffected when immobilized in the lengthened position (571). This indicated that the regulation of collagen synthesis to varying mechanical loading possessed similarities in skeletal muscle and tendon tissue. Further studies of remobilization of skeletal muscle after 1 wk of immobilization in rats showed that activities of P-4-H and GGT as well as concentrations of hydroxyproline (HP) rose within days, whereas remobilization exercise did not cause any rise in tendon P-4-H or GGT (318). This could imply that although activity can activate collagen synthesis in both tendon and skeletal muscle, a higher activity is needed to stimulate tendon than muscle.

V. DEGRADATION OF CONNECTIVE TISSUE IN TENDON AND SKELETAL MUSCLE: EFFECTS OF CHANGES IN MECHANICAL LOADING

Degradation of collagen represents an obligatory step of turnover and of remodeling of connective tissue and during mechanical loading of fibroblasts and extracellular matrix structures. Both intracellular and extracellular degrading pathways are present, using either lysosomal phagocytosis or ECM proteinases, respectively (193) (Fig. 4).

A. MMPs

Collagen degradation is initiated extracellularly by MMPs (or matrixins), which are presented in tissues mostly as latent proMMPs (38, 49, 475). There is evidence to support that MMPs [and tissue inhibitors of matrix metalloproteinases (TIMPs)] are not involved to a major degree in the intracellular lysosomal phagocytosis, but function extracellularly (192). The collagen degradation processes are well described in situations with rapid remodeling, e.g., inflammation or tissue damage (140, 295, 436), but its role during normal physiological stimulation to increase tissue turnover like after mechanical loading is not known (192). Whereas collagenases (MMP-1 and MMP-8) traditionally are thought primarily to initiate degradation of type I and III collagen and thus should be most relevant for tendon, gelatinases (MMP-2 and MMP-9) mainly break down nonfibrillar type IV collagen and other compounds of the ECM. Although some preference for the different MMPs with regard to collagen types exists, the specificity of certain MMPs toward collagen types may be less than thought so far. As an example, MMP-2 can also degrade type I collagen (13), most likely in a two-step fashion (500), and the whole role of MMPs on tissue matrix metabolism seems far more complex (475). MMPs are produced from endotenon fibroblasts and intramuscular matrix fibroblasts, although the secretion is somewhat lower than that of synovial cells (526).

Immobilization leads to an increase in MMP expression at both pre- and posttranlational levels, suggesting accelerated collagen breakdown, which can be partially

prevented by stretching procedures. The regulation of MMPs in relation to exercise remains to be fully understood, but it is known that specific integrins ($\alpha_2\beta_1$) are regulators of the MMP-1 gene expression in fibroblasts cultured in contracting-retracting collagen gel (475). Furthermore, it is known that MMP-1 expression can be modulated by growth factors, inflammatory cytokines, and cytoskeleton-disrupting drugs like cytochalasin D. However, the role of contraction and stress relaxation has not been evaluated. In a retracting collagen gel, MMP-1 is expressed as a result of the tension on the tissue (369) and mediated through $\alpha_2\beta_1$-integrins (545).

Increased fluid flow has in vitro been shown to increase the expression of both MMP-1 and MMP-3, together with an activation of interleukin (IL)-1β and cyclooxygenase (COX)-2 genes (29, 32). Mechanical stress relaxation stimulated MMP-1 gene expression has more recently been shown to depend on de novo protein synthesis, although it occurs independently of the activation of an IL-1 autocrine feedback loop (370, 371). Mechanical stretching is known to elicit an increase in MMP gene expression (29, 32) without any obligatory rise in collagen type I expression or indication of changes in inflammatory meditors in vitro. However, the IL-1β was able to induce marked increases in MMP expression, and a synergistic effect of IL-1β and stretching was observed (29, 32). This fits with findings on human tendon tissue where IL-1α and oncostatin caused an increased production of MMP-1 (117). In lung fibroblasts, stretching is found to increase activation of MMP-9 directly in the absence of any inflammatory mediators (617). Interestingly, shear stress elicited by fluid pressure on rabbit tendon fibroblasts elicits expression and release of MMP-1 and -3, in the absence of any change in intracellular calcium concentration (29, 32). MMP-2 and -9 are known to be overexpressed and present in higher amounts in patients with inflammatory myopathies (329), which may increase ECM degradation and thus facilitate lymphocyte adhesion (132). Furthermore, the attachment of type I collagen to cultured fibroblasts upregulated MMP-2 and MMP-9 production, an effect that was blocked by dexamethasone (547). Finally, MMP-2 is colocalized with integrins placed in vessels (102), and MMP-mediated proteolysis of capillary basement membrane proteins is important for physiological angiogenesis responses to chronic loading of skeletal muscle, and increased production of MMP-2 and MT1-MMP is crucial for new capillary formation during mechanical stimulus (251, 252, 641). Taken together, several of the exercise- and training-related adaptations are coupled to processes that are found to involve MMP responses (409). Recently, it has been demonstrated that acute exercise resulted in elevated interstitial amounts of MMP-2 and MMP-9 in human peritendinous tissue (346), which supports the view that MMPs (and their inhibitors) play a role in ECM adaptation to exercise in tendon tissue.

B. TIMPs

TIMPs inhibit MMP activities (198). Of the four TIMPs so far identified, TIMP-1 and TIMP-2 are capable of inhibiting activities of all MMPs with a preference for inhibiting MMP-2 and MMP-9, respectively. Pro-MMP-2 is upregulated both at the pre- and posttranslational level after a single bout of exercise, suggesting an increase in the collagen degradation (343, 345). In line with this, stretch-relaxation on dermal fibroblasts results in increased activity of MMP-2 through integrin-mediated pathways (369, 372). As mentioned previously, increased MMP activity and thus enhanced degradation of collagen often parallels the stimulated activation of collagen synthesis (345). Interestingly, TIMPs are often activated together with MMPs in response to physical activity (345), indicating simultaneous stimulation and inhibition of degradation. Rather than considering this as a competitive action, it is likely that MMP activity precedes TIMP activity, and thus TIMP serves as regulators of degradation termination to ensure a limited amount of degradation. To support further that an integrated response of MMPs and TIMPs exist, TIMP-2 has been shown to be important for an activation of pro-MMP-2 in vivo (670). TIMP-1 has been found to be correlated with ICTP in patients with cancer, indicating activity in and control of collagen degrading pathways (701).

VI. STRUCTURE OF EXTRACELLULAR MATRIX IN TENDON AND MUSCLE: RELATION TO MECHANICAL AND VISCOELASTIC PROPERTIES

A. Extensibility of Tendons

Tendons vary in their ability to stretch, from 1–2% of lengthening of the animal extensor carpi radialis, to 3–4% of lengthening of the flexor carpi ulnaris tendon, and up to 16% of elongation of the rabbit Achilles tendon (403). Human cadaver data imply that the maximal elongation of human tendon is up to 5–6% when passively stretched (413). In association with this, the aponeurosis of the adjacent muscle generally displays a larger mechanical excursion compared with free tendon under passive stretch (10–12%) (403). Although indicative of the viscoelastic potential of the tissue when challenged to passive loading, these findings do not take into account the in vivo characteristics during muscular activity. Some studies have shown that the free tendon and aponeurosis of the cat triceps surae have comparable mechanical properties during isometric contraction (585, 629). In contrast, the stiffness of the aponeurosis is found to be less than that of free tendon during contraction, whereas others have found the reverse, namely, that tendon strain was 2%

while aponeurosis strain was 8% during passive loading (403) (Fig. 6). Such findings do not, however, take into account that during muscle contraction in vivo in humans it is likely that the contractile apparatus of the muscle will limit the excursions of the aponeurosis. Attempts to separate aponeurosis movement and free tendon movement in vivo have shown varying results (296, 422). Some studies found no difference between Achilles tendon and the adjacent aponeurosis (225, 226, 355, 356). However, in those studies the Achilles tendon was defined as the free tendon plus the soleus aponeurosis. In a study on tibialis anterior free tendon, this was only strained 2%, whereas the aponeurosis was strained up to 7% during submaximal isometric contraction (422). Somewhat in contrast, it has been shown for the human Achilles tendon that the strain of free tendon was six- to sevenfold greater than that of the aponeurosis during intense isometric calf muscle activation (427) (Fig. 6). The difference between studies of viscoelastic properties of the free tendon and skeletal muscle aponeurosis can both be accounted for by measurement limitation, such as accounting for antagonist activity, joint rotation, and the fact that the methodology is limited in its ability to observe three-dimensional phenomenon (85, 425). The pronounced difference between the strain in free tendon and the aponeurosis in the human Achilles region suggests that their functional role during force transmission differs. It is on this background suggested that free tendon permits for storage and release of energy, while the aponeurosis ensures effective transmission of contractile forces.

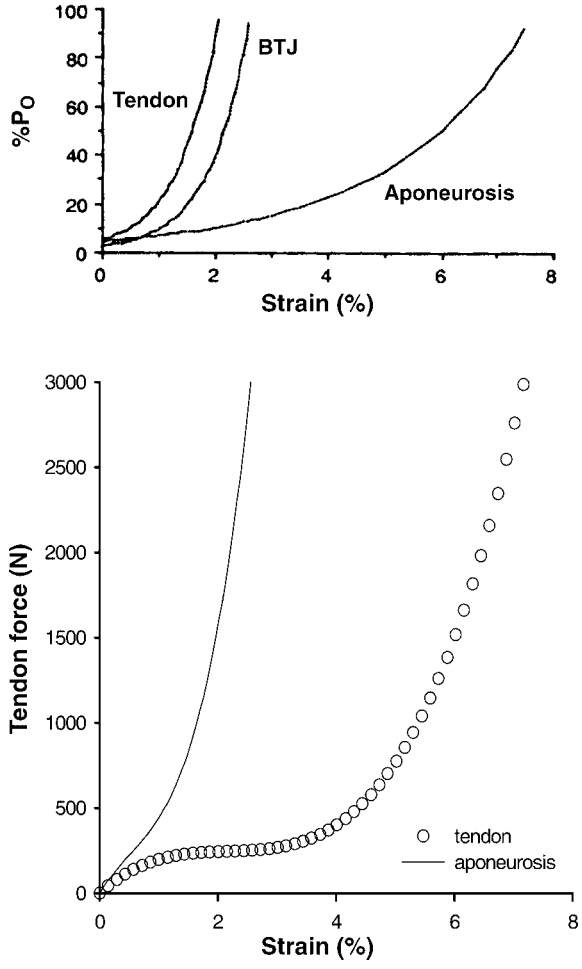

FIG. 6. Load-strain relationship for tendon and muscle aponeurosis during passive and active muscle contraction. *Top*: determination of load-strain on frog semitendinosis during passive loading of structures up to a tension equal to maximum active isometric tension (P_o). The relationship for tendon, bone-tendon junction (BTJ), and aponeurosis is given, and passive loading expressed in %P_o. Note that the strain of the aponeurosis by far exceeds that of the tendon. *Bottom*: tendon load-strain on human Achilles tendon and triceps surae aponeurosis determined on human tendon/muscle with ultrasonography during calf muscle contraction. Note that in the active, contractiing state, the strain of the free tendon is severalfold higher than that of the adjacent aponeurosis. [From Lieber et al. (403) (*top*) and Magnusson et al. (427) (*bottom*), with permission.]

B. Repetitive Loading and Tendon Properties

Several in vitro systems for determination of cellular responses to mechanical tensile stress are available. One way to study mechanical loading of fibroblasts is to seed cells upon a flexible substrate that allows for easy control of strain, whereas actual forces put upon the individual cell cannot be accurately quantified (221, 418). Another method to grow fibroblasts is in a native three-dimensional collagen matrix in which they attach and pull on collagen fibrils. This latter method allows for determination of tensile force developed, whereas strain is more poorly defined (221). It is clear that fibroblast cultures subjected to biaxial mechanical loading often result in uneven strain and loading across the plate, and this model thus only obtains results that represents a mean of the different ranges of movements (498). The in vitro systems evidently have major advantages with regard to localized measurements and the possibilities for intervention; however, it still represents a simplified system that does not always encompass all the growth factors that are needed in the transformation phase from mechanical loading to synthesis of ECM proteins like collagen.

Tendons respond to mechanical loading, and animal studies have provided some evidence that endurance training will influence their morphology and mechanical properties (106, 190, 355, 652, 687, 689). In rabbits, it has been shown that the load-deformation curve of the Achilles tendon was unaffected by 40 wk of training, which implies that no structural properties were influenced by the training (652). However, the same group also showed with similar training that the posterior tibialis tendon displayed a load-deformation curve that was altered without any detectable change in tendon volume or mass, which suggests that the mechanical loading resulted in qualitative rather that quantitative changes (653). Some-

what in contrast, 12 wk of training in swines increased both load-deformation and stress-strain properties of digital extensor tendons, together with an increase in the cross-sectional area (CSA) and total collagen content of the tendon (687, 689). This supports the view that both structural as well as mechanical properties are improved with training. Interestingly, in a similar model, this was shown to be the case only after 12 mo, but not after 3 mo of training, and the shorter training period in fact reduced the tendon size (687). In support of this pivotal adaptation of tendon morphology, training studies on horses revealed that 5 mo of training did not influence the CSA of the Achilles tendon, whereas 18 mo of training increased it by 14% (74, 502–504). Finally, in rats the CSA of the Achilles tendon reduced after 1 mo, but increased after 4 mo of training (505). In both the latter studies a quasi dose-response relationship was obtained in that low-intensity training did not change the tendon morphology, but intense training did so. In two additional studies, training did not alter the dry weight of the patellar tendon of rats (638) or of chicken Achilles tendon (153). A study in turkeys showed that despite only a minimal change in tendon CSA area after training, the mechanical properties changed and an increased tendon stiffness was found (106). This would theoretically yield a larger amount of stored energy in the tendon and thus enhance locomotion economy. This would, however, require a larger force on the tendon, which is unlikely at the same absolute running speed, and it was therefore suggested that the altered properties could contribute to a larger tendon resistance towards material fatigue and subsequent damage.

Somewhat in contrast to other studies, running in mice resulted in unchanged tensile strength of patellar tendon (330), but it has to be acknowledged that the mice were not adult, as has been the case in other studies (652, 687, 689). Finally, rat Achilles tendon was found to increase tensile strength and stiffness after 30 days of training (655). In addition to the classical stress-strain curves, attempts have been performed to address cumulative damage and fatigue development in tendon tissue that is repeatedly loaded with forces that are below the ultimate tensile stress. It was found that time-to-rupture among tendons was similar when tendons were subjected to a load that corresponded to the maximal voluntary contraction of their corresponding muscle (324–326). This would mean that all tendons appear similarly prone to fatigue ruture, and it is suggested that any CSA of a tendon is coupled to the achievement of a certain stiffness.

Only one study has tried to compare strength and endurance training, and in rats they found that 38 wk of training was associated with an age-related decline in ultimate load-to-failure that was counteracted by swimming training, but no effect was seen in response to strength training (595). It could be argued that the strength protocol was limited in that study and that a further major drawback was the lack of any determination of tendon area or volume, which precluded the evaluation of any quantitative versus qualitative effect of training. Only few studies have addressed the effect of training on intratendinous structures (159), and although one very early study did not demonstrate any intratendinous fibril increase as a result of training in rats (292), a subsequent study demonstrated increased fibril diameter after training (453, 454). In the horse, an 18-mo training program did not result in any significant change in collagen fibril diameter of the deep flexor tendon of the horse (502, 504). As horses have been shown to increase the CSA of the tendon in response to such prolonged training (74), it indicates that the number of collagen fibrils was increased. This was also found in one study after 10 wk of training (454), and furthermore, one study demonstrated more densely packed and aligned fibrils as a result of training (655).

It has been shown with ultrasonography in humans that the compliance of the muscle vastus lateralis aponeurosis-tendon complex was lower in long-distance runners compared with that in untrained subjects (355). It was stated that this allowed the complex to store energy and reuse it more efficiently in runners compared with sedentary counterparts. Somewhat in contrast to this, no difference in compliance was found between sprinters and control individuals with regard to both the quadriceps and triceps surae tendon-aponeurosis complex (356). This is interesting, since sprinters are a group of athletes that would need capacity to reuse elastic energy. The same authors found, however, that 8 wk of isometric strength training, but not 4 wk, did increase the stiffness of muscle vastus lateralis in humans, indicating an effect of training duration on tendon-aponeurosis properties (354). However, it has to be remembered that the ultrasonography method used in those studies cannot clearly separate the tendon properties per se from those of the combined tendon-aponeurosis complex.

The highest tolerable tensile load of a tendon is known to depend on its CSA in relation to integrated fascicle CSA of the adjacent muscle, and this relationship varies between tendons in different species but also between tendons in a given individual (63, 64, 325, 326, 512). In this respect it is interesting that a cross-sectional study found that the CSA of long distance runners was 20–30% larger than untrained controls, while the load-deformation curve of the triceps surae aponeurosis-tendon complex did not differ (553). When the ratio between muscle and tendon area (multiplied by 0.3 MPa as a chosen number for maximum isometric stress, Ref. 325) was related to a certain load, differences in fatigue resistance to failure were seen between different tendons (326) (Fig. 7). Interestingly, if the individual tendons were subjected to individual loading dependent on the capacity of the relevant adjacent muscle, the time to rupture was similar

between tendons (326). This implies that fatigue and resistance to rupture are coupled to the tendon-loading pattern, which was shown when high-stress and low-stress tendons in sheep develop their functional capacity matched the working demands of the tendon (510). If we combine this with the data obtained in humans of varying training degree, the larger CSA of the trained tendon results in a lower stress on the tendon during maximal isometric force in trained compared with untrained individuals (553), and thus provides a potentially more injury-resistant tendon (Fig. 8). The safety factor (fracture stress set at 100 MPa divided by the stress during intense activity) has been found to be ~8 in general for most tendons (325). It was shown in humans in vivo that the safety factor was only 2–3 during maximal isometric contraction (431). Therefore, tendon hypertrophy would seem helpful in counteracting overload and prevention of ruptures. These data fit with previous observations on old individuals where there is a tendency toward larger CSA of the well-trained individuals (314, 426).

Sonographic evaluation of the Achilles tendon has shown that the CSA of the tendon is larger in individuals with an active history of physical training than in sedentary counterparts (700). Most likely, increase in tendon CSA in humans requires very prolonged anamnesis of training, as 6 mo of recreational running training in previously untrained individuals was not sufficient to increase the CSA of the Achilles tendon (428).

In muscle, the passive movement of the perimysium is viscoelastic but does not involve any major reorientation movements of collagen fibers in a proteoglycan matrix (519). Rather, the viscoelastic pattern to stretch depends on relaxation processes within the collagen fibers themselves or at the fiber-matrix interphase. In tendon it has been shown that the molecular packing of collagen is extended upon stretch in the rat tail (215, 460). This could be due to molecular straightening and gliding of collagen molecules. However, the strain within collagen fibrils is always smaller than stretching of the entire structure (i.e., the tendon), which implies that additional gliding occurs at the interfibrillar level. That other structures than the collagen fibrils themselves are involved in tension resistance and subject to injury is supported by the demonstration that fibrils do not run through the entire length of a tendon but are largely dependent on cross-linking (630, 632). In line with this, it has been shown that shorter specimen samples of tendons are more resistive to rupture when determining time to failure towards a given test

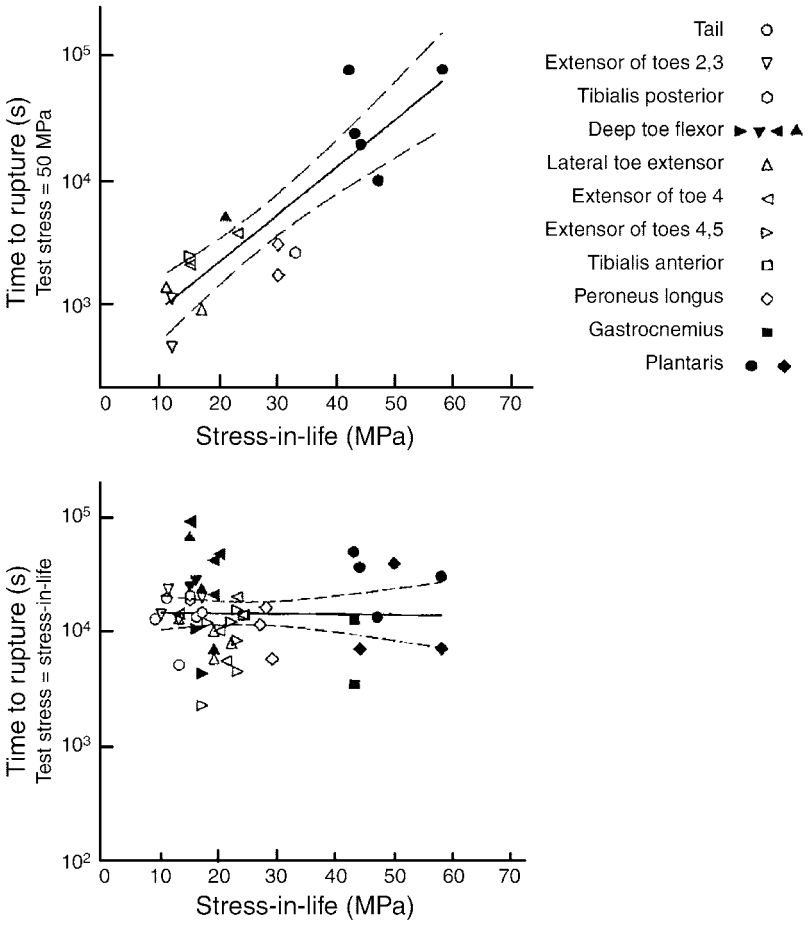

FIG. 7. Tendon time to rupture in animal tendons during mechanical loading. *Top*: time to rupture in wallaby limb tendons when subjected to a constant stress of 50 MPa. Linear regression with 95% confidence intervals are given. *Bottom*: time to rupture at stresses related to those experienced in life. "Stress-in-life" is defined as the area ratio between muscle cross-sectional area (CSA) and the adjacent tendon CSA, and multiplied by 0.3, to illustrate a more relative comparison between tendons. Interestingly, when stress-for-life is used, time to rupture is close to identical for all tendons measured (~4 h). This would indicate that all tendons will have a need for structural adaptation toward loading to counteract overloading and subsequent injury. [From Ker et al. (326).]

stress, indicating that strengthening structures are added and increasingly important when longer tendons are studied (669). The cross-linking between parallel collagen molecules includes both aldimine and ketoimine, of which the former dominates during development of tendon (47, 48). Later on, other cross-links bind collagen molecules together including pyridinoline, and with aging a nonspecific cross-linking through glycation comes into play (54). Only a few studies have looked at the importance of these cross-links, but it has been demonstrated that chemical preparation of tendon to reduce numbers of almidine cross-links was found to increase tendon strength and diminish stress relaxation, implying that these links are involved in the stress relaxation (160).

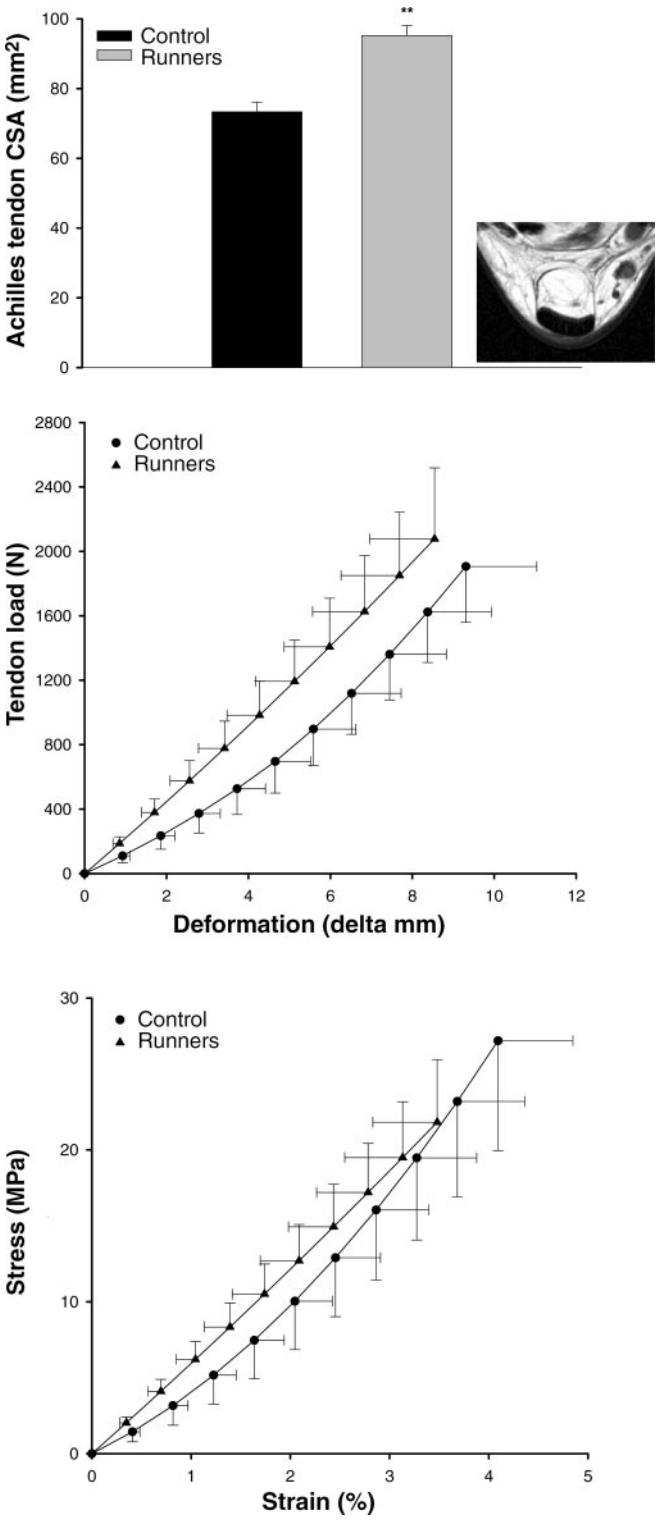

FIG. 8. Mechanical loading of physically trained and untrained human tendon. *Top*: cross-sectional area (CSA) of the Achilles tendon in habitual runners and nonrunners (control) (*left*) as determined from magnetic resonance imaging 6 cm above the calcaneal insertion (*right*). Runners showed significantly larger CSA than controls. *Middle*: load-deformation curve during graded isometric triceps surae contraction, obtained by ultrasonography on human Achilles tendon. No statistical significant difference was found between groups. Mean ± SE is given. *Bottom*: stress-strain relationship of the human Achilles tendon in runners and sedentary controls. Mean ± SE is given. The fact that runners have a higher CSA contributes to the significant lower maximal stress in runners (triangles) compared with controls (circles) and may thus indicate a lower relative stress on the tendon in well-trained athletes compared with untrained counterparts. [Modified from Rosager et al. (553).]

C. Aging, Disuse, and ECM

With aging of connective tissue or in diseased states with elevated glucose levels (e.g., diabetes) the nonspecific cross-linking mediated by condensation of a reducing sugar with an amino group and result in accumulation of advanced glycation end products (AGEs), in tendon tissue (297, 535, 587). It has been shown that glycated tendons could withstand more load and tensile stress than nonglycated tendons (535), but the tissue gets stiffer (648). In chondrocytes it has been demonstrated that not only is a relatively low turnover of collagen in the tissue a prerequisite for the formation of AGEs (648), but that the presence of AGEs feedback to reduce both collagen synthesis and MMP initiated collagen degradation (162). When biochemical markers (pentosidine and fructosamine) of AGEs are correlated to microscopic determination of collagen fibrils in the rat tail tendon, it can be shown that high amounts of AGEs are coupled to tight assemblence and fusion of fibrils, thus displaying larger collagen fibril diameters than in the healthy (293, 489). Likewise, the morphological and biochemical picture of tendons in which AGEs were induced by glucose incubation were strikingly similar to tendons from diabetic animals (361, 489). The accumulation of AGEs with aging thus indicates a stiffer and more load-resistant tendon and intramuscular ECM structure, but on the other hand reduces the ability to adapt to altered loading, as the turnover rate of collagen is markedly reduced (360). In addition to this, it has been shown that AGEs upregulate connective tissue growth factor (CTGF) in fibroblasts that thus favor the formation of fibrosis over time in elderly individuals and patients with diabetes (636).

It is well described in animals that the average fibril diameter increases during development (118, 496, 497) but declines with aging (476) and disuse (477). The effect of training on this is variable (453, 501–504). Somewhat in contrast to animal data, the overall CSA of the Achilles tendon is larger in elderly compared with younger individuals (426). The phenomenon may reflect a compensatory increase in ECM to lower stress on the tendon due to age-related decline in tendon quality and thus in maximal tolerable load (426). This is interesting, since there are observations of reduced expression and synthesis of collagen in aging fibroblasts (47, 124, 239). In addition, covalent intramolecular cross-links are known to increase the elastic modulus, and reduce strain to failure, but do not influence rupture stress (47, 168, 624). This phenomenon is more pronounced in high-load bearing flexor tendons compared with low-stress extensor tendons (47, 73). Interestingly, cross-linking and stiffness are increased with aging, whereas endurance training counteracts these phenomena (244). The same counteractive effect is found in elderly with low-load resistance training (357), but not found with very intense strength training (538). The fact that in association with increased tendon stiffness with aging, bone mineral density is decreasing, which might explain why older individuals are more prone to get avulsions of the bone rather that tendon ruptures compared with younger counterparts (692).

D. Integrated Muscle-Tendon ECM Properties

In vivo determination of viscoelastic behavior of a stretched muscle-tendon unit (423, 424). In the absence of any detectable electromyelogram (EMG) activity in the passively stretched muscles, and during dynamic stretching a curvilinear increase in resistance towards stretch was found, whereas a nonlinear stress relaxation response declining the resistance by 25–35% was demonstrated over the 45 s of static loading phase (433). This effect has no influence on subsequent stretch procedures (424, 435, 443). Furthermore, when a series of stretching procedures was carried out, it was found that this acutely lowered the stiffness and storage of passive energy during dynamic stretch, but that the effect vanished 1 h after stopping the stretching regimen (432–434). This supports the notion that passive stretching of muscle-tendon has no chronic effect on viscoelastic properties of the tissue. If this is the case, chronic stretching of muscle tendon unit in association with physical training should not cause any altered passive properties of the muscle-tendon unit, and thus challenge common clinical belief (227). In an investigation where subjects performed repeated stretching exercises twice daily for 3 wk, no change in passive properties of the muscle-tendon unit was found. It was demonstrated that the maximal flexibility was improved by the training, but this was achieved at the expense of a high resistance to stretch (434). At present it is unknown what mechanism lies behind this phenomenon. Evidently, the passive properties interplay with active muscle contraction in a very complex way. In isolated animal muscle-aponeurosis-tendon preparations it has been shown that rapid elongation of the passive tendon structure takes place upon muscle stimulation and shortening (404). This potentially creates a scenario where muscle fibers shorten at a high velocity and lower force development in the initial phase of contraction. When the passive structure such as tendon subsequently reaches its point of increased resistance towards stretch, the shortening velocity of the muscle will markedly decrease, and thus allow for a higher force output from muscle (404). Perhaps, depending on tissue qualities, tendon and/or muscle will be more fragile toward rupture at high loading, and that muscle rupture can occur at a late time point in the contraction. In addition, surgical transfer of tendon in human arm has been demonstrated to influence functional muscle-tendon performance dependent on the length at which the muscle-tendon complex is surgically inserted (219). Thus an attempt to overstretch the tendon-muscle when inserting will cause the sarcomere length of the muscle to be at a suboptimal length with regard to force development (219).

VII. LOADING AND OVERLOADING OF CONNECTIVE TISSUE STRUCTURES IN TENDON AND SKELETAL MUSCLE: ROLE OF GROWTH FACTORS

The loading-induced adaptation of ECM and especially collagen synthesis is dependent on regulatory hormones and growth factors that together with integrins, cytoskeletal, and certain ion channels may be responsible for mechanically induced cell signaling (127). A role of growth factors for collagen synthesis is in accordance with findings that specific circulating growth factors, such as TGF-β, IL-1, IL-6, and IL-8, insulin-like growth factor I (IGF-I), fibroblast growth factors (FGF), NO, prostaglandins, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF), all have positive effects on fibroblast activation in vitro, when fibroblasts from different tissues are used (14, 25, 68, 234, 259, 262, 518, 633). However, in most studies no isolated attempt has been undertaken to compare this effect with any separate or simultanous role of mechanical loading upon the release or synthesis of such growth factors (536). In one study the importance of PDGF and mechanical strain was shown to be related to PDGF (51). Insulin-like growth factors (IGF-I and -II) are known to influence fibroblast in vitro (7, 8, 10, 51, 121, 576) and are likely to represent an important growth factor, but their exact role for collagen

synthesis of human tendon and muscle remains to be elucidated. Furthermore, it has been shown that mechanical loading induces increased secretion of TGF-β, PDGF and basic FGF (bFGF) as well as expression of growth factors from human tendon fibroblasts (598). Further mechanically loaded fibroblasts result in an increased gene expression for collagen and ECM components (53). The effect of specific growth factors or serum components in combination with mechanical loading on procollagen synthesis and procollagen propeptide gene regulation indicate a synergy between signaling pathways with regard to procollagen gene expression and processing, similar to what has been documented in cardiac fibroblasts (110). Interestingly, in a study where tendon grafts used for reconstructive surgery after ruptured anterior cruciate ligament were analyzed for content of growth factors, only bFGF was present in the control situation (359). Following reconstruction, increased levels of immunostaining of TGF-β and PDGF were noted over the following weeks and were back to initial levels after 12 wk (359).

Only a few of the most important growth factors for ECM in tendon and muscle will be dealt with in the following section. This should, however, not distract from the fact that others also play major roles and that even more factors are suggested but remain unexplored. As an example, the role of NO and prostaglandins seems clear with regard to mediating mechanical signaling to the process of bone formation in the skeleton (134), and it has been shown that this involves fluid-induced wall-shear stress (599) and that osteogenesis acts through COX-2-dependent pathways (708). This fits with findings of increased release of prostaglandins from human tendon fibroblasts that have been mechanically stimulated in vitro (24) and from human tendon tissue in vivo during mechanical loading (385), and suggests a role for prostaglandins in the adaptation of ECM in tendon tissue (543).

A. TGF-β and CTGF

TGF-β with its three mammalian isoforms are known to function as modulators of ECM proteins and to cause induction of both collagen gene activation and protein formation via Smad proteins (28, 123, 158, 289, 304, 408, 487, 513, 657, 707). A coupling between mechanical loading and TGF-β has been demonstrated in in vitro studies in a number of cell and tissue types. In vitro studies with human cell cultures showed stretch-induced TGF-β expression in tendon (598) and cardiac fibroblasts (558), smooth muscle cells (249, 488), and osteoblast-like cells (136, 336). In cardiac fibroblasts it was shown in vitro that mechanical loading and TGF-β had synergistic effects on procollagen formation, despite the fact that mechanical loading in the absence of any growth factors did not result in any stimulation of collagen formation (110). Furthermore, both in vivo and in vitro animal studies support a connection between mechanical strain and TGF-β expression (151, 396, 481, 656, 710), and in cardic fibroblast there is a positive correlation between the degree of cell loading and the expression of TGF-β (394). Studies have also shown that mechanically induced type I collagen synthesis can be ablated by inhibiting TGF-β activity (249, 408). In a human model using microdialysis around the Achilles tendon, it was found that both local and circulating levels of TGF-β increased in response to 1 h of running, indicating a role of this cytokine in the response to mechanical loading in vivo (269, 270). Furthermore, the time relation between TGF-β response and indicators of local collagen type I synthesis was supportive of a role of TGF-β in regulation of local collagen type I synthesis in tendon-related connective tissue subjected to mechanical loading. In view of the strong relationship between mechanical loading and TGF-β synthesis seen in various cell types (100, 101, 136, 151, 488, 598, 698), this could indicate a release of TGF-β from tissues that are mechanically activated during exercise, including bone, muscle, tendon, and possibly cardiac and vascular tissues. The increase in interstitial fluid concentrations of TGF-β after exercise could indicate a local release of TGF-β in tendon-related tissue, but could also be a result of increases in TGF-β content in the circulating bloodstream. Platelet activation is known to stimulate TGF-β release from the α-granule, and prolonged exercise is known to cause platelet activation (172). It cannot be excluded that increases in tissue TGF-β could be linked to a platelet activation caused by exercise-induced local tissue damage. This is supported by in vivo studies that have shown immediate increases in TGF-β levels in the rat in response to endurance exercise (100, 233). TGF-β increases in the circulation with exercise (614, 665) and with daily strength training over 21 days (272). Taken together, simultaneous rises in TGF-β both in circulation as well as locally in the tissue subjected to loading are compatible with a role of TGF-β in regulation of synthesis of ECM proteins such as collagen type I.

In addition to stimulating collagen synthesis with loading, TGF-β has also been demonstrated to increase the expression and synthesis of other ECM proteins, e.g., PGs (548). Both aggrecan and biglycan protein content as well as aggrecan, biglycan, and collagen type I mRNA expression were high after TGF-β administration. Interestingly, in this in vivo model neither contraction, TGF-β, nor a combination thereof stimulated decorin. From healing models, it is known that decorin can bind to TGF-β and neutralize its biological activity (90). It is thus likely that decorin requires other growth factors in combination with loading to be synthesized.

Although TGF-β has long been appreciated as a central growth factor in the formation and maintenance of

ECM, it is thought to be a key player in progressive fibrotic diseases such as scleroderma and keloid formation, and an independent role for CTGF was only recently found in these processes (83, 178, 393, 461, 577). Although it is known that TGF-β can stimulate CTGF synthesis, it has been shown that gene expression activation of CTGF is more dependent on mechanical loading than on changes in TGF-β levels (273, 275, 577), and CTGF is therefore suggested to play a major role in the accumulation of collagen type I synthesis and other matrix proteins in mechanically loaded fibroblasts (577). Therefore, CTGF also represents an effector substance for the profibrolytic activity of TGF-β in the maintenance and regeneration of connective tissue in fibrotic conditions (e.g., formation of a scar) (393).

TGF-β stimulates collagen formation and reduces degradation via stimulating the TIMPs together with a suppresion of MMPs, thus favoring an accumulation of ECM and especially of collagen (182, 493). In many ways TGF-β is considered a "two-edged sword" growth factor, in that an acute early rise in TGF-β is considered physiological after, e.g., mechanical tissue loading, whereas a prolonged rise in TGF-β is associated with uncontrolled formation of fibrotic tissue (393). In several models, it has been shown that the TGF-β role in fibroblast proliferation and collagen synthesis appears to be that low levels stimulate whereas high concentrations of TGF-β inhibit the collagen synthesis and fibroblast proliferation. It has been shown that inhibition of fibroblast proliferation at high concentrations of TGF-β may be mediated by autocrine stimulation of prostaglandin synthesis (PGE_2) (444). A blockade of inflammation in relation to contractile activity could therefore theoretically lead to unopposed collagen formation and favor fibrosis, a phenomenon that has been shown in lung fibroblasts (323). Alternatively, a blockade of prostaglandin formation would inhibit the immediate TGF-β- and/or CTGF-mediated stimulation of collagen and lead to suboptimal recovery after exercise-related tissue injury. In lung connective tissue, TGF-β stimulates collagen synthesis, and this can be inhibited via prostaglandin secretion (518). Interestingly, this effect of prostaglandin (PGE_2) is most likely due to a blockade of CTGF transcription, but shows that both CTGF-dependent and -independent mechanisms exist by which TGF-β and prostaglandin regulate collagen type I expression.

B. FGF

Of the several forms of FGFs that exist, the one with basic isoelectric point (bFGF or FGF 2) and to a lesser extent the acidic FGF (or FGF 1) are potent stimulators of fibroblast proliferation, collagen synthesis, and formation of granulation tissue (264). The effect of bFGF has mainly been studied in relation to tendon injury where healing processes have been shown to be positively related to administration of bFGF (120, 176). It has also been shown that expression of bFGF is present in normal intact tendons, but markedly upregulated in injured tendons (121). This upregulation was observed both in tenocytes within the tendon as well as in tendon sheath fibroblasts and infiltrating inflammatory cells. Mechanical loading has been shown to induce FGF release in vitro from skeletal muscle cells, and growth of these was inhibited by administration of a neutralizing antibody toward FGF activity (138). Somewhat in contrast, a study using cyclic mechanical stretching of human tendon fibroblast for 15 min could not demonstrate any synthesis of bFGF above that of the control fibroblasts (598). However, it must be acknowledged that the concentration in their model increased by 10-fold over time, but despite this, no statistical difference could be detected between control and mechanically stimulated fibroblasts (598). Interestingly, bFGF has been found to stimulate connexin43, which is known to be located in gap junctions between fibroblasts in tendons (169). This suggests a role of FGF for intercellular communication in relation to converting mechanical loading to biochemical activity leading to restructuring of the ECM. Part of the effect of FGF is mediated via PDGF, which is known to stimulate procollagen synthesis of, e.g., pulmonary artery fibroblasts (79), and it has been demonstrated that a combination of bFGF and PDGF results in further increased DNA synthesis in synovial fibroblasts (255). Finally, in chondrocytes, bFGF has been found to inhibit the effect of IGF-I and TGF-β on synthesis of type II collagen (165).

C. IL-1 and IL-6

The cytokine IL-6 is known to be released from fibroblasts (642) and has been suggested to be involved in collagen metabolism in bone tissue (246). IL-6 is produced by cells of the ostoblast and osteoclast lineages and has recently been shown to enhance both the expression and protein content of IGF-I in osteoblasts (213). This was not affected by IL-6 only, but required the presence of the soluble IL-6 receptor and was most likely dependent on prostaglandin to be effective (499). In tendon, the secretion of IL-6 has been found to be significantly induced by 15 min of cyclic biaxial stretching in vitro and remained elevated for at least 8 h (598). In humans experiments have been performed using the microdialysis technique, where IL-6 concentrations were obtained simultaneously in plasma, skeletal muscle, and peritendinous connective tissue in response to prolonged exercise (380). It was demonstrated that exercise-induced increases in peritendinous interstitial concentrations were 100-fold larger than in plasma and 7- to 8-fold larger than interstitial concentrations in skeletal muscle. This demonstrates that

connective tissue around the human Achilles tendon produces significant amounts of IL-6 in response to prolonged physical activity and contributes to exercise-induced increases in IL-6 found in plasma. This does not exclude major contributions of skeletal muscle to changes in plasma, since it has been demonstrated that skeletal muscle releases IL-6 with exercise (505, 607, 685). However, this release from an exercising extremity somewhat overestimates the amount of IL-6 that is produced in the skeletal muscle cells themselves (491). It is therefore likely that the discrepancy can be accounted for by the release of IL-6 from, e.g., intramuscular connective tissue, adipose tissue, or vasculature within the muscle. In accordance with this, cell types known to be located between muscle fibers have been shown to secrete IL-6 (184, 220, 337, 456). Furthermore, it has been shown that in adipose tissue only 10% of the total IL-6 release was origining from the adipose cells themselves, whereas 90% came from collagenase-sensitive ECM (220). Finally, IL-6 mRNA was elevated in fibroblasts and macrophages rapidly after an experimentally induced muscular injury (315).

IL-6 can stimulate fibroblasts to increase the production of collagen and glycosaminoglycans, hyaluronic acid, and chondroitin sulfates, but it only partly mediates the role of IL-1β on the fibroblast (177). In epitenon fibroblasts, microwounds have been shown to result in local release of TGF-β, IL-2, and IL-1 cytokines, and this was found to positively affect cell adhesion, proliferation, fibronectin deposition, and time to wound healing (686). In gingival connective tissue, the levels of IL-1β, IL-6, and IL-8 were higher in inflammed than noninflammed tissue and were inversely correlated to the amount of collagen in the tissue (696). IL-1 has furthermore been demonstrated to function as a potent inducer of MMP in fibroblasts, which induces degradation of the ECM (637). Furthermore, IL-1β has been shown to incude MMP activity and to diminish collagen synthesis in cardiac fibroblasts and thereby contribute to the remodeling of interstitial collagen in cardiac muscle (597). This is interesting, as mechanical loading results in IL-1β produced from fibroblast (590), and more recently that chronic loading of rabbit tendon resulted in rising levels of mRNA for IL-1β (30). It has been shown that mechanical loading of human tendon cells release ATP and that this stimulates expression of IL-1β (and MMPs) (634). Furthermore, the IL-1β response is triggering COX-2, IL-6, MMP-1, and MMP-3 responses, a fact that could initiate tissue degradation and remodeling in response to mechanical loading (635).

D. IGF and IGF-Binding Proteins

IGF-I enhances collagen synthesis in equine flexor tendon in a dose-dependent manner (468), and it has been demonstrated that mechanical stimulation of rat tendons by vibration results in increased IGF-I immunoreactivity of intratendinous fibroblasts (261). From studies on flexor tendons of rabbits it was shown that IGF-I administration was able to accelerate the ECM protein synthesis, with some variation between segments of tendons and between tendons from various regions of the body (8, 10). This is in accordance with a reduced functional deficit and an acelerated recovery after experimentally induced tendon injury when IGF-I was administered (360). Finally, IGF-II was shown to be as potent a stimulator as IGF-I for ECM turnover (7). In cardiac fibroblasts, the combined effect of mechanical loading and growth factors was studied. IGF-I was found to enhance expression of procollagen type I by threefold above that of mechanical stimulation alone (110). Furthermore, a role for IGF-I has repeatedly been documented for mediating the effect of mechanical loading on bone surface cells preceding bone formation (392, 524). In dwarf rats, the administration of growth hormone and the subsequent increase in circulating levels of IGF-I caused an increased expression of both collagen type I and III in intramuscular fibroblasts (684). Together, these findings indicate that IGF-I is directly involved in tendon and muscle ECM synthesis in relation to mechanical loading. The fact that MMPs can stimulate IGF-binding proteins (BPs) to cause a proteolysis of these substances provides a possibility for a regulation of the free IGF-I concentration in tissue and circulating blood which is coupled to the the activity in the collagen degradation pathways (211). IGF-BP-1 can be increased by IL-1β, IL-6, or tumor necrosis factor-α (565), which in turn can regulate the bioactivity of IGF-I. It has been shown that IGF-BP proteolysis occurs in response to prolonged physical training in humans (555).

VIII. COUPLING OF REGULATORY PATHWAYS FOR EXTRACELLULAR MATRIX TURNOVER AND SKELETAL MUSCLE CELLS TO MECHANICAL TISSUE LOADING

A. Development of Skeletal Muscle and Intramuscular ECM

During muscle development it is clear that processes within the cells of the ECM are required to ensure myoblast migration, proliferation, and differentiation (39, 106, 448). Fibronectin promotes myoblast adhesion and proliferation but inhibits differentiation (210) and participates together with decorin in collagen fibrillogenesis, thereby providing the morphogenesis of the intramuscular connective tissue. In contrast, laminin has been shown to promote myoblast adhesion, proliferation, and myotube formation (210, 352, 357a). An important mediator of the

matrix cell interaction is integrin. Interactions seen between myoblasts and ECM components such as collagen type I, fibronectin, and laminin included integrins with β_1-component, and blockade of this inhibits differentiation of the muscle cell (390, 391). In addition, the cytoplasmic domain of the β-unit of integrin is involved in the interaction between the muscle cell and its cytoskeletal proteins (556, 644, 645, 647). Interestingly, in vitro studies have shown that when myoblasts are grown on media with either fibril-forming type I collagen or type I collagen without fibril formation, the former resulted in more pseudopod formations and whenever these crossed collagen fibril focal adhesion spots were localized by staining of talin (390). These findings indicate that collagen fibrils help with the orientation and alignment of muscle fibers. The exact role of small leucine-rich PGs such as fibromodulin, lumican, biglycan, and decorin for development of the myocytes is not known, but it could be that these substances stimulate growth factors such as TGF-β, myostatin, IGF, or hepatocyte growth factor. Overall, the findings are indicative for a close coupling between myogenesis and development of the intramuscular ECM components (86, 145, 578).

B. ECM and Skeletal Muscle Interplay in Mature Tissue

The next question is whether adaptation to mechanical loading in mature muscle and connective tissue involves a similar interplay as in developing muscle (277, 278, 280). Given that intramuscular connective tissue together with cytoskeletal proteins represents a vital structure in the force transmission from contractile elements in the muscle fiber to the resultant movement of a joint, it would make sense if these processes were somewhat interconnected. It is known that intense physical activity like repeated eccentric contraction is associated with ultrastructural muscle damage like Z-line streaming, overextended sarcomeres, disorganization of myofilaments, and t-tubule damage of the skeletal muscle tissue in both animals and humans (103, 104, 218, 219a, 400, 402, 405, 406). Additionally, there is a release of creatine kinase from the muscle, as well as a fall in active tension and a rise in passive tension (26, 517). In line with this, the destruction of the cytoskeletal structures is seen early as well as immediately after intense electrically induced muscle contractions (406), which is subsequently followed by inflammation and regeneration processes (26, 517). Whereas animal studies in general demonstrate quite marked changes in myofibrillar and cytoskeletal protein damage (55, 406), human data often fail to show any major myofibrillar changes or cytoskeletal damage (149, 704). Instead, human data demonstrate inflammatory changes such as positive staining for cytokines and histological demonstration of inflammatory cell infiltration and tissue disruption in the intramuscular connective tissue of the endo- and perimysium, with a surprisingly intact picture of the cytoskeletal proteins (149, 704). As earlier mentioned, an altered loading pattern in animal musculature results in changes in intramuscular collagen formation and degradation (569, 570), and intense eccentric muscular exercise in rats will increase the enzymatic activity of the MMPs and its TIMPs responsible for the degradation of especially collagen type IV in skeletal muscle (346). Also in human skeletal muscle, it has been demonstrated that chronic electrical stimulation over longer periods increases the MMP activity, together with no major change of collagen type IV content in muscle (342). It has been found that MMP-2 and -9 expression is upregulated with experimentally injured skeletal muscle and in mice with lack of dystrophin, in the way that MMP-9 increased for a prolonged period related to inflammation, whereas MMP-2 was correlated with formation of new myofibers (328). Furthermore, it has been shown that the concentration of procollagen propeptides in endomysial and perimysial connective tissue increases, indicating increased collagen turnover (149). Attempts to study simultaneously the response of protein synthesis in both myofibers and fibroblasts to exercise have recently been performed (452). Findings in human thigh muscle indicate that the extent and time course of change in protein synthesis support the view that myofibers and fibroblasts receive input from common signaling pathways, which are responsible for the conversion of mechanical loading into anabolic stimuli (452).

One way to view any potential cross-talk between loading, intramuscular connective tissue, and skeletal muscle adaptation is to investigate myogenic stem cells such as satellite cell activation. It has been suggested that disruption of the cytoskeletal proteins and thus the cellular integrity of the myofiber triggers the release of appropriate growth factors from within the myofiber (284, 402, 416, 449), and in some animal models the time pattern of such changes is compatible with this hypothesis. Satellite cell activation (147, 157) normally is associated with myofiber damage and disruption of the sarcolemma (649), but in vitro studies (26) and human experiments, where variation in training activity was studied either in a cross-sectional or longitudinal design (310, 311), have documented activation of satellite cells in response to chronic exercise as evidenced by positive staining with neural cell adhesion molecule (N-CAM). Detection of fetal antigen 1 (FA1) has recently been shown to determine activition of myogenic stem cells (205, 302), and both the staining for FA1 (and N-CAM) located between the basal lamina and the sarcolemma and the detectable interstitial concentration of FA1 in heavily exercised muscle were found to increase in humans for at least 8 days after vigorous one-legged eccentric contraction (149). Despite

microdialysis and biopsy sampling, no changes in FA1 were seen in the contralateral resting control leg. Accompanying these responses were marked rises in circulating creatine kinase (up to 50,000 IU/ml), pronounced clinical symptoms, and absence of any light-microscopic changes in desmin, dystrophin, or fibronectin proteins. However, activation of satellite cells was accompanied by increased staining for PINP as well as for tenacin C (149). Whereas PINP indicates collagen type I synthesis in the ECM which is known to be coupled to degree of loading, tenascin C is controlled by tensile stress and is regulated at the transcriptional level via stretch-responsive *cis*-acting regions in the promotor gene (207) and reinforces the lateral adhesion of the myofiber to the surrounding endomysium. From these observations it may be hypothesized that during intense muscle loading in humans shear stresses associated with axial force production intramuscularly influences the inhomogeneous ECM network either by inducing a microtear or by signaling to existing fibroblasts to release growth factors that subsequently will initiate an activation of the quiescent satellite cells (446), or by initiating the direct release of growth factors from within the myofiber. In either of these situations, it may be hypothesized that turnover rates for intramuscular connective tissue are not necessarily identical for tendon and muscle, but that ECM turnover in muscle is coupled more to turnover of skeletal muscle such as myofibrillar proteins.

It also remains clear that satellite cell activation can be initiated in the absence of gross disruption to cytoskeletal proteins (522). This does not exclude a role of changes in cytoskeletal proteins for stimulation of muscle contractile protein synthesis. Interestingly, eccentric loading in rat musculature has been shown to result in loss of desmin immunostaining immediately after loading, but followed by a marked increase in desmin above basal levels (55). This could suggest that the intermediate filament system of the muscle may in fact adapt favorably to eccentric loading and become more resistant to subsequent loading, which together with adaptation in the connective tissue could explain the much less damaging effect on muscle to subsequent bout of eccentric exercise (517). However, curiously, the same author group showed that desmin knockout mice were less likely to get injury than control ones (564). Still, it remains clear that the adaptive responses of cytoskeletal proteins and ECM components most likely play in concert when subjected to mechanical loading. This can be shown during regeneration processes, where it is clear that expression and formation of dystrophin, integrin as well as other subsarcolemmal, and transmembrane proteins play an important role in the internal linking of the cytoskeleton to the plasma membrane before a linkage of the myofibers to the ECM occurs (315, 320, 643).

The mechanism behind a potential signaling between the ECM and myofibrillar components is unknown in relation to mechanical loading. It can be hypothesized that stores of ECM growth factors are released upon mechanical loading (649). In line with this, PGs (e.g., decorin) are demonstrated to bind growth factors and control flux of growth factors to and from the ECM (646, 647). Among the proposed growth factors are hepatocytic growth factor (HGF), IGF-I, IL-6, IL-15, insulin, leptin, FGF, leukemia inhibitory factor (LIF), and testosterone. The fact that inflammatory cells infiltrate regions subjected to heavy loading provides the possibility that release of cytokines plays a central role. However, HGF found in noninjured muscle (621) is also a strong candidate.

The reason for the dissociation in localization of damage and tissue reaction between models used in different species (e.g., voluntary activity in human muscle versus electrical induced muscle lengthening in animals) could be due to the degree of motor unit synchronization and thus muscle cell activity coordination during the eccentric activity. As indicated on Figure 9, voluntary eccentric exercise results in high force output, but somewhat low and unsynchronized activity pattern as judged from EMG recorded motor unit synchronization (189, 588). Interestingly, EMG activity increased and motor unit recruitment became more coordinated in trained individuals (1). This implies that individuals who are subjected to unaccustomed eccentric contraction display an uncordinated motor unit activation pattern, an thus place a high stress on intramuscular ECM between muscle fibers that are contracting and those that are relaxed. In contrast to this, electrical stimulation will tend to activate all available muscle fibers irrespective of type and motor unit origin (189). In the latter case, shear stress between fibers will be less than in the former situation, and if tensile strength is sufficiently high it may cause damage within the muscle cell itself rater than in the ECM. Although it remains to be proven, there is reason to believe that ECM plays a greater role in muscle adaptation to voluntary exercise in humans than previously thought, and thus contributes to mechanosensing and to ensure adaptation of connective tissue and skeletal muscle that is coordinated to have the greatest possible functional ability.

IX. CLINICAL PERSPECTIVES: PHYSIOLOGICAL UNDERSTANDING OF TISSUE OVERUSE

Overloading and prolonged overuse of musculotendinous structures leads to tissue maladaptation and damage and to clinical symptoms. Within tendon structures the development of chronic pain associated with subsequent loading in regions of, e.g., the Achilles, patellar, and supraspinatus tendons, remains a major etiological, pathophysiological, and treatment challenge (66, 80, 92,

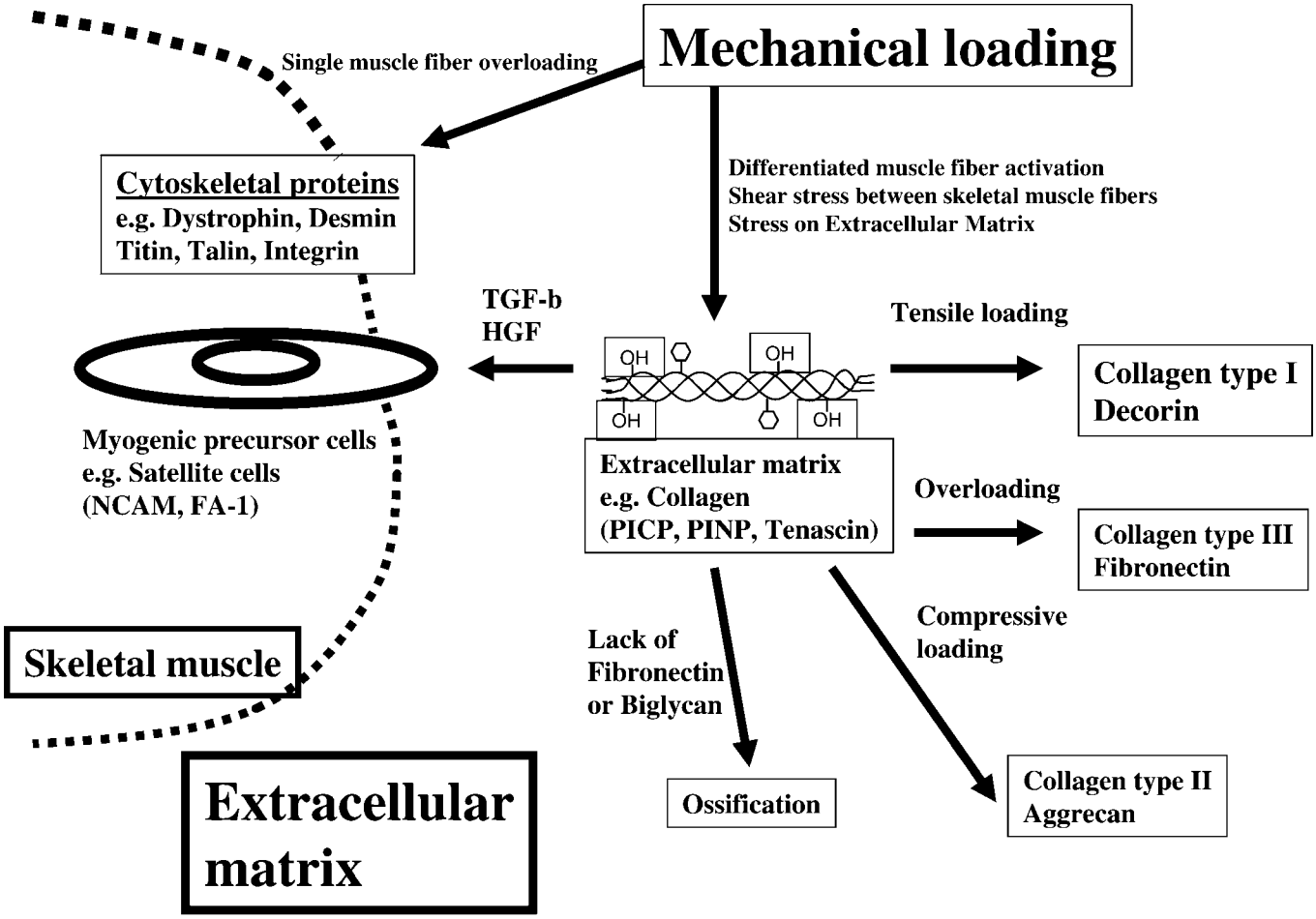

FIG. 9. Intense loading of skeletal muscle and adaptive responses in extracellular matrix. Hypothetical interaction between extracellular matrix, cytoskeletal proteins, and skeletal muscle fibers in response to eccentric loading of the contracting musculature, whether or not they are trained or untrained.

122, 141, 216, 232, 235, 236, 240, 308, 309, 340, 467, 514, 527, 546, 609, 688). In muscle, the delayed-onset muscle soreness, after eccentric loading, as well as muscle-associated chronic pain associated with long-term overuse has been the focus for intense investigations but still demands better pathophysiological explanations (281, 517).

A. Tendon Overuse

Repetitive loading of human tendon tissue often leads to overuse injury that result in severe clinical symptomatology including pain, regional swelling, and soreness elicited either in relation to occupational procedures or to sporting activity in elite athletes and recreational exercisers (305, 332, 351, 362–365, 472). Although the term *overuse* refers to the fact that repetitive loading has elicited the symptoms and suggests that the physical load exerted on the tissue is important for the etiology of this clinical problem (585), only limited knowledge is available regarding the pathophysiological reactions in the ECM in such conditions. This explains part of the difficulty encompassing all tendon-related injuries under one entity (299, 316).

It becomes however clear from the present literature that some of the overuse injuries are associated with changes within the tendon substance itself due to either a primary alteration in the biochemical composition (307) to a preceding mechanical elicited partial rupture (4, 34, 364, 366), or to gradually developing degenerative changes (5, 299). Furthermore, some injuries occur along the tendon, often in relation to the tendon sheet or in the peritendinous region containing loose connective tissue and vessels, and these injuries are often due to the travel of tendon over bony or cartilage structure (62). Finally, other tendon-related overuse injuries are related to the insertion of the tendon upon bony structure (61).

With regard to the pathophysiology of injury development, three major points deserve further discussion. The first is the presence and potential importance of inflammatory reactions with overuse injuries, the second

is regulation of blood flow and tissue metabolism in overused connective tissue, and the third is how pain is originated and mediated in situations with overused tendons or muscle.

B. Development of Tendon Injury: Predisposing Factors

Predisposing factors influence the frequency of tendon overload symptoms and ruptures. As examples, both genetic (59, 596), blood type (306, 358), accompanying presence of chronic disease (316), and drug use (285, 542) have been demonstrated to be significant predisposing factors. The genetic role remains to be elucidated, but heritage and twin studies have shown a definitive role (59, 596). With regard to influence of drugs, especially the use of fluoroquinolones has been found, at least in high doses, to cause an increased activation of MMP activity, which provides a basis for an accelerated degradation rate of tissue collagen (679). Factors such as high body weight, leg length inequality, foot abnormalities (such as pes cavus or planus), and low joint, tendon, or muscle flexibility are identified as moderately important factors for development of tendon injury, but the evidence is mainly based on associations rather than any demonstration of a cause-and-effect relationship (366).

A potential damaging effect on the tendon tissue has been proposed to be elicited by changes in tissue temperature in relation to muscular activity. In equine flexor tendons, it has been shown that gallop exercise elevated the intratendinous temperature by 5–6°C, which is sufficient to theoretically account for some detrimental effect to fibroblast activity. Fibroblasts cultured from the core of the equine superficial digital flexor tendon were subjected to temperatures up to 45°C, and cell survival fraction was determined and compared with control dermal fibroblasts and kidney fibroblasts (72, 75). It was shown that no major tendon cell death occurred by subjecting cells for shorter periods to the physiological temperature increases observed in core tendon tissue found during exercise (75). When the temperature was increased to supraphysiological 46–48°C, a marked cell death was observed (75). These findings cannot directly be transferred to humans in whom longer periods of exposure to tendon loading are often seen. Furthermore, the in vitro experimental setup in the equine fibroblast cultures was done with cells under suspension, which is known to increase their resistance to heating (600). Dramatic temperature increases have previously been shown to alter the viscoelastic properties of tendons (671) and passive structures in skeletal muscle (560) to, at least theoretically, allow for a wider range of motion in the joints and increased extensibility of the tendons. Interestingly, the physiological changes in temperature that occur intramuscularly during exercise in humans do not result in any changes in the muscle-tendon viscoelastic properties when determined in vivo (423). Therefore, at this point, it is unlikely that temperature changes observed during exercise will result in any altered extensibility in tendon or muscle, and it is doubtful whether temperature changes are of any major importance for tendon pathology in relation to exercise.

C. Tendon Rupture: Preceding Overuse

The above-described predisposing factors, to a very minor degree, offer mechanistic explanation for the development of tendon injury. However, studies on overloaded tissue have provided some suggestion as to the reason for tissue overload. In individuals who are subjected to an Achilles tendon rupture it has been found that there is a degenerative region of the tendon that preceded the loading that elicited rupture (5, 316, 622). With a chronic overload injury to a tendon, recent data have indicated an upregulation in both type I and III collagen expression and content with a preference for the latter, and thus a decrease of the type I to type III ratio (294). This fits with observations on ruptured tendon, where the amount of type III was elevated and the ratio between type I and III was lowered at the ruptured site compared with intact cadaver tendons in both humans and equines (72, 139, 146, 307). It has furthermore been shown that cultured fibroblasts from ruptured Achilles tendon produce more type III collagen than fibroblasts from normal tendon (420). Even stronger proof for a local upregulation of type III collagen was found in a study where tendon tissue at the ruptured site contained more type III collagen compared with both cadavers and to more distal sites within the ruptured tendon itself (191). In addition to an upregulation of collagen type III in healing tendon, the amount of fibronectin also rose (677). A determination of procollagen propeptides and collagen fragments revealed that apart from a decrease in the amount of PINP, and thus a reduced collagen type I synthesis, at the ruptured site, no alterations for indicators of collagen type II synthesis or degradation were found (191). This indicates that the rise in type III collagen is occurring slowly and that the process responsible for collagen type III accumulation at the ruptured site occurs far before the actual rupturing trauma. Type III collagen fibrils are thinner than type I fibrils (563), and interestingly, the finding of increased amount of type III collagen in ruptured areas of tendon fits with the observations of Magnusson et al. (431) who found that there was a site-specific relative loss of larger fibrils and thus a relative increase in smaller diameter fibrils both at the deep and the superficial part at the tendon rupture site.

Also in accordance with the biochemical examina-

tions, the fibril size was normal in the more proximal and healthy-looking parts of the ruptured tendon (431). This implies first of all that changes in type III collagen content and in fibril diameter are site specific within the tendon, and furthermore, it suggests that there is biochemical and structural support for a regional decrease in tendon resistance to loading. In horses, the occurrence of small-diameter fibrils has been observed in the core of tendons subjected to long-term intense exercise, which has been suggested to be a result of disassembly of fibrils or a splitting of existing larger fibrils (601). From the available human data it is a result of a gradually altered content of the fibrils from type I to type III fibrils. It has been described that healing tendons have fibril populations of smaller diameter than in healthy tendons (441), and it is likely that small mechanical damages result in local healing of tendon tissue with increased amount of type III collagen, which with continuous training can be exchanged to type I collagen-dominated fibrils. It is interesting that in patients with prolonged pain and signs of unilateral tendinopathy, training increased their collagen type I synthesis compared with the contralateral healthy tendon and moreover improved their overall symptoms by completing a prolonged training protocol with loading of the tendon (M. Kjær, C. Clement, N. Risum, and H. Langberg, unpublished observations). From this it can be suggested that training a reasonable amount increases the collagen type I to III ratio in tendon with chronic overuse and will thus counteract the vulnerability toward acute tendon ruptures. Such a view would also be compatible with the demonstration of a gradual change in collagen expression of individual fibrils, as hybrids of these have been demonstrated (203).

Another important finding in patients with chronic Achilles tendon disorder is the demonstration of lower levels of MMP-3 mRNA, which indicates that ECM degradation and tissue remodeling is impaired in this situation (294). This finding is in agreement with the demonstration of the side effect of tendon pain and problems, when using MMP inhibitor as experimental drugs in cancer treatment trials (171). Interestingly, decreased expression of MMP in chronic tendon problems is in contrast to the documented rise in MMP-2 and TIMP-1 and -2 expression and activation in rabbit supraspinatus tendons undergoing a healing process after surgical rupture (131).

D. Experimental Tendon-Overuse Models

Several animal exercise models have tried to create overload of tendons. Such models would allow for evaluation at early stages of tissue overloading. Dogs and rabbits have been used to stimulate degenerative and inflammatory changes in tendon with the use of different types of electrical muscle stimulation and ergometer devices (31, 45, 46, 92). With these models it has been possible to demonstrate thickening and infiltration of inflammatory cells in the tendon, increased number of capillaries both within and around the tendon, and fibrosis in the paratenon after intense eccentric loading in young, developing rabbits (45, 46). Somewhat in contrast, a more moderate, but also more physiological relevant, stimulation regimen in adult rabbits over several weeks did not result in any inflammatory or degenerative changes within or around the loaded Achilles tendon (31). In the rat, experimental designs to study tendon rupture and muscle injury have been performed (33, 56), but it has been somewhat more problematic to create a model that mimics the chronic overuse disorder that occurs in humans. In one attempt, Messner et al. (450) subjected rats to repetitive electrical-induced eccentric exercise in a kicking machine and found that only around one-half of the animals achieved histological changes in and around the tendon. This occurred despite using a protocol that previously was used to induce muscle damage in rats (455). Furthermore, the changes were discrete and more of a proliferative and reparative nature than they were directly degenerative (450). Hypervascularization and increase of neural elements were mainly observed in epi- and peritendinous tissue (450). Taken together, small animal models only to a limited degree provides inflammatory or degenerative changes. Furthermore, in the cases where overuse histological changes are demonstrated, it occurred after extremely intense artificial and supraphysiological stimulation. When exercised voluntarily it seems far more difficult to create an animal tendon (or intramuscular connective tissue) overuse model. In the horse, the occurrence of tendon-overuse injuries seem more similar to those of humans, and overuse signs in the flexor tendons resembles, to some extent, that of the Achilles tendon disorder in humans (72). The fact is that only horses and greyhound dogs (502), which are undergoing forced regimens of exercise, display overuse injuries similar to those in humans, whereas other animals only display tendon overuse when extreme and unphysiological regimens are imposed. Therefore, there is a puzzling problem of why human tendons are so prone to overuse, and why no signaling mechanism is provided for the human to avoid training into overuse problems.

E. Tendon Overuse and Inflammation

Lack of identification of inflammatory cells in tissue samples from tendons with overuse symptoms (307) has contributed to a skeptical attitude towards the concept of overuse-related inflammation and caused the general injury terminology to be changed from -itis to -osis and -pathy. This is supported by finding of perioperative intratendinous degeneration including increased amounts of noncollagenous matrix, focal variation in cellular content,

and vascularization as well as alterations in the structure and arrangement of collagen fibrils in tendons from individuals with long-term clinical tendon problems (4–6, 34, 299, 306, 462–464). Hyaline, mucoid, and fibrinoid degeneration as well as calcification and formation of fibrocartilago have been observed with electron microscopy (61, 62, 307). However, it has been difficult to completely exclude an inflammatory component in tendon overuse injury, and clinical observations of swelling, pain, and warming along the diseased tendon in relation to acute loading episodes of an overused tendon (25) as well as the proven positive effect of anti-inflammatory medication aiming at an inhibition of the prostaglandin synthesis by blocking cyclooxygenase or by using corticosteroids (216) support this doubt.

The possibilities for monitoring the degree of inflammation within the relevant tissue have so far been limited. More recently, this question has been addressed by determination of tissue concentrations of prostaglandin intratendinously in both the human Achilles and patellar tendon as well as in the lateral elbow with microdialysis, in which no elevated level of PGE has been found in any of the regions during rest (18–20, 23). This is in contrast to determinations of homogenized tendon tissue as well as in fibroblast cultures grown from human tendons in which a detectable concentration level and expression of prostaglandin were demonstrated, and where levels were higher in overused tendons compared with healthy counterparts (223). This was accompanied by an overexpression of PDGF receptor (PDGFR-β) (551) and an elevated expression and production of active TGF-β1 (223). This suggests an altered expression and synthesis of growth factors and inflammatory mediators in fibroblasts from overused tendons. No investigation of inflammatory markers within tendons has been conducted during exercise, but data on peritendinous measurements indicate that in the injured tendon region during exercise prostaglandin levels were significantly higher around the Achilles tendon of an individual that was overuse injured compared with the contralateral healthy tendon (376). This could imply that the injured tendon represents a vulnerable structure that due to adhesions in the peritendon region (9) more easily displays inflammatory reactions upon loading. Whether such a rise in inflammation plays an important stimulating or detrimental effect in the regeneration or on nociceptive processes has not been widely addressed (466, 709).

It has been shown that nonsteroidal anti-inflammatory drugs (NSAIDs) in the form of aspirin, phenylbutazone, or indomethacin increased the strength of various uninjured collagen structures in rats, which is potentially related to an increased collagen cross-linking (659). Furthermore, the cyclooxygenase unspecific NSAID piroxicam increased the strength of healing rat ligaments, but did not influence the ultimate strength once the the healing was complete, nor did it affect uninjured ligaments (154). Somewhat in contrast, recent studies on cycloxygenase specific (COX-2) inhibitors (celecoxib) indicate that a small reduction in ligament strength occurred during early healing (186). In that study no long-term results were provided, and COX-2 inhibition did not affect the intact ligaments of the animals (186). Whether blockade of arachidonic pathways to limit inflammation has any effect on regeneration or healing processes in overloaded tendons in vivo is currently unknown. It is interesting that a recent study documented tissue damage and thereby detrimental effect of prostaglandin administration to animal tendon tissue (611).

F. Tendon Overuse, Blood Flow, and Tissue Oxygenation

The fact that the most frequent location of painful Achilles tendon condition coincides with the area with the most anatomically limited vasculature has led to the suggestion that impaired supply of vasculature and thus insufficient blood flow under loading conditions could lead to tendon degeneration (188, 266). It has been found that degenerated shoulder tendons in humans have a reduced capillary density (67). Interestingly, physical training in hypobaric hypoxic environment resulted in selectively increased collagen type III and IV expression in rat heart ventricular muscle, whereas type I collagen was unchanged (507). It is not known whether the same pattern is present in tendon, but it would fit with hypoxia favoring degenerative changes and a predominance of type III collagen, and thus a reduction in ultimate tensile tendon strength. Furthermore, ischemia in the brain has been shown to result in release of MMP-9 to the extracellular tissue (511), and that it influences the magnitude of postischemia infarction. This is so, as pharmacological blockade of MMP-9 is found to decrease infarct volume and to prevent the oxidative stress-associated blood-brain barrier disruption (230, 552). A similar effect is seen in MMP-9 knock-out mice (38). In relation to experimental spinal cord lesions it has furthermore been suggested that the increased MMP-2 and -9 response is beneficial in tissue remodeling and that it can be used therapeutically (175). Likewise, in hindlimb muscle vasculature, MMP activation is important for an initiation of ischemia-induced angiogenesis through VEGF (594). During pharmacologically induced vasodilation in rat skeletal muscle, MMP-9 is increased, and the presence of MMP-2 and MT1-MMP are important for initiation of the training induced angiogenesis in skeletal muscle (251, 252). Potentially this effect is mediated through collagen-derived proteolytic fragments (438). It can therefore be hypothesized that ischemia in tendon or muscle can initiate processes of collagen degradation.

A higher lactate concentration in the interstitial fluid of human tendon was demonstrated using microdialysis in patients with painful chronic tendinosis compared with healthy pain-free tendons (17). This could indicate a higher anaerobic metabolism in overused tendons, which is a phenomenon that could be related to a more dense ECM area of degeneration in the core of the tendon, that would lead to a compensatory neovascularization in other regions, similar to that found in the ventral part of the Achilles tendon (489a). Speaking against hypoxia of the tendon as a contributing factor for the development of overuse injury is the fact that no demonstrable ischemia could be found intratendinously even with intense loading of healthy tendon tissue (93, 94). It should however be kept in mind that the human tendon can be very heterogeneous along its length with regard to vascularization and morphology. It has been shown in the Achilles tendon that the distal and the proximal part has the highest vascular density, and the lowest was found in the middle part of the tendon (705). Likewise, the CSA of the human Achilles tendon was thickest in the distal part and thinnest in the proximal part (430). The combination of variable CSA and vascularity along the tendon length can indicate that adaptability towards training of the tendon is also region specific (430). Interestingly, the difference in tendon CSA between athletes and sedentary individuals was most pronounced in the distal part of the tendon, which supports the idea of a region-specific hypertrophy in response to habitual running, and furthermore can provide the basis for identifying tendon regions that are vulnerable towards injury development (430).

G. Tendon Injury and Pain

Overused tendons are shown to possess increased levels of glutamate when investigated in the resting state using microdialysis in Achilles and patellar tendons (18, 23). Furthermore, immunohistochemical analysis of tendon biopsies revealed the presence of ionotrophic glutamate receptor *N*-methyl-D-aspartate (NMDA) in relation to nerves (18, 19). The exact role of these responses is not clear, but the excitatory neurotransmittor glutamate is known to be a potent pain modulator in human central nervous system, and glutamate is thus a candidate for causing pain with overuse in tendons. Furthermore, its nociceptive role is known to be additive with that of substance P (8), a substance that has been demonstrated in the peritendinous region of both rats (450) and rabbits (8). In animals, experimental damage to the Achilles tendon has been shown to introduce vascular and nervous tissue into the tendon itself, and thus increase the content of substance P (8). It should be emphasized that in intact tendons without partial rupture, no sign of substance P has been demonstrated within the tendon.

In addition to these findings, mechanical loading is also found to elicit increased interstitial concentrations of the nociceptive agent bradykinin in the peritendinous tissue of human tendon (375), which further adds to the hypothesis that alterations in the levels of several nociceptive agents act in concert to elicit overuse injury-related pain symptoms originated primarily peritendinously. In association with the release of substance P, CGRP has also been demonstrated in animals (8, 450). Levels of this substance have been found to be related to the vasculature and to be relatively higher in tendon compared with both ligament and the joint capsule (8). Furthermore, increased tissue levels of CGRP were associated with mechanical tissue damage due to overloading in animal tendon (8). Whether this is the case in humans is not known, but it could contribute to explain the tendon hyperemia and hyperperfusion that is found in human overloaded tendons (6). Together with CGRP, also prostaglandin and prostacyclins could also contribute to hypervascularization in overused tendons. Interestingly, the exercise-induced rise in tissue prostaglandin can be blocked by cyclooxygenase blocking agents, and it has been shown that the peritendinous blood flow increase is inhibited by ~40% when prostaglandin synthesis was blocked (96).

H. Perspectives for Treatment

Treatment of tendon-overuse injuries and painful muscle conditions are still widely debated due to lack of full understanding of the underlying processes. With regard to chronic tendon problems (tendinopathy), several conservative treatments such as immobilization, physical therapy, stretching, and pharmacological treatment with NSAIDs as well as surgical procedures have by no means produced impressive results (307, 420). Somewhat surprising, the use of heavy resistance exercise has been shown to improve symptoms in these patients. It was shown that resistance exercise had a positive effect on symptoms in patients with prolonged tendon pain and that eccentric training was superior to concentric exercise (421, 482) and that significant results were obtained in patiens with long-term Achilles tendinopathy awaiting surgical intervention undergoing a 12-wk training program (22). Furthermore, long-term results support a lasting effect of this intervention type (592). The mechanism behind the effect of adding load to a chronic overloaded and painful condition in unclear, and resting intratendinous levels of glutamate determined by microdialysis in human Achilles tendinosis are not changed in response to such a 12-wk training program (21). It might be that the loading of a certain magnitude together with stretching the relevant structure induces increased reorganization of the collagen structures, which resulted in new synthesis of espe-

cially type I collagen. In line with this, recent experiments in elite athletes who had unilateral Achilles tendon pain and signs of tendinopathy, the performance of a 12-wk eccentric training program with daily exercise added to their normal activity pattern, resulted in an increase in collagen type I synthesis in the injured tendon, whereas no change was observed in the contralateral uninjured tendon that was not trained (H. Ellingsgaard, J. Jensen, T. Madsen, H. Langberg, and M. Kjær, unpublished observations).

X. FUTURE PERSPECTIVES

Inhibition of MMP activity has been used in clinical trials with the aim to counteract cancer growth (84, 105, 313a). MMP activation potentially involved in the apoptosis processes by being a function of p53 gene expression increase in premature rupture of fetal membranes (209). However, despite the intuitive potential effects that such drugs should have on counteracting degradation of basement mebranes and limiting tumor invasion and metastasis, neither the use of unspecific (192) or more specific MMP inhibitors (60, 65) has so far been proven very successful. One of the reasons for this is that the role of MMP in cancer is far more complex than hitherto thought and involves angiogenesis in healthy tissue, its production in fibroblasts and inflammatory cells in tissue surrounding the tumor, as well as its autocrine action controlling cell growth, death, and migration (148, 713). MMP might play a pivotal role in regenerative processes. This is supported by the finding of an enhanced healing and reduced number of anastomose leakages after colon surgery when MMP inhibitors are given to patients, whereas MMP blockade delayed healing of cutaneous wounds (2, 3). It therefore seems challenging to enlighten the role of MMP (and TIMPs) in relation to mechanical loading and differentiate its role in physiological perturbations of the steady state of the fibroblast and the ECM, from its role in pathological processes like healing after tendon or muscle injury. It can be suggested that collagen-degrading enzymes like MMP and their activity is one of the key points in the tissue adaptability to loading and training. This is at least compatible with the finding that MMP inhibitors used in clinical trials reveal musculoskeletal symptoms as their most prominent side effect (148, 274, 276). Tendinitis, myalgia, and arthralgia are especially seen often, despite change in the activity level of the studied patients. It can therefore be hypothesized that high MMP activity is a prerequisite for rapid adaptation to chronic loading of tendon and muscle and that stimuli that surpass this capacity in any amount will result in suboptimal tissue adaptation and thus result in chronic symptoms. The tight coupling of MMP activity and collagen deposition is supported by observations in cardiac muscle, where MMP and their regulators are crucial in remodeling after myocardial infarction (150, 155) and for development of myocardial fibrosis in heart failure, and that this may be modified by MMP modulating drugs (399, 606). Furthermore, IL-1β and TNF-α decrease collagen synthesis and activate MMPs 2, 9, and 13 (597).

The dimensions and architecture of a tendon influence adaptive collagen responses to mechanical loading. It is known that the tendon microstructure along the length of the tendon reflects differences in mechanical loading either due to external synovial tension (9) or direct compression against bony structures (61, 548), but its unknown to what extent intratendinous gliding (e.g., due to endotenon disruption) contributes to pathological responses to loading during differential muscle activity. Such phenomenon can also play a role under circumstances where the tendon is loaded differentially by activity from different muscle groups (such as the triceps surae, when gastrocnemius is fatigued earlier than soleus) under fatigue. Within muscle it can be hypothesized that in situations with unaccustomed exercise patterns such as eccentric loading, unequal motor unit activation results in shear stress of the intramuscular connective tissue and "spares" the cytoskeletal structures and the myofiber. In contrast, under circumstances where all muscle fibers are contracted in a coordinated fashion, such as under electrical stimulation with forced lengthening or eccentric activity in individuals who have high experience in eccentric loading (weight lifters, etc.), the damage on the muscle occurs in cytoskeletal structures and thus results in less pain (Fig. 9). In addition to this, it is unknown what relative role the different collagen types play in tissue adaptation to chronic loading (133). Preliminary investigations have been performed in humans with collagen defects (430) or with inflammatory muscle diseases (353), but a more systematic investigation of the role of exercise for tissue adaptive responses in diseases that interfere with the ECM is not known. In that respect, the ability of relatively noninvasive imaging techniques will allow for better and more mechanistic insightful investigations in the future (608, 712).

The intramuscular amount of ECM can most likely increase with physical training (350, 507), an interesting phenomenon since the beneficial importance of passive structures in contracting muscle with regard for force production has recently been stressed (273, 680, 681). The balance between the presence of contractile elements and extracellular force transmitting energy-enhancing matrix is yet to be established, but points so far at a more intimate interplay for optimal function of skeletal muscle. It is interesting to note that during remodeling of muscle tissue, ECM substances can to some extent substitute for each other, e.g., agrin can substitute for dystrophin (457). This opens a possibility not only for understanding redundant phenomenon in ECM adaptation to mechanical loading,

but opens wide perspectives with regard to interference into diseases that involve ECM or cytoskeletal errors.

The influence of chronic mechanical stretching of ECM in tendon and muscle deserves further observations. With the use of new visualization modalities like in situ X-ray defraction, it has been possible to demonstrate that the overall strain of a tendon surpasses that of the individual fibrils, and it is proposed that major movement between fibrils takes place (523). This suggests that fibrils and interfibrillar matrix form a coupled viscoelastic system. Furthermore, with the use of confocal laser microscopy, it has recently been possible to demonstrate the mechanical deformation of tendon fibroblast during loading, a phenomenon that may very well explain magnitude of responses in the mechanical signal transduction pathway of ECM in tendon and muscle (35). Finally, the mechanism behind unilateral increased flexibility after chronic stretching exercises, despite unaltered passive viscoelastic properties of the muscle tendon unit (434), calls upon investigating peripheral feedback mechanism from relevant receptors in muscle and tendon, and its potential interplay with central pathways involved in stretch perception. Until these mechanisms are described in detail, we only know that stretching will improve flexibility, but we have no support to use flexibility training as a preventive measure for acute or chronic sports injury development due to altered passive mechanical properties of the tissue.

The fact that data tend to support an adaptive mechanism in ECM to loading that includes both structural and functional adaptations with a potential of incresasing the resistance toward tissue fatigue and rupture raises the ultimate question of how this adaptation takes place (575). Is the ECM, and collagen especially, subjected to repeated microtrauma resulting in tissue damage and subsequent repair processes (324, 470, 593), or is it driven by biochemical and physiological processes that are governed by an exercise-induced increase in protein degradation followed by a stimulation of protein synthesis of relevant substances (540). Neither of the two mechanisms exclude each other, but it is hypothesized that whereas the former mainly takes place when tendon and muscle are subjected to high sudden loads at the loading limit of the structure and causing tertiary creep, the latter is the most common event occurring in relation to repeated loading where the recovery time is too short to allow for a physiological adaptation. This also suggests that overuse injury of connective tissue is a mismatch between synthesizing and degrading biochemical pathways. Clearly, in addition to investigating loading-associated tissue adaptations, findings would have to be related to the possibility that certain collagen gene expressions are more likely to adapt to altered loading than others (144).

We are only at the beginning of understanding the factors eliciting synthesis of collagen and other structural proteins of the ECM in tendon and skeletal muscle in response to mechanical loading. In vitro experiments are gradually being supported by in vivo human experiments [e.g., by use of microdialysis (685), stable isotopes, and various imaging techniques] that allow for a determination of the time pattern of responses to exercise and of the correlation between growth factors and collagen synthesis (44). However, such studies in no way prove that a causal relationship exists between phenomenon, and future studies using administration of potential regulatory factors either administered systemically or locally into the tissue in physiological concentrations are needed to understand the acute tissue growth regulation of ECM of tendon and muscle. This needs to be performed both in the resting state as well as during exercise. Furthermore, to differentiate the adaptation of the tissue to prolonged loading, the development of overuse models in humans will be crucial. Only in this way will it be possible to define and study the borderline between the optimal physiological adaptation with strengthening of tendon as well as ECM in skeletal muscle, and its maladaptation that ultimately leads to tissue changes and symptoms that are associated with an overuse injury. The in vivo models, in combination with modern molecular techniques, can help us not only achieve mechanistic insight, but will also in a physiological sense provide us with tools to integrate the understanding of these processes and most importantly to place the different molecular processes into a hierarchy of tissue responses to mechanical loading. This will be a prerequisite to improve treatment regimens and evaluate pharmacologial intervention in tissue overloading (40).

XI. SUMMARY

The ECM, and especially the connective tissue with its collagen, links tissues of the body together and plays an important role in the force transmission and tissue structure maintenance especially in tendons, ligaments, bone, and muscle. The ECM turnover is influenced by physical activity, and both collagen synthesis as well as activity of degrading metalloprotease enzymes increase with mechanical loading. Both transcription and posttranslational modifications, as well as local and systemic release of growth factors, are enhanced following exercise. For tendons, metabolic activity, circulatory responses, and collagen turnover are demonstrated to be more pronounced in humans that hitherto thought. Conversely, inactivity markedly decreases collagen turnover in both tendon and muscle. Chronic loading in the form of physical training leads both to increased collagen turnover as well as, dependent on the type of collagen in question, some degree of net collagen synthesis. These changes will modify the mechanical properties and the viscoelastic characteristics of the tissue, decrease its

stress, and likely make it more load resistant. Cross-linking in connective tissue involves an intimate, enzymatic interplay between collagen synthesis and ECM proteoglycan components during growth and maturation and influences the collagen-derived functional properties of the tissue. With aging, glycation contributes to additional cross-linking, which modifies tissue stiffness. Physiological signaling pathways from mechanical loading to changes in ECM most likely involve feedback signaling that results in rapid alterations in the mechanical properties of the ECM. In developing skeletal muscle, an important interplay between muscle cells and the ECM is present, and some evidence from adult human muscle suggests common signaling pathways to stimulate contractile and ECM components. Unaccustomed overloading responses suggest an important role of ECM in the adaptation of myofibrillar structures in adult muscle. Development of overuse injury in tendons involves morphological and biochemical changes including altered collagen typing and fibril size, hypervascularization zones, accumulation of nociceptive substances, and impaired collagen degradation activity. Counteracting these phenomenon requires adjusted loading rather than absence of loading in the form of immobilization. Full understanding of these physiological processes will provide the physiological basis for understanding of tissue overloading and injury seen in both tendons and muscle with repetitive work and leisure time physical activity.

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