Tendon and ligament mechanical loading in the pathogenesis of inflammatory arthritis

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Abstract

Mechanical loading is an important factor in musculoskeletal health and disease. Tendons and ligaments require physiological levels of mechanical loading to develop and maintain their tissue architecture, a process that is achieved at the cellular level through mechanotransduction-mediated fine tuning of the extracellular matrix by tendon and ligament stromal cells. Pathological levels of force represent a biological (mechanical) stress that elicits an immune system-mediated tissue repair pathway in tendons and ligaments. The biomechanics and mechanobiology of tendons and ligaments form the basis for understanding how such tissues sense and respond to mechanical force, and several mechanical stress-related tendon and ligament disorders overlap anatomically with joints affected by chronic inflammatory arthritis. The role of mechanical stress in 'overuse' injuries, such as tendinopathy, has long been known, but mechanical stress is now also emerging as a possible trigger for some forms of chronic inflammatory arthritis, including spondyloarthritis and rheumatoid arthritis. Thus, seemingly diverse diseases of the musculoskeletal system might

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have similar mechanisms of immunopathogenesis owing to conserved responses to mechanical stress.

Introduction

The tissues that connect muscle to bone (tendons) and bone to bone (ligaments) have evolved specialized biochemical properties that enable the transmission of mechanical force **[G]** between different parts of the musculoskeletal system. Tendons and ligaments have a fibrous composition and little cellular heterogeneity; characteristics that are relatively consistent throughout the body. By contrast, biochemical and cellular differences occur longitudinally along individual tendons and ligaments, producing microenvironments at the myotendinous junctions (MTJs; the points at which muscle and tendon join) and at the entheses (the points at which tendons and ligaments connect to bone; Figure 1a) that differ from that at the midportion. Biomechanically, tissue failure that results in injury is prone to occur at the point at which tissues of differing physical properties meet[1]. Such a structural mismatch in the presence of high levels of strain **[G]** is particularly evident at the enthesis, where a fifty-fold difference in tissue resistance to tensile load **[G]** occurs between the elastic tendon or ligament and the stiff bone they attach to[2]. Once tissue failure takes place in adult tendons and ligaments, the pre-injury tissue architecture is never regained, making these structures prone to re-injury[3,4]. Indeed, in the USA, tendon and ligament injuries result in a high number of work place injuries[5] and potentially account for the majority of musculoskeletal disorders globally through sprains and strains of the lower back[6,7].

From the perspective of the rheumatologist, tendons and ligaments are usually thought to belong to the remit of other medical specialists (such as orthopaedic surgeons), and are often ignored when considering the pathophysiology of joint diseases such as chronic inflammatory arthritis (encompassing rheumatoid arthritis (RA) and spondyloarthritis (SpA)). RA is characterized by the presence of defined autoantibodies (in seropositive individuals) and arthritis that is generally restricted to the peripheral joints[8]. By contrast, a range of seronegative inflammatory arthritides are covered by the term SpA, the main forms of which are ankylosing spondylitis (AS) and psoriatic arthritis (PsA), which predominantly affect the axial and peripheral joints, respectively[9,10]. Owing to the symptomatic overlap between AS and PsA, SpA is often simply defined as axial or peripheral, depending on the principal location of inflammation[11,12]. These forms of chronic inflammatory arthritis have prodromal periods with measurable extra-articular features, such as autoantibodies in RA and psoriasis or inflammatory bowel disease in SpA, but it has been unclear how systemic inflammation results in localized arthritis of the axial and/or peripheral skeleton in these diseases. However, there is now growing evidence that micro-trauma to tendons and ligaments might function as a joint-focusing trigger in the progression of chronic inflammatory arthritis[13].

In this Review, we introduce the cellular and molecular mechanisms whereby tendons and ligaments sense mechanical force. This knowledge serves as a base for understanding how tendons and ligaments respond to mechanical stress **[G]** to maintain homeostasis under healthy conditions; a process that is heavily dependent on the immune system. The field of

orthopaedics has recognized that mechanical stress-induced immune responses can go awry, resulting in primary tendinopathy[14,15]. We therefore draw parallels between the immunological events that occur in tendinopathy and in chronic inflammatory arthritis (specifically RA and SpA) to demonstrate that tendons and ligaments are relevant tissues to consider in the pathophysiology of arthritis. As such, musculoskeletal diseases that initially seem diverse are potentially more similar than expected at the cellular and molecular levels owing to a shared anatomical basis in their pathophysiology.

Anatomy of tendons and ligaments

Generally speaking, tendons and ligaments have a hierarchal anatomical structure[14,16–18] (Figure 1b). At a molecular scale, the building blocks of tendons and ligaments are tropocollagen monomers, which polymerize into chains of type I collagen. Three of these chains twist to form a triple helix, which cross-links with adjacent chains to form fibrils. Fibrils coil to form fibres, at which point the structure moves from a molecular to a cellular scale. The fibres are bundled together by a sheath called the endotenon to define the unit known as the fascicle for either tendons or ligaments; the endotenon contains nerves and blood vessels to support the fascicle. Multiple fascicles bundle together to form a macroscopic tissue-level unit surrounded by a secondary sheath called the epitenon. Multiple epitenon-surrounded units bundle to form the complete organ that is itself enveloped by a tertiary sheath, which can be either a synovial sheath or a paratenon. Paratenon sheaths function as elastic sleeves to assist the free movement of the tendon against surrounding tissues, whereas synovial sheaths serve as tunnels for tendons and ligaments at locations where they wrap around bony or fibrous processes. These synovial sheaths enable the tendon or ligament to withstand high levels of stress **[G]**.

Although the main extracellular matrix (ECM) component of tendons and ligaments is collagen, other ECM components are also required for their function[19]. The non-collagenous ECM of tendons and ligaments consists of two main groups of molecules: proteoglycans and glycoproteins, which have protein and sugar cores, respectively[20,21]. Small proteoglycans such as fibromodulin are essential in regulating collagen assembly, whereas large proteoglycans, such as aggrecan, have hydrophilic properties and function to dampen compressive forces[21,22]. Glycoproteins can provide lubrication (such as lubricin), elasticity (such as elastin) or bind to inactive growth factors (such as tenascin-C, which binds to latent transforming growth factor-β (TGFβ))[20,23].

A range of cell types are found in healthy tendons and ligaments. Fibroblast-like stromal cells, commonly referred to as tenocytes, constitute 90-95% of the cells in a healthy tendon[18]. These cells are also commonly found in ligaments[24–26], where they can be referred to as ligamentocytes, however they are less well characterized than their tendon counterparts. Tenocytes are interspersed among collagen fibres within fascicles and can be phenotypically identified by the transcription factors scleraxis (Scx) or mohawk (Mkx)[27,28] (Box 1). However, although highly expressed by tenocytes, these markers are not tenocyte-specific and can also be found in other tissues, including the heart and testis[29,30]. The primary function of tenocytes is to build tendons and ligaments by producing collagen, or to break them down via protease release[14,31]. Populations of tenocyte-like progenitor cells

reside in the supportive tissue (the endotenon and epitenon) and can replace tenocytes as they die[32–34]. The endotenon might also contain resident immune cells such as M2-like macrophages[35–38]; however, it is unclear as to whether these cells are present under healthy conditions, as most studies have been performed in diseased tissue.

The basic anatomical and cellular information about tendons and ligaments outlined above enables the comparison of these two classes of load-transferring tissue. In general, ligaments are thought to have slightly less collagen content and a greater density of tenocytes than tendons[39]. For example, in the ligaments and tendons in the knee, the cruciate ligaments have a greater cell density, more glycosaminoglycans and a higher amount of type III collagen than the patellar and Achilles tendons[40]. However, the dominant mechanical forces exerted on a tendon or ligament are actually thought to be a more important promoter of tissue phenotype than the anatomical distinction of connecting muscle to bone or bone to bone. For example, a detailed ultrastructural and biochemical analysis of knee tendons and ligaments revealed that the properties of these structures differed depending on their intra-articular or extra-articular location: the anterior cruciate ligament (ACL), which is intra-articular, had less compact collagen and more elastin, aggrecan and versican than extra-articular knee tendons and ligaments, an outcome attributed to the high compressive forces exerted on the ACL[41].

Notably, non-classical tendons and ligaments also exist at specific locations in the body. As discussed above, the body of a tendon can wrap around bones to function as a pulley. At the point of contact with bone, such tendons lose their typical structure, widen to spread the force and become fibrocartilagenous, with woven rather than parallel collagen fibres[22]. Atypical ligaments also exist, such as the outer annulus fibrosis (AF) of the intervertebral disc (IVD) (Figure 1c). Although the outer AF contains tenocytes that express Scx and Mkx[24] and has organized type I collagen fibres and a sheath-like structure that contains progenitor cells with proliferative capacity, it does not have the hierarchal compartments that are typically found in ligaments[25,42].

Anatomy of entheses and MTJs

Distinct cellular and molecular transitions are present at the MTJs and the entheses. At the MTJ, these changes are abrupt and tenocytes directly interact with myocytes[43]. Although the transition zone between tissues is short at the MTJ, it is worth noting that ECM changes are present, such as an increase in type VI collagen and other components, including laminin, relative to the tendon and the muscle[44].

The changes at the enthesis are more substantial than at the MTJ; the complexity of these changes depends on whether the enthesis inserts directly into the bone, or indirectly, via the periosteum [G]. These attachments can be distinguished by the amount of fibrocartilage present; indirect insertions have little fibrocartilage and are termed 'fibrous entheses', whereas direct insertions have more fibrocartilage and are thus termed 'fibrocartilaginous entheses'[4]. Anatomically, tendons and ligaments that attach to the metaphyses [G] or diaphyses [G] have fibrous entheses. By contrast, those that attach to the epiphyses [G] of long bones typically have fibrocartilaginous entheses[4]. Fibrous entheses, such as the deltoid,

have straight insertions into the humerus that experience limited compressive or shear forces and are thus structurally less complex than curved fibrocartilaginous entheses, such as the Achilles tendon[39,40].

At the microscopic level, the fibrocartilaginous enthesis has defined strata and a collagen gradient (Box 2). Entheses are considered to be avascular at the point of attachment to bone because the presence of blood vessels conflicts with the requirements of load bearing and smooth movement at these locations[45]. The bulk of cells in the enthesis are tenocytes, although chondrocytes constitute up to 10% of entheseal cells[46]. Enthesis-resident immune cells are relatively rare. Resident lymphocytes have been reported in mouse and human tissues, including $\gamma\delta$ T cells and type 3 innate lymphoid cells[47–49], and IL-23-producing CD14^{+} myeloid cells have been observed in human spinal ligament entheses[50].

Biomechanics of tendons and ligaments

In the field of biomechanics, the fundamental principles of mechanics are applied to biological problems through the examination of the forces acting upon and within biological structures[51]. The amount of force exerted on tendons and ligaments is substantial: it is estimated that regular activity can induce forces of up to 3 times the weight of a body on the human Achilles tendon, whereas intense activities induce forces of 10 times body weight[52,53]. Yet despite anatomy-imposed variations that occur between tendons and ligaments, all tendon and ligament tissues are remarkably resistant to mechanical force (mechano-resistant). Although a detailed cellular and molecular discussion of the biomechanics of tendons and ligaments is beyond the scope of this Review, the basic types of force and the response of tendons and ligaments to these forces are outlined in the following sections. Readers are referred to several excellent resources for further information[16,31,54–57].

Types of mechanical force

The different types of mechanical force that act on tendons and ligaments are not equivalent[16] (Figure 2a and b). Tensile force, the mechanical force generated as a result of stretching an object along its primary axis, is the dominant force exerted on tendons and ligaments, and as such, these tissues have a high degree of resistance to it[58]. Compressive force, which is exerted on tendons and ligaments in a direction that is perpendicular to their primary axis, is high at the entheses and in wrap-around tendons[59,60]. Compressive force can also be exerted by the tertiary (paratenon or synovial) sheath in pathological conditions such as trigger finger[61]. Shear force occurs between adjacent objects that are moving at different speeds or in different directions, such as when two fascicles slide past one another or when a tendon or ligament slides in its synovial sheath[62]. Additional types of mechanical force are unique to different anatomical locations. For example, the AF is resistant to axial rotation in addition to longitudinal compressive and tensile forces[22]. The AF can also withstand hydrostatic force that occurs as a result of volumetric changes in the IVD, the water content of which can vary by 20% throughout the day[63]. Finally, it is important to note that these forces do not act alone, and it has been suggested that a combination of tensile and compressive forces can function as a trigger for the onset of tendon pathology[60].

Resistance to mechanical stress

The ability of tendons and ligaments to resist mechanical force lies in the biochemical properties of the ECM. In biomechanical studies, the strength **[G]** of a tendon or ligament is often represented as a stress–strain curve (Figure 2c), in which the stress is the force normalized to the cross-sectional area of the tissue it is being applied to, whereas the strain can be thought of as the ability of the tissue to stretch[57]. The slope of the stress–strain curve in the elastic region is the modulus **[G]**, which can be used to describe the stiffness **[G]** of the tissue. The shape of the stress–strain curve in tendons and ligaments is largely a result of the physical properties of collagen. In a resting state, collagen fibres assume a crimped orientation. Tension straightens out the collagen fibres, enabling the tissue to rapidly stretch from its crimped state, followed by a slower stretch as straightened fibres pull away from one another. Removal of this tension allows tendons and ligaments to return to their pre-stretched length, whereas an increase in tension leads to microdamage of the tissue (such as tearing of the collagen fibres)[64]. Multiple factors enable the return of tendons and ligaments to their pre-stretched length; for example, proteoglycan-mediated accumulation of water enables hydrostatic resistance to compression, and elastin molecules, which are highly organized around tenocytes[65], can resist tensile stress[66]. However, this 'elasticity' is not limitless: tendons can only stretch up to 8% of their length before reaching their breaking point[67], after which rupture occurs. By contrast, ligaments are able to resist greater stress than tendons owing to a higher elastin content and can subsequently stretch up to 30% of their length before rupture[68].

The response of a particular tendon or ligament to a specific mechanical load depends on many factors, including the type of mechanical stress, the anatomical function of the tendon or ligament and age. The type of mechanical stress involved can cause changes in the ECM; tensile stress induces the expression of decorin and versican, whereas biglycan and aggrecan are induced in response to compressive stress[21,69,70]. Such changes in the ECM composition subsequently affect the ability of the tissue to withstand mechanical stress. For example, biglycan and aggrecan protect the tendon against compression, but reduce its resistance to tension, injury and rupture[71,72]. The anatomical function of the tendon or ligament also has a direct effect on its biomechanical properties. Flexor tendons in the hand have a 'grasping' function, and thus have a high stiffness, are resistant to failure and have a high energy storage capacity compared with extensor tendons in the hand, which function to straighten digits[73]. Similarly, ligaments in the knee that stabilize the tibiofemoral joint have a higher stiffness and resistance to failure than ligaments in the ankle that stabilize the tibiotalar joint owing to the high mechanical forces exerted on the knee ligaments during tibiofemoral joint stabilization[74,75]. Finally, resistance to failure reduces as the tendon increases in age as a result of a reduction in cellularity and ECM component expression[73,76].

Mechanotransduction

Mechanical stress, like any biological stress, has a physiological range in which a tissue can mount a response to return it to its homeostatic set point. Tendons and ligaments adapt to mechanical stress by modifying their ECM to adjust their stiffness, as previously discussed[16,31,77]. However, it is the cells within tendons and ligaments that sense and

orchestrate the response to mechanical stress. The tenocyte is thus the master regulator in charge of transforming mechanical signals into adaptive responses in tendons and ligaments.

The tenocyte is particularly adept at mechanotransduction **[G]**, a process that utilizes a variety of cytokines, adhesion molecules and small molecules[31] (Figure 3). The transcription factors Scx and Mkx orchestrate mechanotransduction in tenocytes both in vitro and in vivo[78,79] by stimulating the expression of mechanical stress-activated genes, including those encoding ECM molecules such as collagen and adhesion molecules such as integrins[80]. The molecular mechanisms by which Scx and Mkx are activated are poorly characterized. Scx is known to shuttle between the cytoplasm and nucleus in cell lines[81], and can be phosphorylated at serine residues[82], thereby implicating cytoplasmic kinases as activators of Scx. Once activated, Scx binds to the co-transcriptional factors E12 and E47, which enables Scx to bind to specific motifs in the DNA of genes that define tenocyte function, such as *COL1A1*[26,83]. Less is known about the control of Mkx activity, although one study has shown that mechanical force can induce the activity of cytoplasmic GTF2IRD1, a transcription factor that can translocate to the nucleus and induce Mkx expression[78].

But how then is mechanical force translated into chemical signals that induce a cellular response via such transcription factors? Research in the field of mechanobiology has identified a number of mechanisms to achieve this translation of the physical into the chemical, either directly through cellular mechanosensors, or indirectly through mechanical stress-induced release of molecules from the ECM. The following section introduces several mechanisms of mechanotransduction. A detailed discussion is beyond the scope of this Review, but readers are directed towards excellent in depth reviews for further information[31,84–87].

Focal adhesions.

A dominant mechanism of direct mechanotransduction in tenocytes is through focal adhesions, which consist of collagen-binding, membrane-embedded integrins and their intracellular adaptor proteins[88] (Figure 3). The intracellular domains of integrins are connected to the actin cytoskeleton via an intermediate protein called talin[89]. Through tensile force-induced rearranging of protein domains, talin can function as both a shock absorber[90] and a molecular switch via tension-revealed binding sites for focal adhesion kinase (FAK)[91] and focal adhesion stabilizing proteins such as vinculin[92]. Although not extensively studied in the context of tendon and ligament biology, parts of focal adhesion complexes are known to mediate mechanotransduction. Mechanical force applied to tendon-derived tenocytes in vitro causes an upregulation of focal adhesion components, particularly integrins[80,93]. Furthermore, in ligament-derived tenocytes, FAK is recruitment to integrin clusters at the cell surface is associated with increased collagen expression[94]. Interestingly, in vitro stretching of mesenchymal stem cells induces the expression of a pattern of genes found in tenocytes, an upregulation that can be inhibited if parts of focal adhesions complexes, such as FAK, are specifically blocked[95].

FAK can also activate the transcription factors YAP and TAZ[96]. These ubiquitous mechanical stress-sensing transcription factors can also be activated by changes to the nucleus-associated cytoskeleton that occur during nuclear deformation[97]. The activation of

YAP and TAZ induces the expression of a range of genes, including those encoding focal adhesion complex components[98] and those that regulate apoptosis and cell proliferation[99]. The roles of YAP and TAZ in tendons and ligaments are not well defined; however, these transcription factors are known to be important in regulating muscle fibre size[100] and to protect against experimental osteoarthritis in mice by interfering with the transcription factor NF-κB[101]. Furthermore, nuclear deformation in tenocytes can occur during mechanical loading of tendons[102], suggesting that YAP and TAZ might be activated under such circumstances.

Mechanical stress-activated ion channels.

Cells are able to directly sense mechanical stress through stretch-activated ion channels such as Piezo molecules, which are activated upon cell membrane deformation[103]. Mechanistically, Piezo molecules selectively allow cations such as calcium into the cytoplasm when activated. Although Piezo activity in tenocytes has yet to be studied, it is worth noting that Piezo molecules have an important role in chondrocyte mechanosensing[104]. Interestingly, individuals with *PIEZO2* mutations develop joint contractures and scoliosis[105]; however, it should be noted that this phenotype is probably caused by altered proprioceptor function[106]. Transient receptor potential vanilloid 4 (TRPV4) is another stretch-activated ion channel that has a role in mechanical sensing via calcium flux[107]; however, TRPV4 has also yet to be studied in tenocytes.

Calcium signalling itself, such as that facilitated by stretch-activated ion channels, probably has an important role in tenocyte mechanotransduction[108,109] (Figure 3). A transient increase in intracellular calcium can be translated into molecular signals through calcium-binding molecules such as calmodulin[110] and the calpain enzymes[111], which can cleave molecules associated with focal adhesions[112]. Intracellular calcium flux can also be passively transmitted to adjacent cells through gap junction-mediated cytoplasm sharing[113]. In tenocytes, physiological levels of mechanical stress promotes gap junction permeability, whereas excessive mechanical stress is inhibitory[114,115]. The functional relevance of gap junctions in tenocytes is not yet clear, but the longitudinal arrangement of inter-fascicle tenocytes suggests that cell–cell contact is important[116].

Mechanical stress-induced cytokines.

Another method of relaying mechanical stress signals between adjacent cells is through the release of cytokines and signalling molecules, such as prostaglandin E_2 (PGE_2), TNF and TGFβ[117]. For example, the tenocyte stem cell phenotype is reinforced by low concentrations of PGE_2, whereas high concentrations promote transition to an osteoblast phenotype[118]. In vitro, TNF reduces collagen protein expression in human tenocytes while increasing the expression of genes encoding MMPs[119]. Furthermore, TNF induces the expression of integrins and pro-inflammatory cytokines (such as IL-6 and IL-8) in cultured human tenocytes[120]. In tenocytes, Mkx and Scx control the expression of TGFβ, which is incorporated into the ECM in an inactive form[43] (Figure 3). TGFβ can be released and activated by exposure to proteases, interaction of integrins with the ECM or by mechanical shearing of the ECM[19,121]. Physiological concentrations of TGFβ reduce tenocyte proliferation and promote collagen expression at the gene and protein levels and *SCX*

expression in rabbit and rat tenocytes in vitro[122,123]. TGFβ receptor signalling can also activate integrins to promote their adhesion to the ECM[121]. By contrast, high concentrations of TGFβ promote tenocyte death[79], which occurs within hours of tendon transection in vivo and within one day of tendon microdamage (induced by low level loading ex vivo)[79,124]. Mechanical stress-induced tenocyte cell death causes the release of a range of potent cell activators, including IL-1β, probably through inflammasome activation[125] (Figure 3). Indeed, both tenocytes exposed to mechanical stress and tendinopathic tissues express inflammasome components and active IL-1β[126–128]. Interestingly, IL-1β can function in an paracrine manner to trigger an anabolic response in adjacent tenocytes[129–131]. Cell death can also release Toll-like receptor (TLR)-activating danger-associated molecular patterns (DAMPs). The DAMP, HMGB1, is found in damaged tendons and can induce the expression of inflammatory molecules including IL-1β, IL-6 and CCL2[23]. Relevant to chronic inflammatory arthritis, monosodium urate (MSU) crystals are another class of DAMP that can be found at the enthesis in patients with gout[132] and can induce new bone formation in mice[133]. MSU crystals rupture cell membranes, causing cell death, inflammasome activation and the subsequent release of IL-1β[134].

ECM-mediated tenocyte activation.

Mechanical stress can also indirectly activate tenocytes through alterations in the ECM. Fibronectin is a collagen-associated, mechano-sensitive ECM component that is found in tendons and ligaments and is upregulated with injury[135–137]. DAMPs can be released from fibronectin via enzyme-mediated degradation and mechanical stress can expose cryptic integrin binding sites on collagen fibres that promote cell adhesion to the ECM[19] (Figure 3). Tenascin-C is less well-characterized than fibronectin but is highly expressed in healthy and injured tendons and ligaments[138]. Tenascin-C contains integrin-binding fibronectin domains and TGFβ binding motifs, and fragments of tenascin-C are potent activators of TLR4[138,139]. Hypothetically, ECM molecules such as tenascin-C function in part to concentrate cytokines and DAMPs at the tenocyte cell surface[140].

Such indirect responses of tenocytes to mechanical stress, similar to direct responses, function to elicit a homeostatic response. If mechanical stress exceeds the physiological upper or lower thresholds in tendons and ligaments, tenocyte death can occur within hours[32], which will subsequently initiate tissue repair processes.

Tendon and ligament repair processes

Generic tissue repair follows a conserved process[141,142]: trauma-associated cell death and tissue damage causes the rapid recruitment of immune cells, particularly neutrophils and monocytes, to maintain sterility and clear debris. After the initial insult, macrophages coordinate the deposition of a temporary matrix with the resident stromal cells, which in turn enables a return of tissue to its pre-injury state through stromal cell differentiation. It is worth highlighting the prominent role of the macrophage in the healing process and its capacity to transition through a range of phenotypes depending on the inflammatory milieu[143]. The tissue healing process is dependent on immune cell polarization; excessive inflammation mediated by T helper 1 (T_H1) cells and/or T_H17 cells causes necrosis and

excessive T_H2 cell-mediated inflammation causes fibrosis[141]. Damage to the tendons and ligaments can effectively be considered sterile inflammation, a process characterized by DAMP-induced IL-1β release[144].

As with generic tissue repair, injured tendons and ligaments follow a prescribed tissue repair process[16,145] (Figure 4). Initially, 1 to 5 days post-injury, an inflammatory response occurs in which haematoma and neutrophil infiltrates are common. Following this stage, fibroblastic proliferation occurs between 6 days and 6 months post-injury, during which time new collagen (predominantly type III collagen) is synthesized. Finally, collagen remodelling takes place 6 to 12 months post-injury. This repair pathway is potentially perturbed in systemic inflammatory conditions such as RA or SpA; however, no evidence currently exists to support or reject this hypothesis.

Tendon and ligament healing is initiated by fascicle damage. Acute or chronic tendon injuries cause the unloading of tenocytes through rupture or microdamage, respectively[16]. Tenocyte death occurs within hours of unloading[32,79,146]. As discussed above, cell death is associated with the release of pro-inflammatory factors such as PGE_2, IL-1β, IL-6 and TNF, which can in turn activate a pro-inflammatory and phagocytic response in myeloid cells[14,37,147]. In wound healing, resident myeloid cells function as sentinels of tissue damage and are rapidly activated by such pro-inflammatory molecules[148]. However, whether resident myeloid cells truly exist in healthy tendons and ligaments is not yet clear owing to a scarcity of studies on healthy tissue.

The recruitment of immune cells and aqueous elements of blood creates a haematoma, thereby marking the early stage of wound healing. This stage is characterized by monocyte and neutrophil influx, mediated in part by CCL2. Indeed, running-exacerbated peripheral arthritis is mediated by CCL2[13] and IVD expression of CCL2 strongly correlates with oedema and fatty lesions in patients with degenerated discs[149]. These recruited myeloid cells are activated by DAMPs and cytokines in the damaged tissue, triggering the removal of debris via phagocytosis[147]. Activated myeloid cells further promote the degradation of damaged ECM through MMP release and stimulate the deposition of a temporary matrix of type III collagen[32] and fibronectin[135] to facilitate tissue healing. During this stage, a positive feedback cycle probably exists between tenocytes and immune cells, which promotes the conversion of monocytes and/or macrophages into a pro-inflammatory, M1-like phenotype[120].

Compared with myeloid cells, the role of lymphocytes in tendon and ligament healing is poorly defined. Enthesis-resident populations of lymphocytes exist in mice and humans[47,48,150], and lymphocytes are also recruited during injury to tendons and ligaments[151]. One possibility is that resident or recruited lymphocytes fine-tune the immune response in tendon and ligament repair through their known role in macrophage activation[152]. It is also important to highlight the role that tissue-resident lymphocytes have in tissue repair and homeostasis, specifically through their promotion of stromal cell function[153–155]. One possibility is that such a function could be carried out by entheseal-resident lymphocytes; however, this hypothesis has yet to be explored.

During the intermediate stage of tendon and ligament healing, days-to-weeks post-injury, tenocyte progenitor cells differentiate and migrate from the sheath into the damaged tissue following acute rupture[32] or chronic overloading[156]. TGFβ and Scx are crucial for the promotion of tenocyte phenotype during this phase[79]. Failure of Scx induction in tenocyte progenitor cells promotes a chondrogenic or osteoblastic phenotype[43] and, ultimately, ossification at tendon wound sites[32]. Immunologically, the intermediate phase is characterized by a transition of macrophages from a pro-inflammatory, M1-like phenotype to a pro-resolving, M2-like phenotype[35]. Pro-resolving macrophages have an increased phagocytic capacity, which enables them to remove collagen, potentially through mannose receptors such as CD206[157]. These macrophages also have an increased capacity for promoting ECM production compared with pro-inflammatory macrophages[143]. Interestingly, CD206, a marker of pro-resolving macrophages is highly expressed in patients who are free of pain following tendon surgery, supporting a role for these macrophages in tendon and ligament repair[37].

Finally, the tendon and ligament tissue repair process ends with the late remodelling stage, which is characterized by the replacement of the temporary type III collagen matrix with a long-term type I collagen matrix, as well as a reduced cellularity of repaired tissue. In adults, this repaired tissue never regains its pre-damage architecture despite regaining some function[16,158,159].

Mechanical stress in disease

The field of musculoskeletal research has used knowledge of the mechanobiology and of the healing process of tendons and ligaments to make advances in understanding the basic biology of tendon and ligament disorders. These disorders cover a spectrum from those of an acute, self-resolving nature, such as strains, to chronic conditions involving tendon and ligament failure (Box 3). The pathophysiology of chronic tendon or ligament inflammation, however, such as occurs in tendinopathy, is less well-understood, in part owing to limitations of current in vivo models[16,145].

In this section, we focus on mechanical stress and immune aspects of tendon and ligament failure of the peripheral and axial skeletons, namely tendinopathy and IVD degeneration, respectively. Lessons from these examples are juxtaposed to forms of chronic inflammatory arthritis, in which evidence is emerging for mechanical stress as an environmental trigger for the onset of arthritis, thereby demonstrating the relevance of tendons and ligaments in the pathophysiology of arthritis. Before diving into the discussion, it is prudent to note that although mechanical stress is an important factor for triggering tendinopathy and inflammatory arthritis, it is not the only factor. Inflammatory arthritis has clear genetic and microbial associations[160], whereas factors such as inappropriate innervation and vascularization have been proposed as triggers for tendinopathy[161].

Tendon and ligament disorders

Tendinopathy versus inflammatory arthritis.—The role of mechanical stress in tendinopathies has been comprehensively characterized by basic research. Broadly speaking, trauma causes a shift in collagen isotype expression and tertiary structure in tendons, as well

as the rounding of stromal cells[162]. In animal models of tendinopathy, adult tendons fail to regain full function and do not regain their pre-injury architecture[158]. The failure of tendons in humans to completely heal after injury potentially explains why patients with tendinopathy are at risk of re-injury, and why surgical intervention for tendinopathy often fails[4,159]. Abnormal cartilage and bone formation occurs in response to injury or excessive stress in the axial and peripheral skeletons of mice deficient in Mkx or Scx[24,163], highlighting the important role of the tenocyte in tendon and ligament homeostasis. Likewise, in human tendinopathy, hardening of the tendons and ligaments often occurs and can vary in presentation from cartilaginous metaplasia[164] to ossification[165].

By contrast, less is known about the role of mechanical stress in chronic inflammatory arthritis. Mechanical loading can induce measurable signs of tendon and ligament inflammation, albeit often at a subclinical level; assessments of healthy individuals undergoing intense physical activity, such as athletes or military recruits, often reveal sacro-iliac joint lesions on MRI similar to those seen in patients with SpA[166,167]. Epidemiologically, physical trauma is associated with the onset of PsA[168], and physical workload increases the risk of developing RA[169]. Indeed, enthesitis is a well-established prodromal symptom in patients with SpA[170] and tenosynovitis can be predictive of the development of RA[171]. Importantly, although both RA and SpA involve bone erosion localized to points of enthesis insertion, only SpA presents with coincident bone formation at these locations. In RA, bone erosions of the small joints of the peripheral skeleton have traditionally been described as 'peri-articular'[172], although a study from the past year has linked the site of erosions to entheseal insertions[13]. In SpA, new bone formation occurs at peripheral entheses, such as at the Achilles tendon and metacarpophalangeal joint insertions, and at axial entheses, such as the sacro-iliac joint, vertebral facet joints and between vertebral bodies[173,174]. Peripheral and axial entheses are considered to be a principal site of clinical symptoms and pathological changes in SpA, despite the presence of systemic perturbations to the immune system[175,176].

Genetic studies, evidence from animal models and current therapeutic strategies all suggest an important role for systemic inflammation in SpA[117] and RA[141]. Although some of inflammatory pathways (such as TNF signalling) seem to be involved in both RA and SpA, other inflammatory pathways seem to be specific for one disease or the other. For example, the IL-17–IL-23 pathway has a role in active joint inflammation in SpA, whereas it seems to only be involved in early stages of RA, prior to the onset of arthritic symptoms[178]. This discrepancy is reflected in the efficacy of IL-17 inhibitors in treating SpA[179,180] but not RA[181]. Notably, IL-23 seems to be important in peripheral SpA[182] but its involvement in axial SpA is uncertain[183]. In RA, IL-6, IL-1β and B cells have well-defined roles, as reflected by the success of therapeutics blocking these cytokines and cells[184]. However, these systemic inflammatory components do not explain why these diseases affect particular anatomical locations in the axial and peripheral joints.

Although a few studies have explored the genetics of tendinopathy, little progress has been made in comparison to the genetic understanding of chronic inflammatory arthritis. Large genetic studies have yet to be performed in patients with tendinopathy to connect common genetic variants to disease. Small-scale studies have linked a few genetic variants to

tendinopathy, particularly in genes encoding ECM-related molecules such as collagen, and pro-inflammatory or tissue remodelling molecules such as IL-1β and MMPs[185]. However, the functional relevance of such variants are unknown. At the transcriptomic level, microarray analyses of tendinopathy tissue samples have revealed changes in the expression of genes related to ECM molecules and ECM-interacting molecules such as integrins, as well as TGFβ and components of IL-1β signalling pathways[186].

Despite the suggestions of immune involvement in these genomic studies[149,150], and the known role of the immune system in tendon healing (outlined in the previous section), the contribution of the immune system to tendinopathy is not well-understood. A 2018 meta-analysis of tendinopathy reviews concluded that over the previous 5 years, a paradigm shift has occurred in the field of basic tendinopathy research regarding ideas about a bona fide immune contribution to the disease, rather than tendinopathy being viewed purely as a degenerative disorder[15]. The studies driving this paradigm shift examined haematopoietic cell subsets using general cell markers such as CD68 for macrophages or CD3 for T cells[187], which revealed the presence of immune cells in damaged tendons, but few studies have reported a deeper level of immunological analysis. Persistent activation of NF-κB in tenocytes is thought to promote tendinopathy[37,188,189]; however, it is unclear exactly what is activating this transcription factor, as it can be activated by many pro-inflammatory stimuli, including IL-1β, TNF and IL-17. In early rotator cuff injury, evidence suggests a role for IL-17, which is present in macrophages and mast cells and causes tenocytes to produce IL-6, IL-8 and CCL2[151]. In addition, a shift in tenocyte phenotype has been identified in tendinopathy, whereby integrins and angiogenic markers are upregulated and the cells become hypersensitive to IL-1β stimulation[38,188]. In summary, immunological studies of chronic inflammatory arthritis and tendinopathy display remarkable similarities in terms of their molecular mediators. Despite this similarity, research in the two fields has been relatively independent.

Lessons from IVD degeneration.—Notably, the pathology of spinal ligament injury is biologically comparable to that of tendinopathy. Mechanical stress can be a trigger for IVD degeneration through damage to the outer AF[25,190], resulting in severe back pain[191]. As with tendinopathy, injury to the IVD involves ECM degradation and an appreciable immune contribution, with IL-1β and TNF being strongly implicated[191]. AF stromal cells, like classical tenocytes, also die in response to mechanical stress in the IVD[192]. In support of a role for inflammation in IVD degeneration, mice that express human TNF and mice that cannot negatively regulate IL-1β both develop spontaneous inflammatory disc degeneration[193,194]. Mice that lack Mkx also have spontaneous disc degeneration and ectopic bone formation between vertebrae, which can be expedited by exerting mechanical stress on the axial skeleton through prolonged bending of the tail[24]. Interestingly, new bone growth between vertebral bodies in patients with AS seems to occur in areas associated with the outer AF, and not with longitudinal ligaments[195–197]. In fact, studies estimate that over 40% of patients with axial SpA have signs of IVD degeneration[198,199], and end-stage disease in SpA is characterized by complete fusion of the axial skeleton, making a discussion of IVD degeneration and the outer AF particularly relevant for this disease.

Tendons and ligaments in arthritis

Evidence from mouse models of inflammatory arthritis is generally supportive of tendon and ligament involvement. Although some models have mild tendon and ligament inflammation, such as in aged DBA1 mice[200], LysM-cre.A20 mice (which have a conditional knockout of A20 in myeloid cells)[201], TNF ARE mice[202] (which have a dysregulation of TNF mRNA, resulting in systemic TNF overexpression) or mice with collagen antibody induced arthritis (CAIA)[150], other models have severe entheseal inflammation, such as in SKG mice[203] or B10.RIII mice with plasmid-induced overexpression of IL-23[150]. In addition to revealing the important roles of cytokines such as TNF and IL-23 in tendon and ligament-associated arthritis, studies in mouse models of disease also led to the discovery of a population of enthesis-resident $\gamma\delta$ T cells[47]. Studies from the past few years have also demonstrated that mechanical stress can exacerbate inflammatory arthritis in some of these mouse models. Hind limb unloading to relieve mechanical stress in TNF ARE mice and in mice with collagen-induced arthritis (CIA) limited enthesitis in these animals[13,204]. By contrast, increasing mechanical stress by allowing mice to undergo voluntary running accelerated the onset and worsened the severity of arthritis in mice with CIA, mice with CAIA and in TNF ARE mice[13]. Notably, these studies do not report an effect of mechanical stress on systemic immunity, as reflected by equivalent autoantibody titres with or without mechanical loading in mice[13]. However, surprisingly, RAG knockout mice, which are deficient in T cells and B cells, still developed mechanical stress-exacerbated arthritis[13,204], ruling out a role for adaptive immune cells in the initiating phases of disease.

Given the importance of tenocytes in responses to mechanical stress, questions arise as to the extent of tendon and ligament stromal cell involvement in inflammatory arthritis. Currently, little data is available to address this question. An elegant study involving TNFRI deficiency in non-haematopoetic cells revealed an essential role for TNF in stromal cells in the onset of arthritis in TNF ARE mice[202]. However, this study did not specifically address tenocytes, as the authors used a type VI collagen-Cre system to delete TNFRI in a range of stromal cells, including those in the bone, cartilage and muscle[205]. Further evidence of altered tendon and ligament stromal cells in inflammatory arthritis comes from the observation that CCL2 is induced in mechanically stressed tendons[13]. CCL2 is also induced by mechanical stress of tenocytes in vitro[13]. Finally, mice with CAIA undergoing voluntary running developed arthritis in the absence of an LPS boost, which is usually required after anti-collagen antibody administration[13]. This result suggests that mechanical stress-induced activation of complement[206], or release of DAMPs, such as HMGB1, from injured tendons[23,126] might contribute to the focusing of systemic inflammation at the tendons and ligaments.

To fully address the question of how mechanical stress-induced inflammation is diverted from resolution of injury to joint destruction in inflammatory arthritis (Figure 5), it is important to highlight that the dominant location of articular inflammation differs by disease: in SpA, inflammation is predominantly entheseal, whereas in RA it is synovial[207]. This difference in location suggests that the underlying immune perturbations in SpA and RA promote different mechanisms of pathogenesis in each disease. In SpA, mechanical stress-induced microdamage might fail to completely heal owing to systemic increases in IL-17–IL-23-mediated immunity, resulting in ectopic bone formation as the tissue fails to

adapt to subsequent mechanical loading. In RA, tendon and ligament damage could trigger the deposition of autoantibodies in the synovioentheseal complex, after which epitope spreading could facilitate the transition of inflammation to the synovium. Such a provocative hypothesis requires mechanistic studies that interface immunology and biomechanics to fully understand the relationship between mechanical load and chronic inflammatory arthritis.

Conclusions

Musculoskeletal disorders are a substantial burden to society[5–7] therefore it is paramount that the mechanobiology of tendons and ligaments be understood. Tools and knowledge are being developed in the fields of biomechanics, cellular biology and immunology that, when combined, will provide great insight into musculoskeletal diseases of seemingly diverse origins, such as tendinopathy and chronic inflammatory arthritis. Homeostatic responses to mechanical stress is a fundamental concept in biology: a concept that involves elements of the immune system. Although an appreciation for immune involvement in mechanical stress-associated disorders of tendons and ligaments of the peripheral and axial joints is emerging, the underlying immunopathogenesis is poorly understood in comparison to inflammatory arthritis, which could serve as inspiration for future tendinopathy research. Similarly, mechanical stress is an important co-factor that should be considered in future studies of inflammatory arthritis, especially during the initiating phases. In vitro and in vivo models of mechanical stress that are used routinely in tendinopathy research can be leveraged to properly understand the interaction between perturbed immunity and mechanical stress in the onset of arthritis. Undoubtedly, future research will shed new light on responses to mechanical stress in musculoskeletal diseases, which will uncover novel therapeutic opportunities.

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Glossary terms

Force	A vector quantity that describes the action of one structure on another; measured in Newtons.

Strain	Deformation that occurs at a point in a structure under loading; measured as the percentage change in length from the resting state.
Load	The sum of all force components acting on an object or body.
Mechanical stress	Mechanical load acting on cells or tissues as a physical stressor that elicits a biological response to ensure homeostasis.
Stress	The force per unit area that develops within a structure in response to externally applied loads; measured in Newtons per m^2 or Megapascals.
Periosteum	A fibrous tissue that envelops non-joint surfaces of bone and contains supportive tissue for the cortical bone, such as blood vessels and nerves.
Metaphyses	The flare (or cone-shaped) portion of long bones that connects the diaphysis to the growth plate.
Diaphyses	The conical shaft of long bones.
Epiphyses	The portion of bones above the growth plate that interfaces with other bones to form the joint.
Strength	The maximum amount of force that a material can absorb before failure.
Modulus	The ratio of stress to strain in the elastic region of a stress–strain curve.
Stiffness	The ratio of load to elongation in the elastic region of a stress–strain curve.
Mechanotransduction	The processes through which cells sense mechanical force and translate it into biological responses.
ToC blurb	Mechanical load is an important factor in the development of tendon and ligament disorders. In this Review, the authors discuss the evidence for the known role of mechanical load in tendinopathy and its potential role in inflammatory arthritis.

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Box 1.

The developmental biology of tenocytes.

A number of molecules have essential and non-redundant roles in tenocyte development, including transforming growth factor-β (TGFβ), mothers against decapentaplegic homolog 3 (SMAD3), the transcription factor Egr1 and the transmembrane glycoprotein tenomodulin[43]; however, the transcription factors scleraxis (Scx) and mohawk (Mkx) are the best characterized. Scx is thought to be upregulated at an early stage in tenocyte development during limb bud formation, in which it initiates tenocyte differentiation and tendon development[208,209]. Scx is also essential for the development of the enthesis[210]. By contrast, Mkx is upregulated at a late stage during tenocyte development and is responsible for modifying the strength of a tendon once it has been formed[211]. Tenocytes are developmentally linked to other joint stromal cells, particularly chondrocytes and osteoblasts. Whereas Scx-expressing progenitor cells maintain some flexibility and can differentiate into chondrocytic cells given the right cues[212], Mkx strongly prevents the expression of the transcription factors Sox9 and Runx2, which define chondrocytes and osteoblasts, respectively[213,214]. As both Mkx and Scx are induced and/or activated by loading[78,79], tenocyte development and survival depends on exposure to mechanical stress.

Box 2.

The structural zones of the enthesis.

When examined at a histological level, the fibrocartilaginous enthesis comprises four distinct zones (see the figure). Zone 1 contains a pure tendinous or ligamentous tissue with aligned type I collagen fibres and sparse tenocytes. Zone 2 is a region of uncalcified fibrocartilage with an increased tenocyte density and an increased amount of aggrecan compared with zone 1. A transition from type I collagen fibres to type II and type III collagen fibres occurs in zone 2. Zone 3 is a region of calcified fibrocartilage in which type II collagen is dominant. In this zone, type II collagen forms a mesh to anchor the tendons and ligaments to the bone[215]. Morphologically, tenocytes transition from an elongated morphology in zone 1 to rounded 'chondroid' cells in zones 2 and 3. Finally, in zone 4, the bone is highly vascularized to provide nutrients to the avascular enthesis. The entire transition from tendon to bone occurs over ~0.5mm of tissue[215].
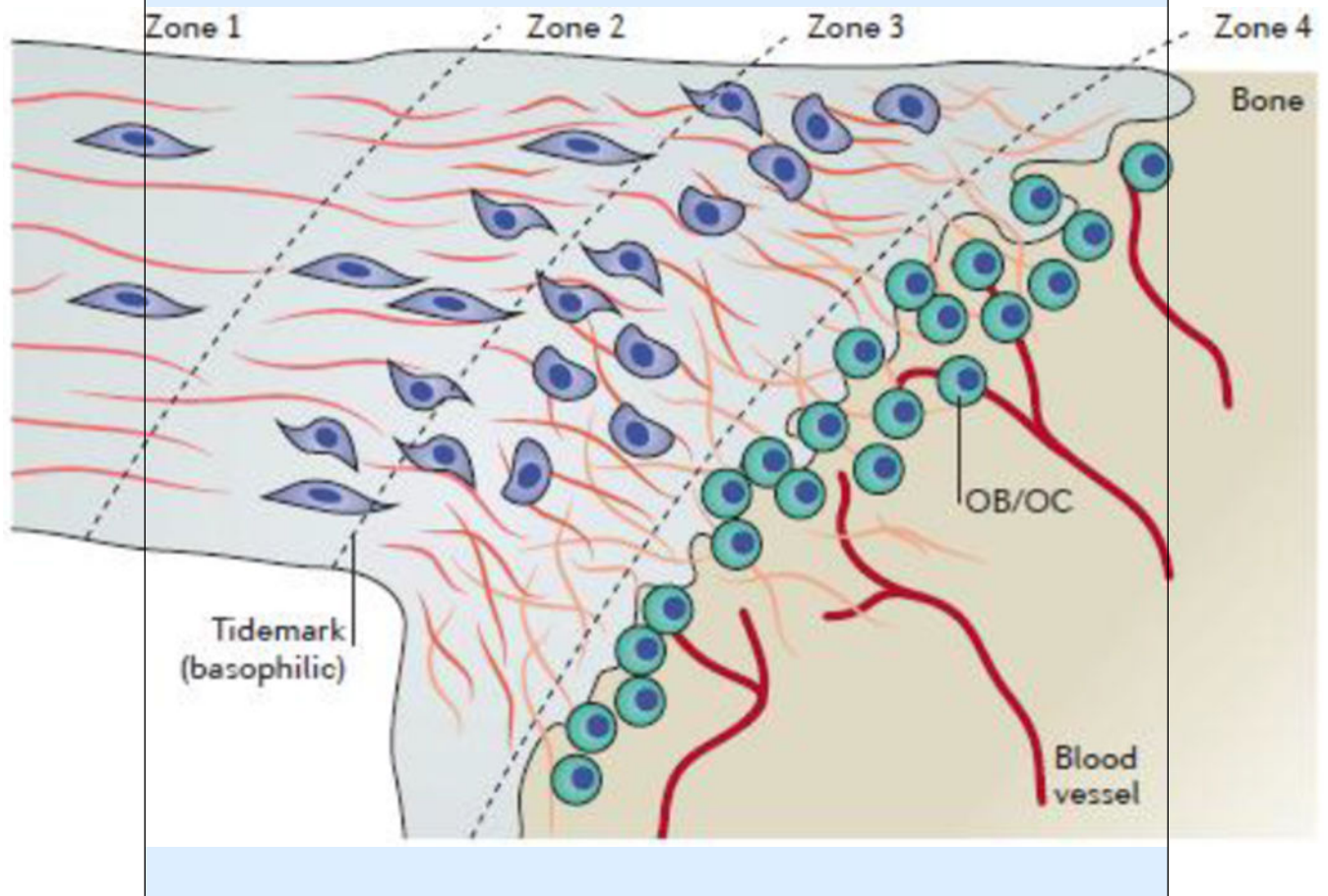
Box 3.

Types of tendinopathy.

Tendinopathy is a broad term to describe pain and decline of tendon and ligament function associated with overuse. Classic examples of tendinopathy include those of moderate severity, including tennis elbow and Achilles tendon inflammation, and more serious injuries, such as tears or ruptures of the rotator cuff. On the basis of available evidence, it can be assumed that the repair process in tendinopathy is similar to acute tendon injury healing, as pro-inflammatory cell types, fibroblast proliferation and type III collagen turnover are present, but for reasons that are poorly understood, the repair process fails to enter the resolution phase, resulting in long-term inflammation and fibrosis[151,216].

The two main categories of tendinopathy (or ligament injury) are classified according to their anatomical location[52]: insertional tendinopathies occur at the entheses, whereas non-insertional tendinopathies occur at the midportion of tendons (for example, 2 to 6 cm proximal to the enthesis of the Achilles tendon)[217]. In an epidemiological investigation of 1,394 non-athletes presenting at an orthopaedic clinic, Achilles tendinopathy was found in 5.6% of individuals with a roughly equal presentation of insertional and non-insertional types[218]. Insertional tendinopathy tends to occur more frequently in active individuals, whereas, when controlling for confounding factors, non-insertional tendon injury tends to occur in older, less active and overweight individuals[219]. By contrast, the majority of ligament injuries seem to occur in the midportion[220,221]; however, certain ligaments, such as the medial collateral ligament, more commonly fail at the insertion[222]. These differences in location are seldom addressed in studies, and it is unknown whether mechanisms of pathogenesis differ between insertional and non-insertional tendinopathy or ligament injury.

Key points

- Mechanical loading is a biological stressor that elicits a homeostatic response to ensure the health and survival of the cells and/or tissues it is applied to.

- Tissues that encounter high amounts of mechanical stress are prone to damage, especially the tendon and ligament entheses.

- The immune system is crucial in responding to and orchestrating the repair of damaged tendons and ligaments.

- Mechanical loading is a well-defined factor in the immunopathology of tendon and ligament disorders such as tendinopathy.

- Mechanical loading is associated with the onset of chronic inflammatory arthritis, including spondyloarthritis (SpA) and rheumatoid arthritis (RA).

- Microdamage associated with mechanical loading potentially focuses systemic autoimmune disease on the joint in the initiating phases of SpA and RA.
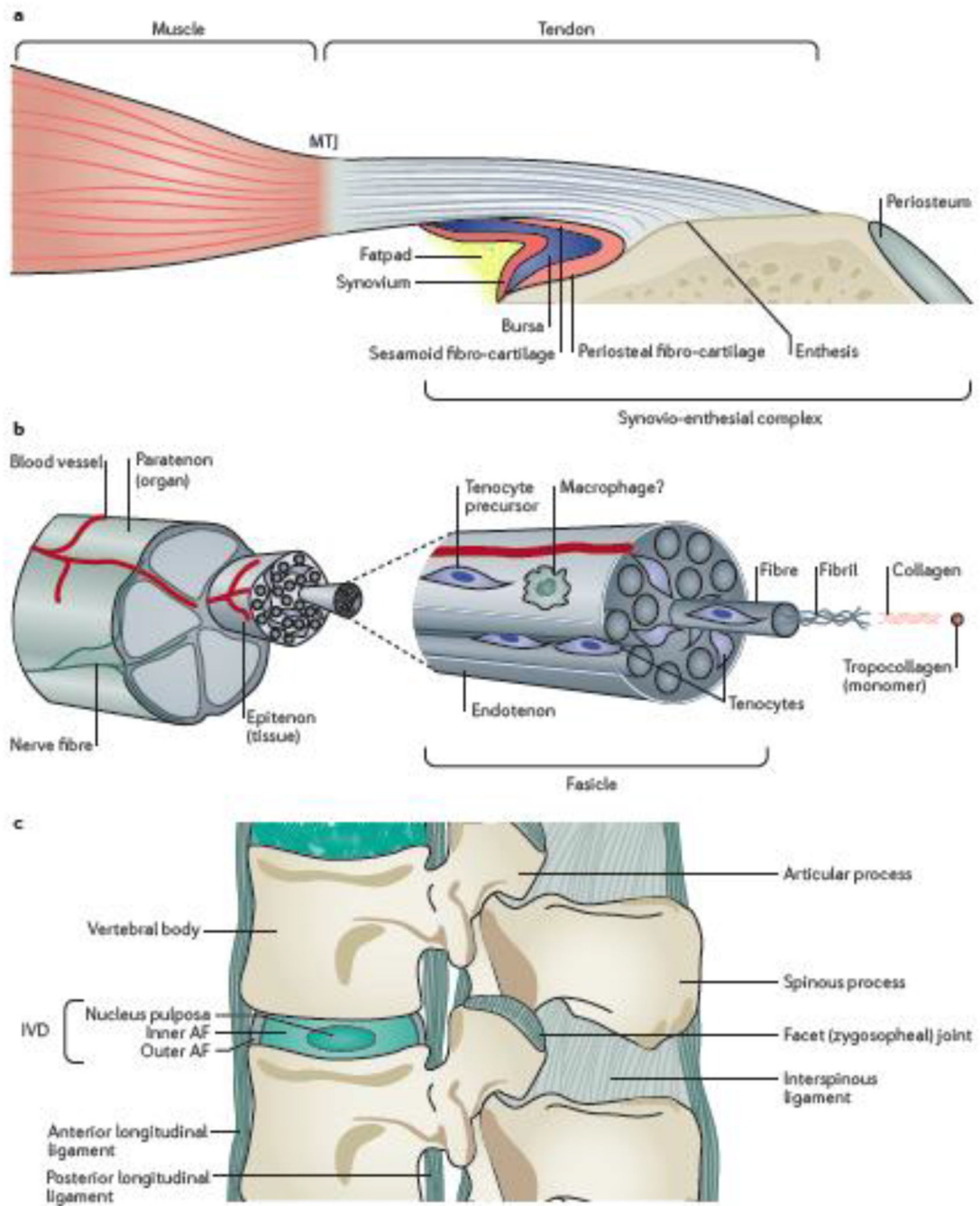
Figure 1. The anatomy of tendons and ligaments in the peripheral and axial skeletons.
a| A macroscopic overview of tendon structure and the fibrocartilaginous synovio-entheseal complex at the bone insertion. **b**| A cross-sectional view of a tendon showing the hierarchal structure of the organ at tissue and molecular levels. **c**| The anatomy of spinal ligaments and the intervertebral disc (IVD). AF, annulus fibrosus.
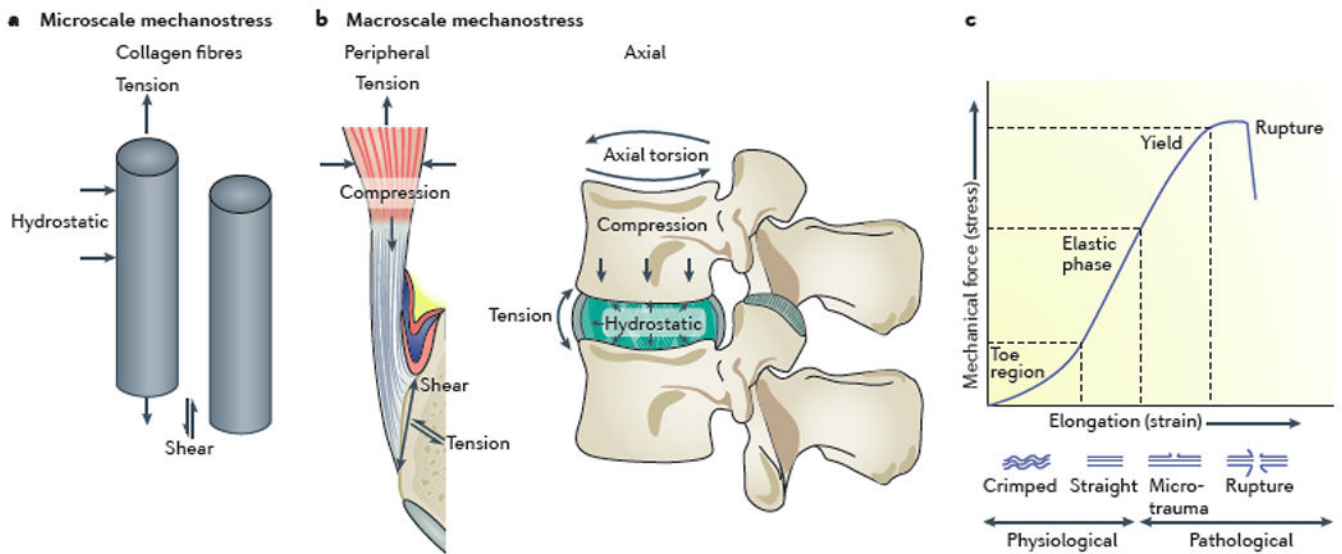
Figure 2. Mechanical forces exerted on tendons and ligaments.
The types of mechanical forces that are exerted on tendons and ligaments can be examined at the microscale, in which forces act on and between collagen fibres (**a**) and at the macroscale, in which forces act on the complete tendon or ligament (**b**). Whereas microscale mechanical forces are common to all tendons and ligaments, macroscale mechanical forces differ depending on the anatomical location (axial skeleton or peripheral skeleton) of the tendon or ligament. The relationship between normalized force placed on a tendon or ligament, and the subsequent tissue elongation, can be represented by a stress–strain curve (**c**). Each phase of tendon or ligament stretch is defined by physical changes to the structure of collagen fibres as they go from a resting (crimped) state to an undamaged stretched state, on to a microdamaged stretched state and finally to complete rupture. The slope of the linear elastic region represents the modulus of the tissue.
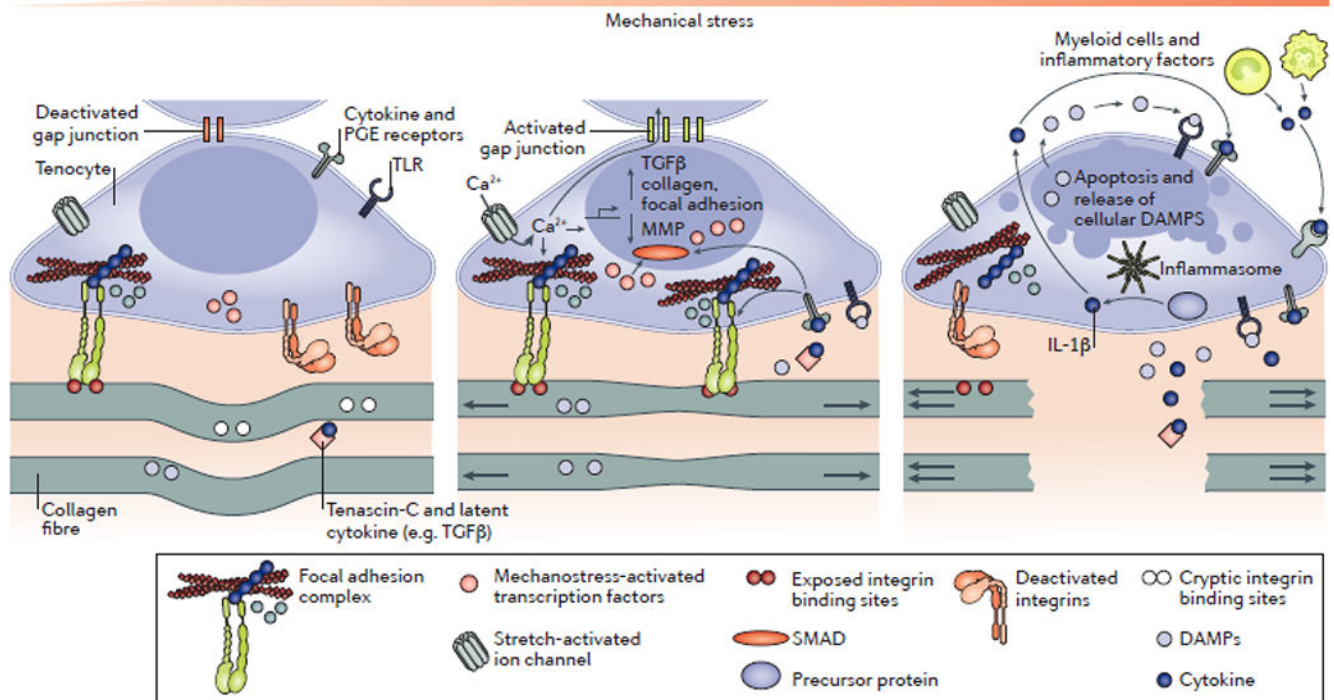
Figure 3. Proposed tenocyte response mechanisms to mechanical stress.
The mechanical loading of collagen fibres in tendons and ligaments is sensed by tenocytes, which mount a biological response to alter the extracellular matrix (ECM) composition of the surrounding tissue. In the unloaded state (left-hand side), collagen fibres are crimped and tenocytes receive minimal internal and external mechanical stress signals. Inactive integrins do not form focal adhesion complexes, and active integrins do not initiate mechanotransduction. As a result, mechanical stress-related transcription factors are either destroyed, such as YAP and TAZ, or fail to enter the nucleus, such as Scx. The result is a catabolic programme to reduce tenocyte and tendon strength in an effort to maintain homeostatic tension. At physiological levels of mechanical stress (centre), internal and external mechanisms of mechanostransduction are engaged, resulting in increased formation and activation of focal adhesions and the buffering of internal mechanical stress by talin. Actin tension is converted to the activation of YAP and TAZ, whereas Scx is activated via post-translational modification to induce the expression of a tenocyte-defining transcriptional programme. Transforming growth factor-β (TGFβ) promotes a tenocyte phenotype and integrin activation, potentially through the proximity of integrins and TGFβ receptor, mediated by tenascin-C. Calcium might also enter the cells through stress-activated ion channels such as Piezo and transient receptor potential vanilloid 4, and might subsequently be transmitted to adjacent cells via gap junctions. Excessive mechanical stress (right-hand side) results in ECM damage and a rapid loss of mechanotransduction in the tenocyte. The result is cell death and the release of danger-associated molecular patterns (DAMPs) and inflammasome-activated cytokines such as IL-1β. These molecules can propagate cell death in adjacent tenocytes and can promote the recruitment of pro-inflammatory cells, which perpetuate the inflammatory cycle by releasing pro-inflammatory

molecules such as TNF, IL-6, IL-17 and prostaglandin E_2 (PGE_2). MMPs, matrix metalloproteinases; TLRs, Toll-like receptors.
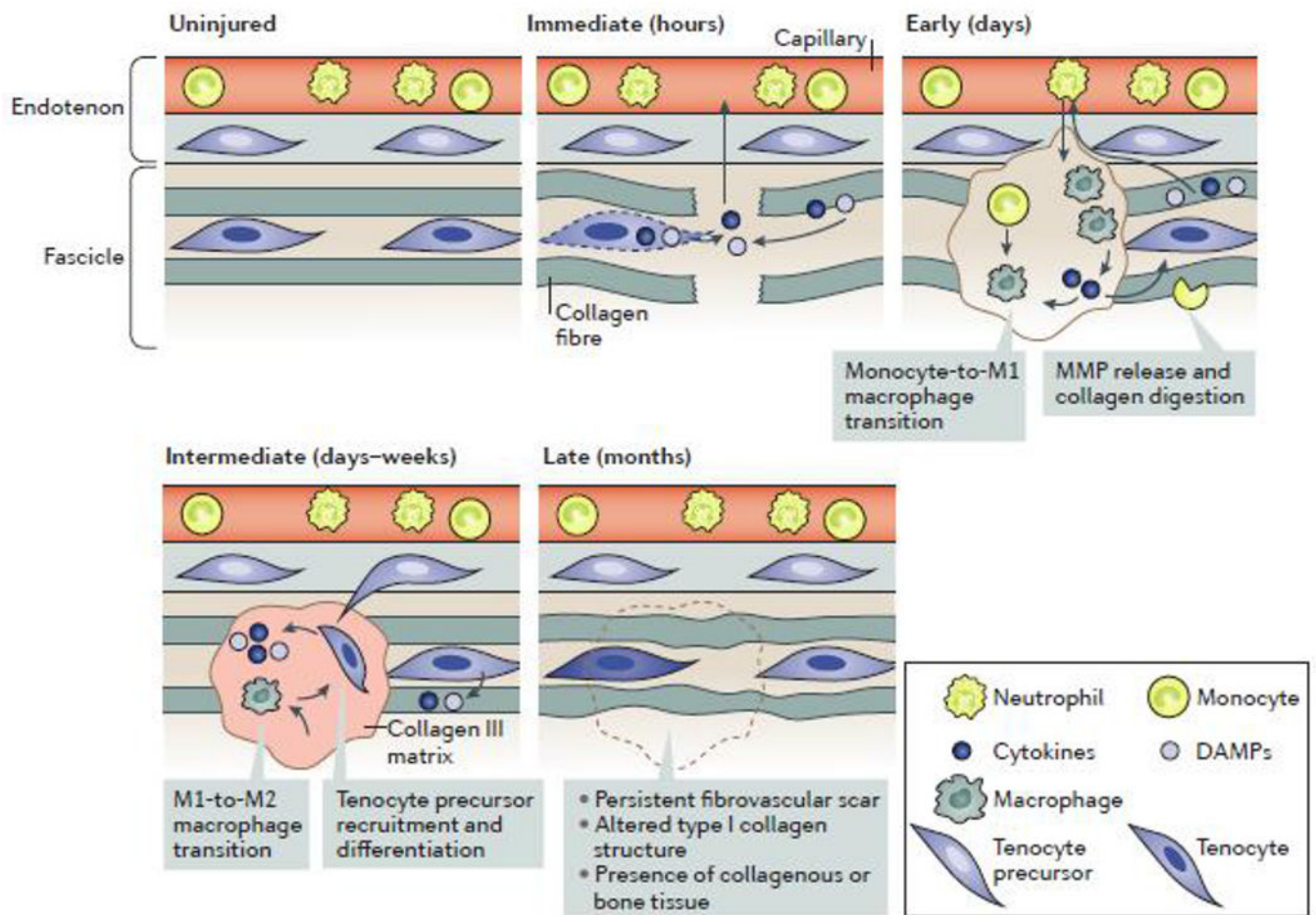
Figure 4. The tendon and ligament tissue repair process.

Tenocyte death occurs following unloading of tendons, which happens after rupture and microdamage, causing the release of cytokines and damage-associated molecular patterns (DAMPs). This death results in the rapid activation of adjacent stromal cells and, potentially, tissue-resident immune cells, propelling the injured tissue into a state of repair. The early phase of tendon and ligament repair is an inflammatory phase, characterized by myeloid cell recruitment, the transition of monocytes to pro-inflammatory (M1) macrophages and the removal of apoptotic tenocytes and extracellular matrix (ECM) debris by phagocytosis. Tenocytes and myeloid cells work together to ensure an adequate catabolic response. The intermediate phase of tendon and ligament repair is characterized by a resolution of inflammation and an increase in pro-resolving (M2) macrophages. During this stage, tenocyte precursor cells are recruited into the lesion to assist with ECM repair through the deposition of a temporary type III collagen matrix. In the late phase, this temporary matrix is slowly remodelled to a permanent, type I collagen-dominated matrix. The recovered tissue in adult tendons and ligaments never regains its pre-injury architecture and is frequently scar-like in appearance.
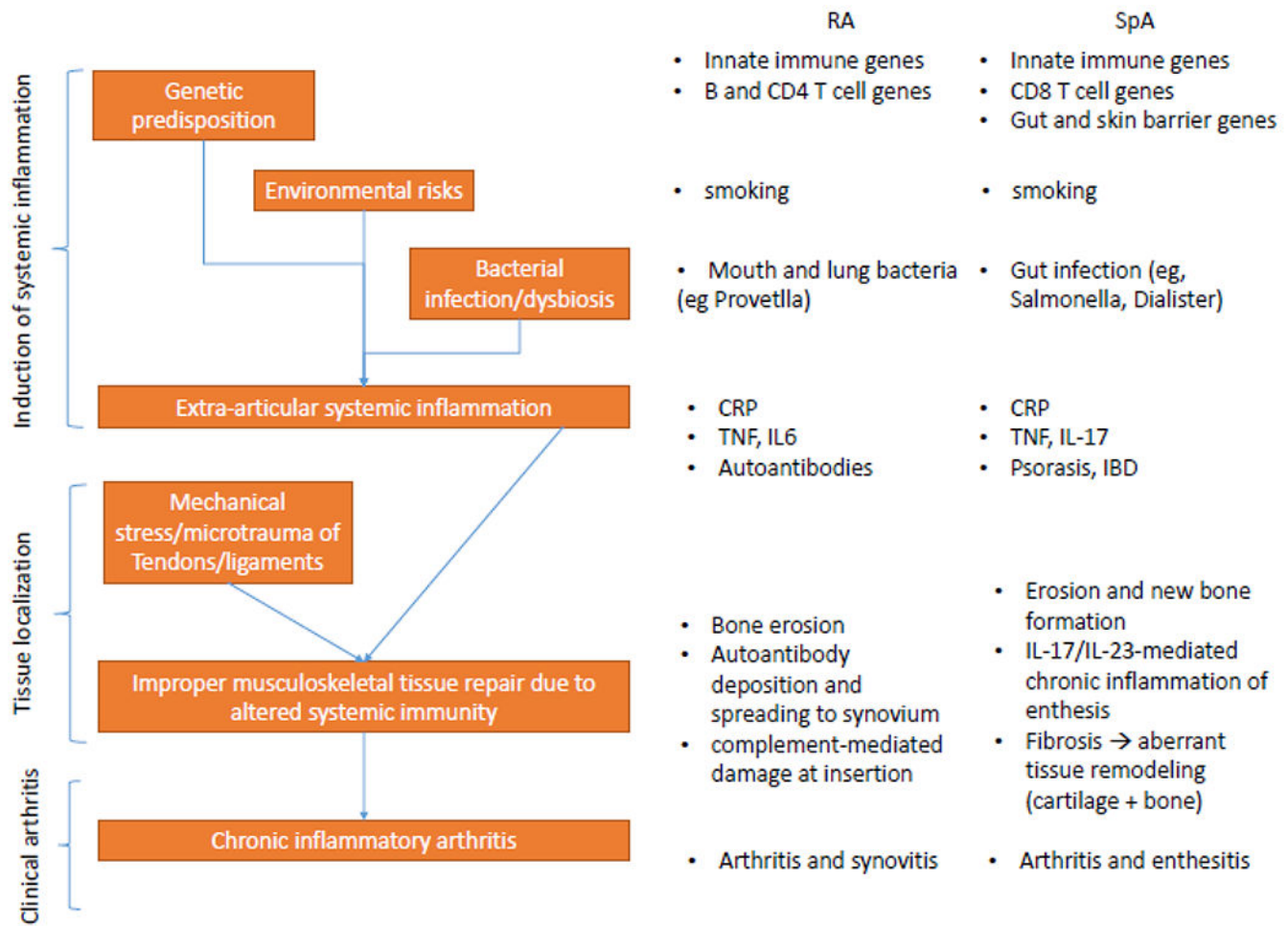
Figure 5. Proposed model of the relationship between mechanical stress and inflammatory arthritis.

Chronic inflammatory arthritis, including rheumatoid arthritis (RA) and spondyloarthritis (SpA), has defined genetic and environmental risk factors, but the relative contribution of these factors to the onset of systemic inflammation differs between diseases. Smoking is a well-recognized environmental risk factor for both SpA and RA, as are bacterial infections of barrier surfaces, albeit at different anatomical locations in RA and SpA. Genetic and environmental risk factors synergize to promote systemic inflammation that has both shared and distinct features in RA and SpA. The normal healing process that occurs after mechanical stress-induced microdamage at entheseal sites is hijacked by perturbed systemic immunity resulting in sustained entheseal inflammation and aberrant tissue healing. In RA, the result is bone erosion, probably as a result of protracted osteoclast activation in the subchondral bone adjacent to the enthesis. In SpA, subchondral bone erosion occurs coincident to entheseal fibrosis and subsequent ossification, possibly owing to persistent tenocyte activation through the IL-17–NF-κB axis. IBD, inflammatory bowel disease.