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Review article

Tendon injury and repair – A perspective on the basic mechanisms of tendon disease and future clinical therapy

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ABSTRACT

Tendon is an intricately organized connective tissue that efficiently transfers muscle force to the bony skeleton. Its structure, function, and physiology reflect the extreme, repetitive mechanical stresses that tendon tissues bear. These mechanical demands also lie beneath high clinical rates of tendon disorders, and present daunting challenges for clinical treatment of these ailments. This article aims to provide perspective on the most urgent frontiers of tendon research and therapeutic development. We start by broadly introducing essential elements of current understanding about tendon structure, function, physiology, damage, and repair. We then introduce and describe a novel paradigm explaining tendon disease progression from initial accumulation of damage in the tendon core to eventual vascular recruitment from the surrounding synovial tissues. We conclude with a perspective on the important role that biomaterials will play in translating research discoveries to the patient.

Statement of Significance

Tendon and ligament problems represent the most frequent musculoskeletal complaints for which patients seek medical attention. Current therapeutic options for addressing tendon disorders are often ineffective, and the need for improved understanding of tendon physiology is urgent. This perspective article summarizes essential elements of our current knowledge on tendon structure, function, physiology, damage, and repair. It also describes a novel framework to understand tendon physiology and pathophysiology that may be useful in pushing the field forward.

Contents

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1. Introduction

Tendon and ligament problems represent the number one musculoskeletal complaint for which a patient seeks medical attention [1,2]. Tendon disorders bring an extremely high personal burden to the individual patient by reducing quality of life, and collectively place enormous economic burden on society [3]. The most common clinical tendon condition is tendinopathy, related to overuse and characterized by an underlying state of tissue degeneration that is often painful. Until now clinical treatment of tendinopathy focuses on physiotherapy (passive [4,5] or active motion [4,6]) or anti-inflammatory drugs, e.g. corticosteroid injections (which are largely ineffective and potentially harmful to the patient [7]). The net outcome however, typically results in prolonged suffering of the patient with a substantial loss of personal productivity [8], reflecting the fact that tendons play a central role in normal human movement.

Tendons enable effective skeletal force transmission and energy-efficient locomotion [9]. In this function, tendons are exposed to some of the most extreme mechanical demands in the human body. The foot flexor tendons of healthy humans, for instance, are able to withstand up to eight times body weight and store up to 40% of deformation energy during gait [10]. The ability of tendon tissues to bear these loads originates from a unique structural organization and adaptability of the tendon tissue in adjusting its load-bearing capacity [11]. Although tendon cells can reinforce tissue upon increased loading demand, net extracellular matrix synthesis in healthy tendons is low compared to other connective tissues [12,13]. Sudden exposure to elevated mechanical stresses can put tendon tissues at risk of damage, and overloading is widely considered to be a causative factor in the onset of tendinopathy [14–16]. Mechanical loading can thus be viewed as a delicate "state switch" between functional tissue remodeling and the development of chronic tendon disease.

At first glance, tendon may seem to be a relatively simple tissue with a straightforward function, adapting to mechanical loads and self-repairing after damage [17]. However, a closer look into the repair capacity of tendon reveals that it is actually a complex physiological system, with tightly coordinated interplay between an "intrinsic compartment" that comprises the fibrous collagen core (tendon cells and the multiscale arrangement of collagen assemblies), and an "extrinsic tendon compartment" that consists of synovium-like tissues connecting the immune, vascular, and nervous systems [18–20] (Fig. 1). The extent of intrinsic and extrinsic compartment coordination in functional repair, and discord in degenerative processes, is still poorly understood [20–24].

It is important to note that tendon represents an under-researched tissue. Unlike muscle, it is generally not possible to biopsy healthy tendon tissues from patients or volunteers. Almost all existing data regarding basic mechanisms of tissue physiology, or detailed investigations of tendon damage and repair stem from non-primate animal studies. In the sections below, we attempted to stitch together the relatively sparse evidence that is available into a still emerging picture. While many features of tendon structure and biology are conserved across species, it must be acknowledged that aspects of tendon physiology gleaned from animal studies, or from in vitro experiments on isolated human cells may not validly reflect the human system. For instance, experiments on rodents (mice, rats) and rabbits form the basis of much of our controlled experimental knowledge on healing response to injury, yet heal in an accelerated manner that deviates from humans [25,26]. Further, genetic and epigenetic variations between individuals and epigenetic differences between the many tendons within a single individual, further cloud efforts to inter-

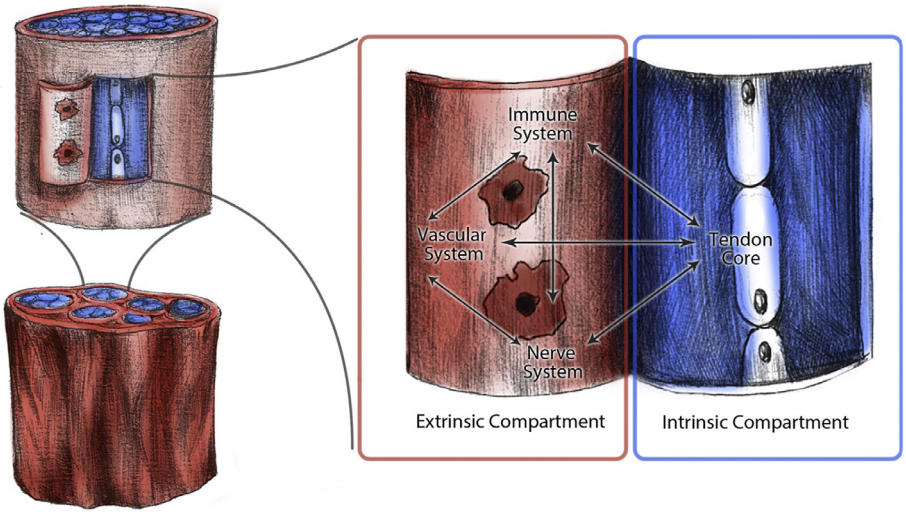

Fig. 1. Tendon is a complex physiological system. Tendon fascicles represent the basic unit comprising the "intrinsic compartment" (tendon cells and a multiscale arrangement of collagen assemblies). The "extrinsic tendon compartment" represents synovium-like tissues that connect to the immune, vascular, and nervous systems [19,20,24]. The possible synergism between the intrinsic and extrinsic compartment, and the role that individual compartments play in the maintenance of healthy tissue versus the initiation, progression and healing of tendinopathy, remains poorly understood [20–24].

pret research findings with respect to clinical reality. That said, the studies we highlight in this article are collectively coherent with clinical evidence from humans, and we interpreted them in the spirit of adding clarity to a still quite diffuse picture.

Ultimately, we wrote this perspective article with the aim to introduce a few essential elements of our own understanding of tendon structure, function, physiology, damage, and repair. We also aimed to provide a novel view on mechanically driven physiological mechanisms that may steer the balance between functional remodeling and chronic tendon disorders, and give a glimpse of how biomaterials could play a central role in future treatment strategies.

2. Muscle and tendon – An intricate, multiscale, multi-tissue handshake

This article focuses almost exclusively on the "tendon proper", and leaves aside a detailed consideration of the highly specialized muscle-tendon [27–29] and tendon-bone junctions [30–34]. Nonetheless, the structure of tendon proper is tightly coupled to the architecture and function of the muscle to which it is attached. The muscle-tendon unit is an exquisitely tuned viscoelastic structure with active and passive elements that both contribute to biomechanical function [35,36]. At the muscle-tendon junction, tendon fibers fan out like a river delta. Although the mechanical and physiological interactions between tendon and muscle remain poorly understood [27], the junction provides a mechanically stable transition with large contact surface between both tissues.

Collagen structures in healthy tendon tend to be highly-aligned [37] when compared to collagen structures in fascia, skin, joint capsules, and other tissues that bear more heterogeneous mechanical loads. Nonetheless there is a wide range of structural configurations that a tendon can adopt, in direct accordance with the diverse functional range of muscles to which they attach [37]. Tendons transferring muscle forces over longer distances generally display more aligned collagen structures (e.g. the digital flexor tendons, or rodent tail tendon) [38,39]. Tendons spanning shorter distances, or with broad insertions to the bone, may adopt a more distributed array of collagen structures (e.g. the rotator cuff tendons) [40]. In a similar vein, tendons emanating from "simple" muscles that generate torque around a single joint axis (e.g. the distal biceps tendon; the soleus tendon) are more likely to be highly crosslinked – reflecting the fact that collagen structures within these tendons are generally loaded in unison and toward a unified purpose [41,42]. Tendons that function over large ranges of motion or provide torque around multiple joint axes, feature anatomical subdivisions that are loaded depending on the current state of joint position and muscle activation (e.g. the deltoid; the gastrocnemius). Here a large degree of lateral sliding between collagen fascicles enables such joint motions [43–49].

3. The tendon proper, its composition and structure

One may consider the tendon proper (or midsubstance between the muscle and bone insertions) as being roughly composed of two, not always physically distinct, tissue compartments. The first (extrinsic) compartment is a family of synovium-like fascias that comprise the paratenon (tendon sheath), epitenon (subtendon sheath), and endotenon (fascicular sheath) [19]. These tissues include differentiated and progenitor cell populations related to the mesenchyme as well as the nervous, immune, and vascular systems [19]. The extrinsic compartment envelops the second (intrinsic) compartment, which is often referred to as the "tendon core". The tendon core consists of densely packed Type-I collagen matrix and the fibroblastic cells that maintain it [50]. Although increasingly realized to have distinct functions in the context of tendon disease and repair, the physiological roles of many of the cells within both compartments and possible communication between the compartments is still poorly understood [50–54]. We proceed by outlining what is known about the intrinsic compartment that

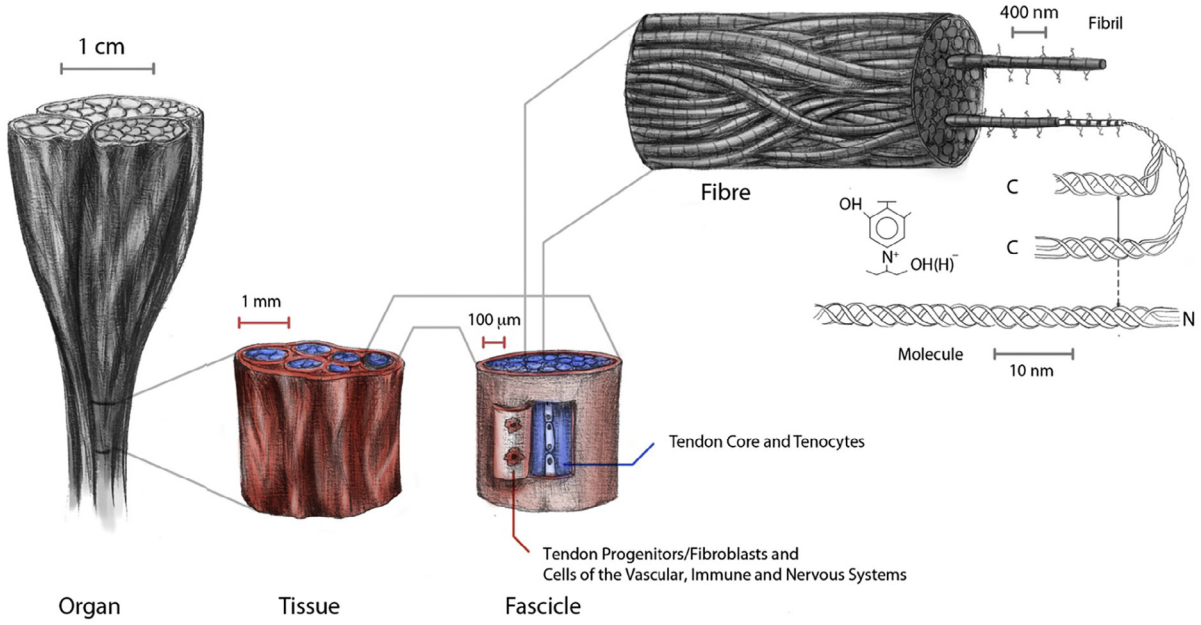

Fig. 2. Multi-scale tendon hierarchy. Cross-linked collagen molecules assembled into collagen fibrils make up the minimal structural/functional mechanical unit of the tendon core. The core consists of densely packed type-I collagen matrix and the fibroblastic cells that maintain it [17,55]. The tendon core is wrapped with endotenon (the lowest level extrinsic compartment) to form fascicles, i.e. "intrinsic tendon core structures" that form the basic functional unit of the tendon [19]. In turn, fascicles, cross-linked to various degrees, assemble into tissue level constructs, surrounded by the epitenon (mid-level extrinsic compartment) [50,52]. Finally, the highest level structural organization of tendon tissue reflects the organ that may or may not be surrounded by paratenon [19]. At three levels, interface "handshaking" between the intrinsic and extrinsic tendon compartments is possible.

gives the tissue its mechanical strength, and later return to the involvement of the extrinsic system in tendon maintenance, damage, and repair.

4. Tendon core – Multiscale structure and function

Our current understanding is that the tendon core is occupied by tendon fibroblasts (also widely referred to as tenocytes), with more diverse cell populations found in the tissue barriers that comprise the extrinsic compartment of the tendon [50,52]. Within a healthy tendon core, tenocytes attach to a highly ordered fibrillar collagen matrix (ECM) (Fig. 2) that is primarily composed of type-I collagen (65–80% of its dry mass), and small leucine-rich proteoglycans that regulate collagen self-assembly into collagen fibrils, which in turn are ordered by the cell into collagen fibers [17,55]. The structural terminology distinction is important – as fibrils are the basic subcellular collagen building blocks, whereas fibers are the relevant cell-scale structural units with which cells physically interact. The core tendon fibers are ultimately encompassed within "fascicles". A fascicle can be considered as the fundamental functional unit within the intrinsic tendon, embodying tenocytes and their collagen fibers within a structure that is delineated by the first synovial tissue barrier (endotenon). This tissue barrier represents the first interface of "handshaking" between the intrinsic and extrinsic tendon compartments. Higher level structural organization of tendon tissue reflects the function of the muscle-tendon

Table 1
Extracellular Matrix Components of Interest in Tendon Disease and Healing – Fibrillar Collagens: Key: "T": Transcriptome; "P": Proteins; "Both": Transcriptome & proteins; "RC": Rotator Cuff; "AC": Achilles tendon; "LHB": Long head of biceps tendon; "PT": Patellar tendon; "PTT": Posterior tibialis tendon; "+/−": Trend; "++/−−": Significant upregulation/downregulation; "+++/−−−": Highly significant upregulation/downregulation; "NC": No change; "ND": Not detected "LC-MS/MS": Liquid chromatography–mass spectrometry; "IHC/IF": Immunohistochemistry/Immunofluorescence; "WB": Western blot; "RT-PCR": Reverse transcription polymerase chain reaction; "ISH": In Situ Hybridization; "FTIR": Fourier transform infrared spectroscopy; "SDS-PAGE": Sodium Dodecyl Sulfate - Polyacrylamide Gel Electrophoresis.

ECM Component	Healthy Tendon	Tendinopathy				Comments	Refs
		Model	Species	Phenotype	Method		
Collagen Type I	-60–80% by dry weight -Highly ordered	Often disordered, may be elevated, or diminished.					
		Patient tissues	Human, ruptured AC	++	T: RT-PCR		[277]
		Patient and cadaveric tissues	Human, AC	++	T: cDNA array and RT-PCR		[278]
		Patient and cadaveric tissues	Human, different tendons	+++	T: RT-PCR		[279]
		Patient tissues	Human, AC	++	T: RT-PCR	Total collagen was unchanged	[280]
		Patient tissues	Human, PT	–	T: RT-PCR		[281]
		In vivo	Equine, SDFT	+	Both: ISH & IHC		[282]
		Patient tissues	Human, RC tears	–	P: FTIR		[283]
Collagen Type II	Typically, not present in healthy "mid-portion" tissue	Can be present in degenerated tissue, near zones of bony impingement or fibrocartilage					
		In vitro	Human, AT	+	P: IHC/ICC	Cells from Chondral Metaplasia of Calcific Insertional Tendinopathy	[284]
		Patient tissues	Human, PT	UC	T: RT-PCR		[281]
		Tendon biopsies	Human, AC	ND	P: IHC		[285]
		Patient tissues	Human, RC tears	–	P: FTIR		[283]
Collagen Type III	~3–5% of total collagen Limited to sheaths	- May be elevated in pathological tissue; Associated with collagen I fibers in the tendon enthesis and degenerated tendon - Associated with decreased strength and stiffness					
		Patient and cadaveric tissues	Human	+++	P: SDS-PAGE & WB		[286]
		Patient and cadaveric tissues	Human, AC	+++	P: Reverse phase-HPLC		[287]
		In vitro	Human, AC	++	P: ICC		[193]
		Patient and cadaveric tissues	Human, AC	++	T: cDNA array and RT-PCR		[278]
		In vivo	Rat, PT	+++	Both: RT-PCR and IHC		[288]
		Patient tissues	Human, different tendons	+++	T: GeneChip® microarray		[289]
		In vivo	Equine, SDFT	++	P: SDS-PAGE & IHC		[290] [291]
		Patient tissues	Human, RC tears	–	P: FTIR		[283]
		Patient tissues	Human, AC	++	T: RT-PCR	Unchanged total collagen	[280]
		Patient tissues	Human, PT	–	T: RT-PCR		[281]
Collagen Type V	Limited quantities	Patient tissues	Human, PST	+	P: IHC/ICC		[292]
Collagen Type VI		Patient tissues	Human, RC	++	P: Label-free quantitative LC-MS/MS		[293]
		Patient tissues	Human, RC tears	++	Both: RT-PCT & IF		[294]

Table 2
Extracellular Matrix Components of Interest in Tendon Disease and Healing – Glycoproteins: Key: "T": Transcriptome; "P": Proteins; "Both": Transcriptome & proteins; "RC": Rotator Cuff; "AC": Achilles tendon; "LHB": Long head of biceps tendon; "PT": Patellar tendon; "PTT": Posterior tibialis tendon; "+/−": Trend; "++/−−": Significant upregulation/downregulation; "+++/−−−": Highly significant upregulation/downregulation; "NC": No change; "ND": Not detected "LC-MS/MS": Liquid chromatography–mass spectrometry; "IHC/IF": Immunohistochemistry/Immunofluorescence; "WB": Western blot; "RT-PCR": Reverse transcription polymerase chain reaction; "ISH": In Situ Hybridization; "FTIR": Fourier transform infrared spectroscopy; "SDS-PAGE": Sodium Dodecyl Sulfate - Polyacrylamide Gel Electrophoresis.

ECM Component	Healthy Tendon	Tendinopathy				Comments	Refs
		Model	Species	Phenotype	Method		
Fibronectin	- Present in small quantities - Associated to vascular walls, myotendinous junction, and sheaths	Patient tissues	Human, AC	+	P: IHC		[295]
		In vivo	Equine, SDFT	+	P: IHC	Acute healing model of tendon injury	[296]
		Patient tissues	Human, RC	+++	P: IHC/IF		[297]
		Tendon biopsies	Human, AC	++	T: RT-PCR		[298]
		Patient tissues	Human, RC	+	P: Label-free quantitative LC-MS/MS	Fibronectin type III domains	[293]
Cartilage oligomeric matrix protein (COMP)	- Associated with collagens - Abundant in flexor tendons compared to extensors	Patient tissues	Human, RC	–	P: Label-free quantitative LC-MS/MS		[293]
		In vivo	Equine, SDFT	++	TP: ISH & IHC	Co-localized with collagen type III	[282]
		Explant model	Equine, SDFT	++	P: LC-MS & WB	Evidence of COMP fragmentation in response to IL-1β	[299]
Elastin	- Present in small quantities - Enriched in pericellular matrix	Patient tissues	Human, RC tears	NC	Both: RT-PCT & IF		[294]
		Patient and cadaveric tissues	Human, LHB	−−−	P: WB		[300]
		Patient tissues	Human, RC	ND	P: Label-free quantitative LC-MS/MS		[293]
		Patient tissues	Human, RC tears	–	P: FTIR		[283]
Fibrilin-1	- Present in small quantities - Enriched in pericellular matrix	Patient tissues	Human, RC tears	++	Both: RT-PCT & IF		[294]
		Patient tissues	Human, RC	–	P: Label-free quantitative LC-MS/MS		[293]
Fibulin-1		Patient tissues	Human, RC	–	P: Label-free quantitative LC-MS/MS		[293]

unit, with fascicle-fascicle kinematics (sliding and stretching) that dictate the mechanical behavior of the tendon [12,17,55–60].

The fibrillar collagen matrix also includes collagen III in various quantities. Collagen III synthesis is understood to be involved in early stages of wound repair, following on fibronectin matrix templating by tendon fibroblasts [61]. Increased presence of collagen III is considered to be a hallmark of degeneration, with adverse effects reflected in tissue disorder and reduced mechanical properties [62]. In lesser quantities, collagen V is another fibrillar protein present in tendon that plays a key role in ordering and stabilizing type-I collagen structures during collagen I self-assembly [63]. Proteomic screening studies have suggested that collagen Type VI may be an important component of the tendon ECM [64], being a pericellular matrix protein that plays a role in collagen fibrillogenesis [65]. Beyond the fibrillar collagens, elastin is a fibrillar glycoprotein contributing 1–2% of tendon dry mass that plays a role in recoil of the matrix after repetitive mechanical loading [66]. Binding the fibrillar matrix are numerous FACITs (fibril-associated collagens with interrupted triple helices) that regulate interactions between the fibrillar matrix and other ECM molecules. Surrounding the bundled components of the fibrillar matrix is a proteoglycan-rich matrix that is well hydrated, contributes to resistance against compressive mechanical stresses, and facilitates nutrient and metabolite diffusion. Among the important proteoglycans are the fibril bound small leucine-rich repeat proteoglycans (SLRPs) decorin and biglycan, whose core proteins are covalently bound to the "D-period" striations of type-I collagen fibrils at 67 nm intervals. The SLRPs are known to bind growth factors and a range of matrix proteins such as tenascin. They also play a pivotal role in fibrillogenesis, in both the formation and assembly of collagen fibrils [67].

It is known that diseased and poorly healed tendons often feature substantial structural and compositional ECM derangement [2]. Structural alterations that occur in the diseased tendon extracellular matrix are diverse and complex (Tables 1–3), with many open questions regarding the mechanisms that underlie the dysfunctional tendon ECM assembly [68]. Ultimately, tissue function requires cellular control over mechanical properties, with coordination of matrix assembly not only at the level of fibril and fiber, but also across higher size scales. In principle, there are many potential mechanisms that cells might exploit to regulate tendon mechanics and/or tune tendon tissue structure toward an optimized organ level function (Table 4). Which of these dominates tissue adaptation and repair remains only partly understood. Among long-standing questions are the relative contributions of the tendon synovial tissues (peritenon, endotenon) versus the tendon core in adaptation to increased mechanical demands or after traumatic injury [69,70]. How intrinsic and extrinsic healing mechanisms act, interact, and are regulated in diverse physiological contexts (development, homeostasis, repair) will require substantial research efforts to elucidate.

Table 3
Extracellular Matrix Components of Interest in Tendon Disease and Healing – Proteoglycans: Key: "T": Transcriptome; "P": Proteins; "Both": Transcriptome & proteins; "RC": Rotator Cuff; "AC": Achilles tendon; "LHB": Long head of biceps tendon; "PT": Patellar tendon; "PTT": Posterior tibialis tendon; "+/−": Trend; "++/−−": Significant upregulation/downregulation; "+++/−−−": Highly significant upregulation/downregulation; "NC": No change; "ND": Not detected "LC-MS/MS": Liquid chromatography–mass spectrometry; "IHC/IF": Immunohistochemistry/Immunofluorescence; "WB": Western blot; "RT-PCR": Reverse transcription polymerase chain reaction; "ISH": In Situ Hybridization; "FTIR": Fourier transform infrared spectroscopy; "SDS-PAGE": Sodium Dodecyl Sulfate – Polyacrylamide Gel Electrophoresis.

ECM Component	Healthy Tendon	Tendinopathy				Comments	Refs
		Model	Species	Phenotype	Method		
Decorin	- Most dominant PG - Found associated with dermatan sulfate in tendons	Patient tissues	Human, AC	–	T: cDNA arrays		[301]
		Patient tissues	Human, ruptured AC	++	T: RT-PCR		[277]
		Patient tissues	Human, LHB	NC	Both: RT-PCR and IHC		[302]
		Patient tissues	Human, PT	NC	T: RT-PCR		[281]
		Patient and cadaveric tissues	Human, AC	- NC (painful AC) - (ruptured AC)	T: RT-PCR		[303]
Biglycan	- Thought to contribute to growth factor and cytokine sequestration - Main ECM component of TSPCs niche [304]	Patient tissues	Human, PT	+	T: RT-PCR		[281]
		Patient and cadaveric tissues	Human, AC	+ (painful AC)	T: RT-PCR		[303]
		Patient tissues	Human, PTT	+	T: RT-PCR		[305]
		Tendon biopsies	Human, AC	+++	P: IHC		[285]
Aggrecan	- Enriched in areas subjected to compressive load (e.g. fibrocartilaginous zones in tendon)	Patient and cadaveric tissues	Human, AC	+ (painful AC)	T: RT-PCR		[303]
		Patient tissues	Human, PTT	+	T: RT-PCR		[305]
		Tendon biopsies	Human, AC	+++	P: IHC		[285]
Fibromodulin	- Main ECM component of TSPCs niche [304]	Patient tissues	Human, PT	–	T: RT-PCR		[281]
		Tendon biopsies	Human, AC	++	T: RT-PCR		[298]
Versican		Patient and cadaveric tissues	Human, different tendons	−−−	T: RT-PCR		[279]

Table 4
Structural Biology & Regulation of Collagen Matrix, Tissue, and Organ Mechanics.

Primary mechanisms to regulate mechanical properties	
Molecular scale	**Mediators of collagen fibril assembly:** Types of fibrillar collagen (Col-I vs Col III); Assembly mediators (e.g. FACITS, SLRPs), and relative content of other ECM molecules (e.g. elastin and GAGs)
	Crosslinking: Covalent bonds between collagen monomers (high cross-linking = stiff collagen fibrils, the basic tissue building blocks)
Cellular scale	**Fiber-Fiber Coupling:** May be covalent cross-linking, or physical entanglement between collagen fibers
Tissue scale	**Fascicle-Fascicle Coupling:** May be covalent cross-linking, and/or physical entanglement between collagen fascicles.
Organ scale	**Fascicle kinematics:** Higher order partitioning of fascicles or groups of fascicles that enable/prevent large kinematic movements between such structures
Secondary mechanisms to regulate mechanical properties	
Subcellular scale	**Collagen packing**: (length, diameter, directionality, tortuosity) of collagen fibrils
Across scales	**Collagen hydration:** (e.g. mediated by proteoglycan content; osmotic and hydrostatic force balance)

While the structural biology of tendon tissue is complex and thorough understanding is elusive, the emergent mechanical properties of tissue substructures across size scales have been heavily investigated in both animals and humans [59,71]. At the organ level, an enormous body of literature provides a highly variable range of reported mechanical properties [72]. The variability of reported mechanical properties reflects the manifold technical difficulties of characterization outside the body: precise dissection, robust mechanical clamping that avoids artefactual stresses in the tendon tissue, accurate measurement of tissue dimensions including cross-sections, limited visualization of tissue stretch versus kinematic movements within the tissue, and limitations on the application of theoretical engineering frameworks to describe the material properties of biological specimens. As such, in vivo measurements relying on non-invasive measurement of human tendon lengthening under voluntary muscle contraction provide something like a gold standard, with elastic moduli of the gastrocnemius tendon having been estimated within the range of 1–2 GPa under maximal stresses of 50–100 MPa, with tissue strains on the order of 10–15% [73]. These in vivo measurements well correspond to ex vivo experiments on the Achilles tendons [72] (Fig. 3).

At the level of the tendon fascicle – which, as mentioned, one may view as the "basic functional unit of tendon" – experiments on rat and mouse tail tendon form the basis of most of our knowledge. Rodent tail tendon fascicles can be isolated with minimal mechanical or biological damage, in contrast to more highly cross-linked tendons (e.g. the bovine Achilles tendon) that are difficult to isolate. Rat and mouse tail tendons thus have historically played an important role in studies of tendon structure-function [74]. Tail tendon explant models arguably provide the most reproducible and human-relevant *in vitro* models of tendon physiology that are available [75–79]. Regarding mechanical properties, rodent fascicles range in elastic modulus from several hundred MPa to over 1 GPa, depending on the anatomical location of tissue harvest, as well as the age, breed, sex, and/or diet of the animal [80–84]. The failure properties of isolated tail tendon fascicles reflect those of whole tendon, with failure stresses on the order of 80 MPa and failure strains of approximately 10% [72]. Mechanical properties at the fascicle level depend highly on the structural organization of the collagen fibers and the degree of cross-linking within and between fibers [85,86]. It is at the level of the fiber where biologically relevant cell-level mechanical stimuli emerge,

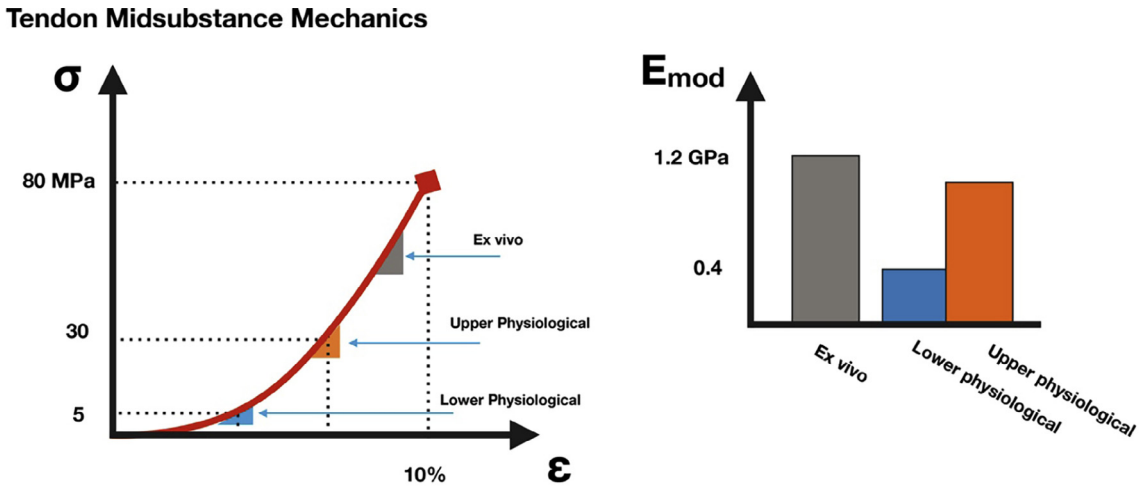

Fig. 3. The commonly measured "ex vivo" material curve of an isolated tendon or explant typically depicts the elastic modulus (E_{mod}), stress (σ) at failure, and strain (ε) at failure of the tendon midsubstance. In vivo ultrasound imaging has revealed that the nonlinear "toe region" corresponds to lower physiological loading by active muscle stresses, while maximal muscle contraction coincides with the upper physiological limit, i.e. the transition to a "linear region" in the tendon material curve [203]. This upper physiological tissue stiffness is generally representative for ex vivo measurements on tissue stiffness [72,73]. Numerous ex vivo experiments have shown that tendon tissue loads in the lower physiological "toe region" manifest as a progressive recruitment of higher-order collagen structures (fascicles, fibers) that increasingly align to the direction of applied loading, thus increasing tissue stiffness [59,71,87]. Although widely underappreciated, capturing physiological nonlinearity of the tissue is likely to be an important design goal of any effective biomaterial based therapy.

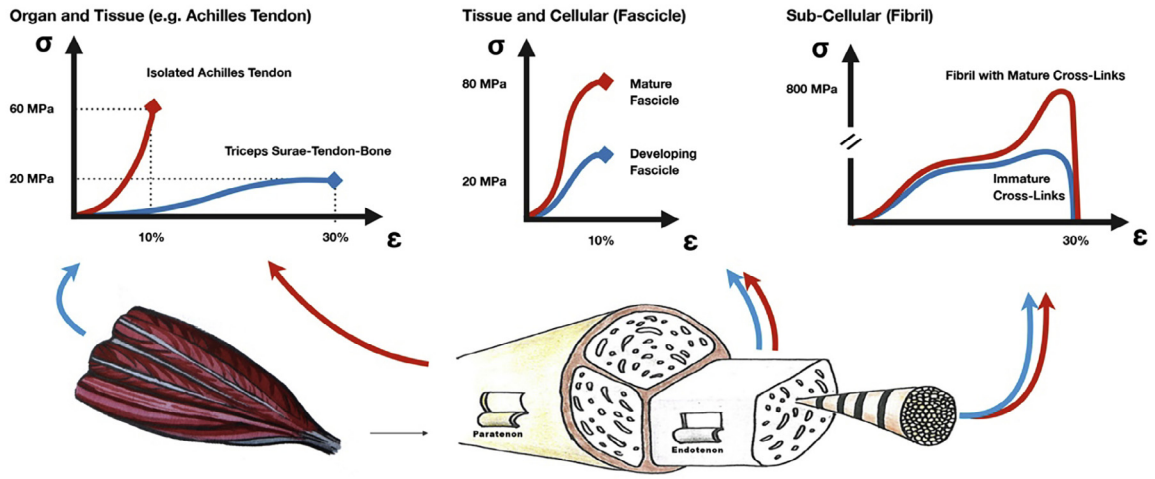

Fig. 4. Multi-scale architecture and molecular-scale biochemistry lie behind the overall mechanical function of the tendon. The mechanical properties of tendon emerge both from higher-level structures (grouped fascicles) and also from the basic building blocks (grouped fibrils) [12,17,55–60]. The passive mechanical properties of the entire organ (muscle-tendon-bone unit) reflect a highly deformable structure that is difficult to characterize ex vivo [10]. Isolation of tendon midsubstances facilitates characterization, and these range from moderately to extremely stiff with apparent elastic moduli (E_{mod}) on the order of 0.1 to 2 GPa [72,73]. Isolated tendon fascicles also demonstrate mechanical properties in this range, with elastic modulus and the tensile stress (σ) and strain (ε) at failure depending upon cellular-and molecular-scale factors such as collagen packing and cross-linking [90,105]. Lastly, mechanical properties of collagen fibrils are highly dominated by cross-link density, which explains their wide mechanical variability [56,57,85,101].

since the fiber comprises the structural unit with which tendon cells directly interact.

Finally, the properties of the individual collagen fibrils (submicron-scale) that comprise the collagen fiber (cell-scale) are increasingly well described [87–90]. These supramolecular collagen structures range in diameter from tens to hundreds of nanometers, with lengths that can span centimeters [91]. The collagen fibril is an exquisite example of cellular mediated protein self-assembly [92,93] – with emergent mechanical properties that depend on the diameter of the collagen fibril [88], as regulated by small leucine-rich proteoglycans [60,94–100]. The properties are also highly dependent on the extent of covalent collagen molecule cross-linking as regulated by the enzyme lysyl-oxidase [85,86,101–104]. Consequently, depending on the degree of collagen packing and extent of collagen crosslinking, collagen fibrils have elastic moduli on the order of several GPa, and failure properties on the order of 0.5–1 GPa [90,105].

The multi-scale assembly of tendon tissue, for which each scale is equipped with its own mechanical properties (Fig. 4), results in a tissue that is highly tunable towards its function [106]. Tendons that require an ability to respond to muscle contraction without much energy dissipation can be highly cross-linked to allow for minimal gliding (e.g. Achilles tendon), whereas others that are designed for more precise movements (e.g. the digital tendons) are low in cross-links [42]. Aging tendons are increasingly cross-linked resulting in altered viscoelastic properties, with potentially increased risk for micro-damage accumulation and onset of tendon disease [56,57,85,101].

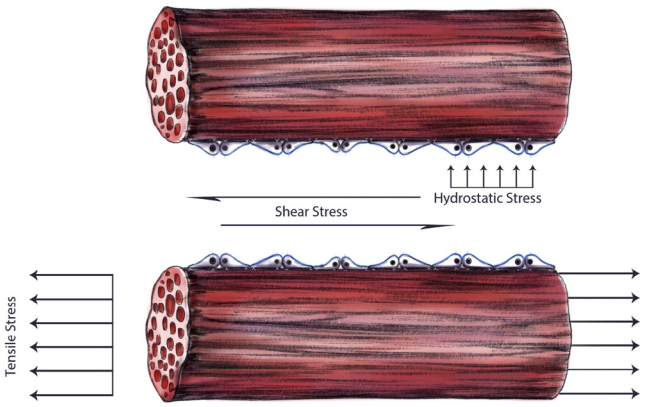

Fig. 5. Tendon tissue remodeling is driven by cell-level mechanical stresses, i.e. shear stresses from fluid flow and fascicle sliding, tensile stresses from direct elongation of collagen structures and hydrostatic stresses from the volumetric changes with external loading [116,138,139]. These mechanical stresses are responsible for the activation of candidate "vectors" by which tendon cells can potentially "transduce" mechanical forces within the tissue to regulate cell signaling and behavior: 1) stretch activated ion channels (SACs) as mechanosensitive ion channels, 2) focal adhesion-mediated mechanical signal transduction, 3) the primary cilium and 4) nuclear deformations [109–113,116].

4.1. The tendon cell as a mechanical sensor and arbiter of tendon structure

The paradigm that cell-level mechanical stresses drive tissue remodeling is a central tenet of mechanoregulation in bone, tendon and other tissues. The relationship between mechanical forces and functionally optimized tissue structure has been recognized for well over a century [107]. Tendon cells feature various cellular machineries for sensing a range of distinct mechanical stimuli within their matrix (Fig. 5) [108–110]. A cell can rapidly respond to tension and shear by adjusting its physical coupling to its local matrix [111,112], or by remodeling its cytoskeleton [113]. Such adjustments affect not only the loading of mechanosensory elements of the cell, but also affect sensory proteins within the cell membrane and nucleus that are mechanically coupled [114]. In the longer term, cells cope with transient mechanical perturbations by coordinating the structure and composition of the extracellular matrix until their mechanical environment reaches homeostasis [75]. In connective tissues like tendon this is primarily achieved by modulating the filamentous composition and structure of collagen networks [115]. In tendon tissue there are four candidate "vectors" by which tendon cells can potentially "transduce" mechanical forces within the tissue to regulate cell signaling and behavior (Fig. 6) [116].

4.1.1. Stretch activated ion channels (SACs) or other mechanosensitive channels

Due to their implication in muscle function and pathologies, particularly cardiac muscle, SACs are among the best characterized vectors for mechanical signal transduction in mammalian cells [117]. Mechanosensitive ion channels fall into three distinct families with the so-called Transient Receptor Potential (TRP) family representing a class of (non-specific) ion channels that has implications in mechanosensitivity of the musculoskeletal system [118,119]. Stretch-activated channels are triggered in response to local membrane tensions across the channel, and may be activated not only by tissue elongation, but also during tissue shearing, compression, and/or intra/extracellular osmotic pressure gradients [120–122].

4.1.2. Focal adhesion-mediated mechanical signal transduction

Because quiescent cells in healthy tendon tissue (tenocytes) are physically coupled to a collagen fiber, collagen fiber stretch is likely to play a role in biological response of the tissue to functional mechanical loading. Loss of collagen fiber tension has been shown to trigger downstream consequences including tenocyte apoptosis, collagen matrix protease secretion [123,124], and TGFβ1 signaling [125]. As such, it is reasonable to hypothesize that focal adhesion-mediated signaling may play a key role in tendon mechanotransduction [116]. While focal adhesion signaling has been shown to be important in tendon cell migration [126] and differentiation in models of tendon healing [127] – a specific role of focal adhesion-mediated mechanotransduction in tendon tissue homeostasis has not been clearly established. Age-related changes in extracellular matrix mechanics, particularly changes in elastic properties (i.e. fiber stretch), would be likely to affect cell-collagen binding and related focal adhesion mediated signaling

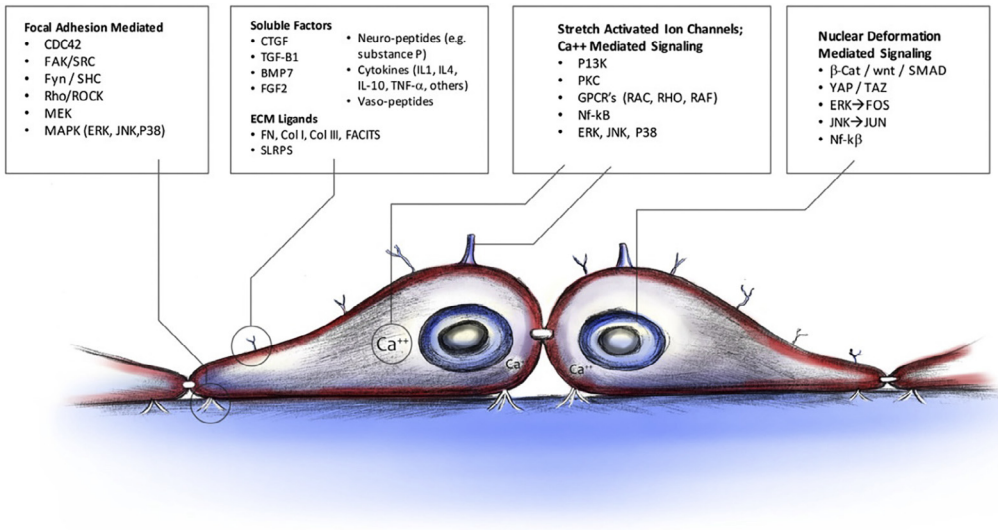

Fig. 6. The candidate "vectors" by which tendon cells can potentially transduce mechanical forces within the tissue to activate typical mechanotransduction pathways, resulting in a cellular response [116]. How mechanically activated downstream pathways potentially flip the balance between functional remodeling and fibrotic scarring will undoubtedly result in more targeted treatment of tendon disorders. For details on the pathways implicated in tendon mechanotransduction see [17,116,271–274].

[57], thus potentially playing a role in age-related tendon disorders.

4.1.3. The primary cilium

The primary cilium is a microtubular, mechanosensitive structure that extends like an antenna from the surface of most mammalian cell types [128]. The primary cilium has been established to be mechanosensory in epithelial cells, cartilage, and bone. In the latter, it has recently been linked to specific stretch-activated ion channel function [129]. Mechanosensory function of the primary cilium is tightly linked to SAC (e.g. Transient Receptor Potential Vanilloid 4) [130]. Little is actually known regarding the function of the primary cilia in tendon tissue mechanotransduction, however they have been identified in tendon cells [131], have been shown to deflect in response to applied mechanical tissue loads [132], and their length is apparently affected by mechanical signaling from the ECM [77,133]. Assuming that primary cilia play a central role as mechanosensory elements for tendon cells, we have hypothesized that age-related changes in the extracellular matrix, particularly loss of viscoelastic relative fiber movements (i.e. fiber shear), may have potentially adverse consequences for cell-mediated tissue homeostasis and repair [57,85].

4.1.4. Nuclear deformations

Accumulating evidence increasingly suggests that the cell nucleus is an important mechanosensitive element [134], with a mechanistic link between tissue-specific mechanical stresses and the structural composition of the cell's nuclear envelope. It has been demonstrated that mechanical distortion of the cell nucleus provokes a relative shift in nuclear envelope composition [109]. This change is not only associated with very direct modulation of several important cell signaling pathways [135], but may more generally regulate gene expression by physically modulating chromatin accessibility - potentially acting as a molecular "state switch" [110]. While tendon nuclei have been established to deform under tissue loading [136], a current challenge is to unravel the implications of these deformations. Again, age-related changes in the extracellular matrix, particularly loss of viscoelastic relative fiber movements (i.e. fiber shear) or diminished tissue hydration (i.e. matrix compression) are likely to potentially affect the manner in which the nucleus deforms under mechanical stress [85,136].

5. The fundamental role of mechanical forces in regulating tendon homeostasis and repair

Scarce data on mechanical regulation of tissue repair, leaves many open questions related to the role of external loading in healing outcomes. On one hand, sub-regions of weakened or otherwise damaged tissue likely create a cellular niche that may mechanically stimulate a tendon cell from normal quiescence into an active, reparative mode [43,69,137]. On the other hand, localized damage can also induce high stress concentrations and strains [137] that potentially overload sensory vectors to drive an adverse remodeling response [125] (Fig. 7). Important questions to be resolved here include "How does the intrinsic compartment deal with such (localized) damage and (locally) high matrix stresses?", "How is the extrinsic compartment activated?", and "How does cross-talk between both compartments contribute to repair quality?".

Although we remain far from full understanding, numerous interacting cellular and inter-cellular signaling pathways have been shown to be directly regulated by mechanical load [116,138] and play a role in the adaptive response towards new homeostasis [139]. We suspect that tendon cell sensitivity and downstream signaling response to these mechanical triggers is modulated by the overall state of health of both the intrinsic (matrix structure & composition) and extrinsic compartments (tissue vascularity, state of inflammation, pain) [24,140,141]. When loaded above a certain threshold, functional adaptation is a likely result. Convincing support from models of partial tissue dissection, where loads are shunted to intact tissue, show resulting anabolic net synthesis of functional collagen matrix, probably in direct response to increased mechanical stresses and strains in the tissue [43,69,137]. Additionally, mechanical loading has been observed to upregulate collagen synthesis of tendon fascicles [142] and whole tendons [143]. Although net collagen synthesis is generally viewed as a positive sign of functional healing, how these collagens are structured is also important (highly aligned vs. more randomly distributed). Conversely, much evidence suggests that both overload and underload (e.g. post-rupture) of tendon tissues can trigger net catabolic matrix remodeling pathways [123,124,144,145]. However, the complexity of tissue response to mechanical loading viewed in terms of associated collagen turnover [146] is exacerbated by the multi-faceted role that remodeling enzymes play in tissue remodeling.

The breakdown of damaged tendon collagen matrix, and the initiation of various tissue repair events, centrally involves matrix metalloproteinases (MMPs) [147–149]. In tendon, there is a close but still poorly understood relationship between mechanically mediated MMP activity/inhibition, and how MMP-regulated signaling may govern collagen matrix modeling and remodeling [150]. In tendon, triggering of MMP activity is thought to be driven both by increased mechanical stimulus (tissue overload) as well as removal of mechanical stimulus (e.g. breakage of elastic matrix fibers; loss of cellular pre-tension) [123,124,144,145]. Also important in this frame are tissue inhibitors of metalloproteinases (TIMPs) known to regulate MMP activity and ECM turnover [12]. TIMPs act as endogenous inhibitors of MMPs by binding to the active site of the MMP catalytic domain [151]. Four TIMPs have so far been identified, with all being expressed in tendon tissue [151]. Similar to MMPs, mechanical regulation of TIMP activity is central among a wider range of signaling pathways, with many of these still being poorly understood [2,147–149,152–154]. Since the interplay between MMPs and TIMPs drives tissue remodeling outcome [147–149,153–158], the role of both MMPs and TIMPs are highly contextual, both spatially and temporally [147,148,158].

The matrix metalloproteinases most likely to play central roles in immediate tendon tissue response to mechanical loading/damage include the "collagenase" MMPs that degrade fibrillar assemblies of triple helix collagen molecules (MMP-1, MMP-8, and MMP-13), the "gelatinase" MMPs that target Type-III collagen and Type-I collagen fragments (MMP-2 and MMP-9), and finally the so-called membrane-type 1 MMP (MT1-MMP, also known as MMP-14) that has been shown to play an essential role in enabling fibroblast motility within tightly packed ECM of many connective tissues [152,159]. An immense body of scientific work has shown that connective tissue MMP gene expression is regulated by various cytokines and signaling molecules (most importantly TGF-β, IL-1β, TNF-α, and Wnt) [160–165] but it is only vaguely understood how these signal transduction pathways are initiated and then coordinated toward a successful tissue repair [152]. Substantial scientific research effort is required to enable better understanding of how these aspects contribute to tissue repair outcome.

Aside from local mechanical regulation of MMP expression, apoptotic pathways have been shown to be initiated by mechanical overload/matrix damage [125]. The acute disruption of the tendon collagen matrix has been shown to trigger release/activation of transforming growth factor (TGF)-β (perhaps secondary to MMP-mediated breakdown of the ECM) that subsequently has been tied to apoptosis in tenocytes (as demonstrated by prevention of apoptosis by the small molecule TGF-β receptor inhibitor SD208 [125]).

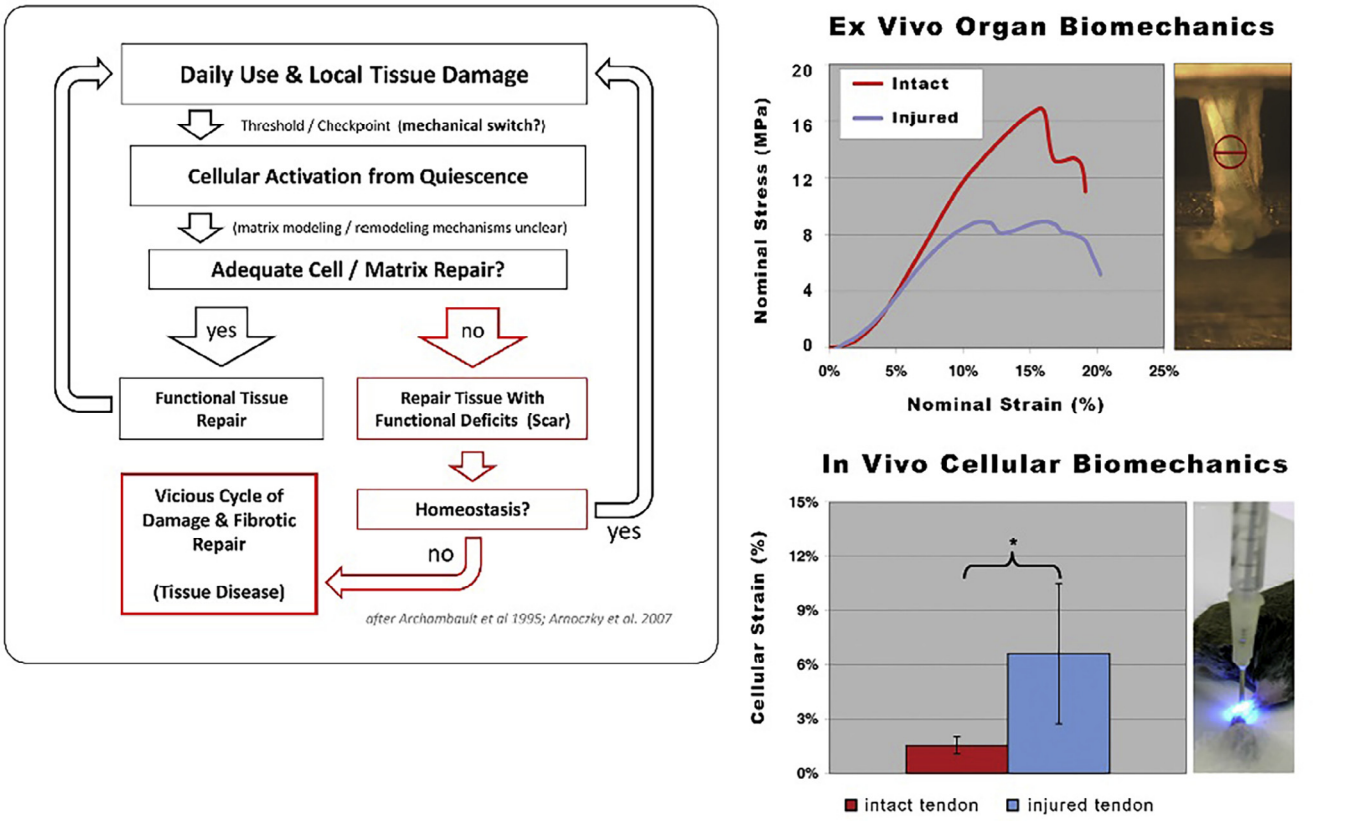

Fig. 7. (Left) We extend Arnoczky's paradigm of damage-mediated tissue remodeling to consider in detail how tendon damage leads to shunting of mechanical loads to the remaining intact tissues that may provoke a (dys)functional cellular response [43,275,276]. (Right) Our own experiments have shown that resection of the medial gastrocnemius leads to reduced nominal stress (upper image) but elevated cell-level strains in the remaining tendons (lower image)[43]. In intact murine tendon, such cell-level strains remain consistently below 3% – a threshold that is dramatically exceeded after tendon injury. These data support that "mechanical overload" could be an important factor in the onset of cell-induced tissue remodeling.

Although this sequence of events (acute matrix disruption, TGF-β activation, apoptosis) has been demonstrated to occur in vivo, important mechanistic details are still lacking on how this process is mediated by mechanical forces [166].

6. Tendon damage and Repair: Intrinsic microdamage vs. Damage crossing tissue compartments

We consider tendon damage as being conceptually dividable into two subclasses: acute damage (traumatic damage of previously healthy tissue), and chronic (degenerative) damage. Acute injuries (e.g. laceration of the finger flexor tendons) involve a sudden external disruption of originally healthy tendon. Although such injuries often heal with acceptable recovery of function, the tissue quality of biological and/or surgical repair rarely returns to preinjury levels [5,167]. Tendon ruptures may also occur spontaneously during activities of daily living. It is now widely viewed that such tendon ruptures can be attributed to underlying accumulated tissue damage associated with degenerative tissue remodeling processes [168].

Tendon matrix damage can stem from many sources including acute tearing or cutting, oxidative damage [169], accumulation of micro-tears [170–174], or de novo generation of aberrant matrix within the tendon (e.g. ectopic calcification) [175,176]. Damage may ultimately result in the mechanical and biological propagation of a tendon lesion until catastrophic structural disruption at the organ level (Fig. 8). Strikingly little is known regarding the actual mechanisms by which originally healthy tendon accumulates damage, and then how the intrinsic and extrinsic compartments activate and coordinate tissue remodeling [18,21–23]. Only slightly more is known about this process after acute injury, however studies using animal models of acute injury and repair are beginning to shed some light [53,54].

Consistent with the classic view of wound healing, tendon injuries first repair with an initial matrix that provides both stop-gap mechanical integrity and a tissue template to guide later matrix remodeling [177–179]. The cells that participate in this early repair are thought to originate primarily from the extrinsic compartments, as resident cells of the intrinsic tendon core are understood to be limited in their reparative capacity, with low numbers and a low metabolic rate [180–182]. As such, repair of larger tissue defects likely involves cells from the epitenon and endotenon that migrate into the wound [23,183]. The coordinated activities of cells from these two compartments has been suggested to promote optimal healing [184], and extrinsic compartment involvement in healing is often demonstrated as extensive vascular and nerve outgrowth from the peritenon into the tendon proper [19,184–188]. Here the tissue barriers between the intrinsic and extrinsic compartments are violated, following a classic wound healing paradigm that includes bleeding, clot formation, recruitment of immune and progenitor cells to an assembly of granulation tissue, early tissue remodeling, and finally late tissue remodeling that should ideally involve resolution and retreat of neo-vasculature and neo-innervation (Fig. 9) [9,18,187]. Inflammation plays a key role in the early stages of healing, with intricate coordination and cross-talk between the tendon core and the vascular, nervous,

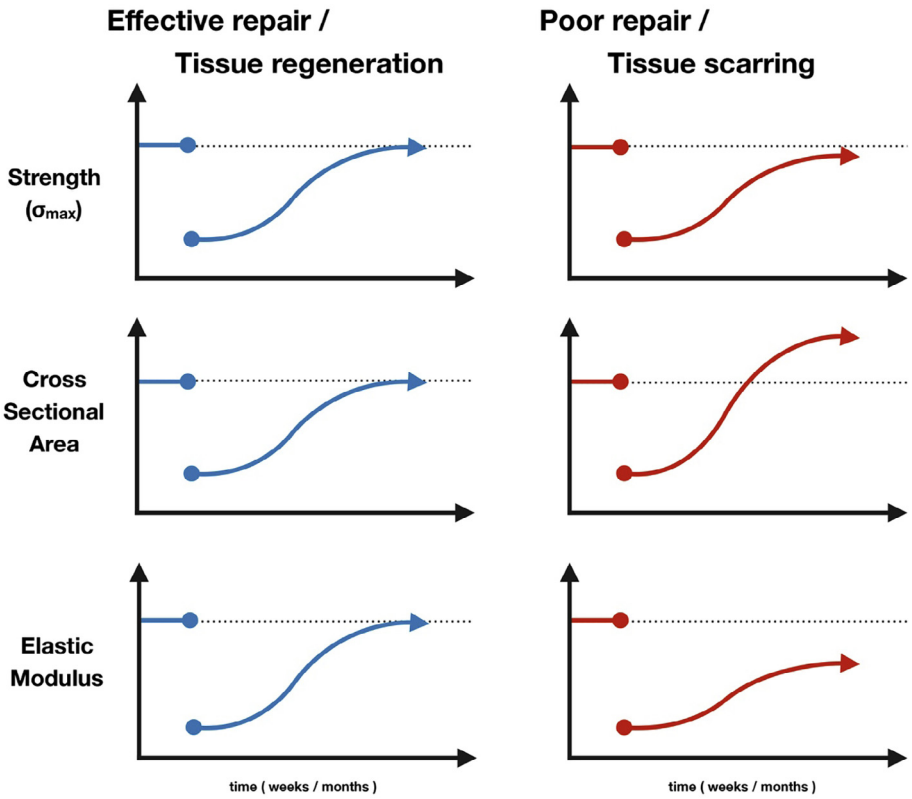

Fig. 8. (Left) A schematic representation of "ideal" tendon healing after which a tendon recovers its pre-injury strength, dimensions, and material quality. (Right) The typical course of tissue healing by scar formation leads to near-full recovery of tissue strength, but with non-efficiently packaged collagen structures and an accordingly diminished "material quality" as reflected by lower elastic modulus.

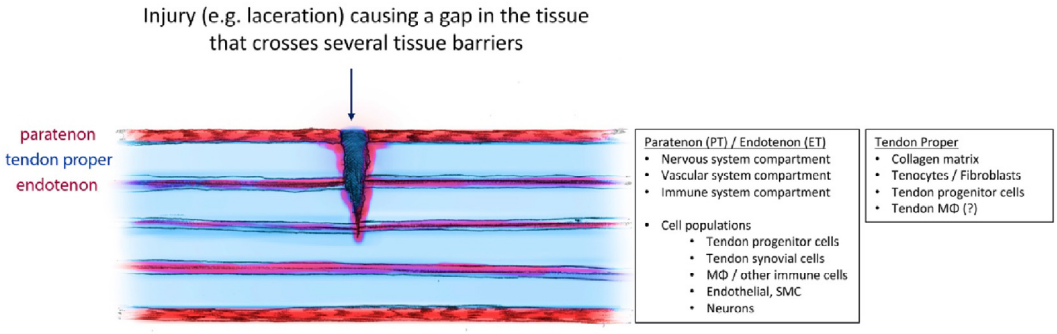

Fig. 9. An acute injury crosses from the intrinsic tendon core into the extrinsic (synovial) tissue compartment. Thus, tendon healing after rupture involves complex coordination between the tendon proper and the vascular, nervous, and immune systems [18,21–23]. Healing after such injuries generally results in a scar tissue that fails to re-establish tissue boundaries to appropriately compartmentalize the tissue [189,190]. This lack of compartmentalization may adversely affect tendon function (multi-scale structure-function) and may prevent a return to homeostasis of the tendon.

and immune systems [24,52]. The complexity of these interactions is potentially immense, and elucidation of them will be a major area of research focus in the coming years.

An important consequence of the involvement of the extrinsic compartment is the formation of a fibrotic scar [189,190]. Tendon scar tissue is generally characterized by resident cell phenotypes that differ from healthy tenocytes in morphology and function [139,191]. The matrix surrounding these cells is typically less well-structured, with inadequate hierarchical compartmentalization at the level of fascicles and above, and relatively disordered collagen structures at the level of fibers and below [192]. Additionally, the associated biochemical composition of the tissue may promote a chronic state of tissue inflammation, since among others pathological levels of collagen III with fewer cross links and increased presence of fragmented fibronectin are detected [191,193–199]. At the levels of the tissue and organ, the effect of this aberrant tissue remodeling is an increased tendon cross-section that can provide adequate overall strength, but with suboptimal stiffness and function [8,200–203]. In synovial tendons such as the digital flexors of the hand, the scar tissue may become entwined with the tendon sheath [204–206]. Such adhesions can severely limit joint function, and are a common complication following surgical tendon repair [204–206]. However, the manner in which injury is initiated remains a poor predictor of whether the affected tissue will proceed to functional healing, chronic scarring or adhesion formation.

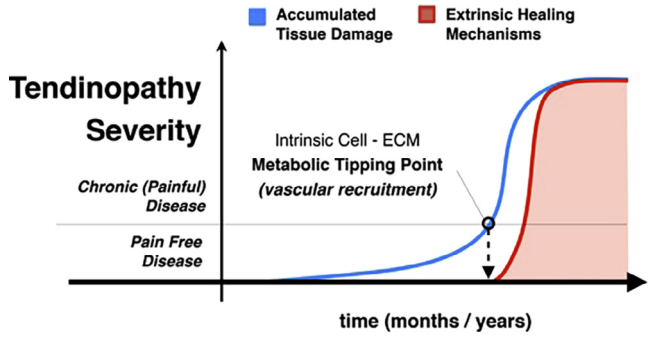

Fig. 10. A proposed mechanism for development of painful tendinopathy. Damage accumulates in the tendon until "intrinsic repair mechanisms" are overwhelmed. At this point, the metabolic cost of extracellular matrix remodeling exceeds the locally available nutrient supply. At this "Metabolic Tipping Point", the vascular system is recruited along with accompanying nerve supply (and pain) and the tissue enters into a chronic disease state characterized by high matrix turnover and increasingly poor tissue quality.

Many key details of the repair response remain unclear: Which are the cell-level stimuli that trigger central aspects of matrix synthesis and remodeling? Do tenocytes modulate intrinsic tendon matrix repair, or is the process coordinated by cells from the extrinsic tendon compartment? If any individual tendon cell becomes activated, what is its role in the repair process, and what becomes of these cells after the repair is achieved? What are the interactions between the intrinsic compartment, and neurovascular and immune components of the extrinsic compartment?

7. A suggested paradigm to explain the onset and propagation of degenerative tendon disease

Poor clinical outcome in both acute and chronic tendon disorders is multi-factorial, and not only due to limited intrinsic regenerative capacity of the tendon core [180–182]. Complex interactions between the tendon core and the vascular, nervous, and immune system components of the extrinsic (synovial) compartment of the tendon play a major, but poorly understood role [18,21–23]. In chronic tendon disorders we propose that a progressive accumulation of intrinsic tissue damage occurs until the tendon core reaches a "metabolic tipping point" (Fig. 10). Based on our own collective experiences in the laboratory, we speculate that this tipping point is reached when the metabolic demands of the tendon core (activated by mechanical stimulus) exceed the available nutrient supply of the normally avascular core [140]. Beyond this tipping point, we suspect that the extrinsic tissue compartment is recruited by the tendon core to participate in organ/tissue remodelling (Fig. 11). This could be a chemotactic process whereby low oxygen levels and high lactate levels stimulate angiogenesis [186], mediated by the release of TGF-β1 and VEGF [184,207]. This paradigm resonates with studies using animal models that report mechanical overload triggers appositional tendon growth at the organ perimeter [69]. We suspect that mechanically driven recruitment of vasculature and associated nerve supply to the tendon core may lie at the cause of tendon disease and the tendon pain that often accompanies chronic tendon disease [208]. Relatedly, we speculate that tissue vascularity and innervation that fail to fully resolve after a tendon disruption may lie behind perpetuation of chronic tendon disease. While the importance of cross-talk between the nervous system the vascular supply is increasingly appreciated [209], how this signaling may be dysregulated is relatively unexplored [20], providing substantial ground for fruitful future study, and potential therapeutic exploitation.

8. Unmet clinical needs, and the role of biomaterials in addressing tendon disorders

In our view, the application of biomaterials to the clinical treatment of tendon disorders falls into three potentially overlapping categories: drug delivery, mechanical augmentation, and re-establishment of appropriate tissue compartmentalization. Although any biomaterial-based therapy will likely aim to address several of these aspects, the functional needs are distinct and should be explicitly considered.

- **Mechanical augmentation** is important for short- and medium-term survival of a surgical repair. This demand reflects the immediate need to restore functional continuity ("primary

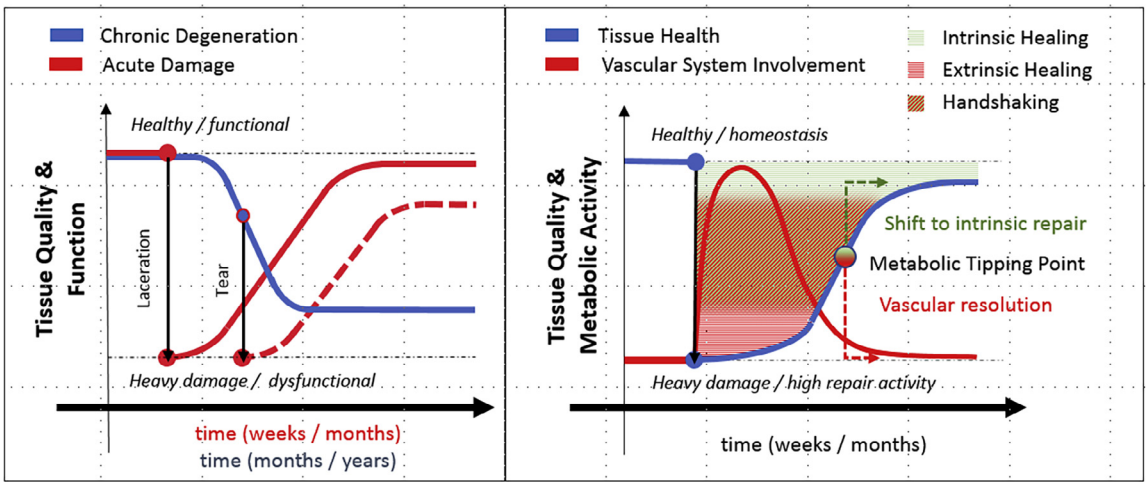

Fig. 11. (Left): Acute tendon injury typically manifests as either a laceration of originally healthy and intact tissue, or as a rupture of already degenerated tissue [168]. In the case of a laceration, the tissue ideally returns to pre-injury quality and function. However, injured tendon often does not fully attain "normal" levels of tissue quality and function, particularly in torn tendons with pre-existing tissue degeneration [5,167]. (Right): Following acute injury, the extrinsic healing system (vasculature, nerve, and immune system) is heavily involved in early stages of wound healing [19,184–188]. Ideally, the involvement of these systems resolves over time, with vascular system suppression perhaps being tightly coordinated by the intrinsic tendon compartment. A successful tissue repair process should thus conclude with "fine tuning" within the tendon proper, as the organ returns to levels of pre-injury function.

stability") of the muscle-tendon-bone unit. Augmentation should aim to facilitate optimal tissue templating and initial tissue remodeling – setting the longer-term repair process onto a good track.

- **Guiding appropriate tissue compartmentalization** is well appreciated in the context of preventing formation of adhesions between the tendon sheath and surrounding tissues [204–206,210]. However, the subtler need for appropriate "internal compartmentalization" is less well recognized (Fig. 9). As we have discussed in previous sections, individual tendon architecture is exquisitely tuned for optimal function, and scar-like healing generally fails to return to its pre-injury structure. Biomaterials that can guide fine tuning of tendon structure may play an important role in longer term recovery of tissue structure and biomechanical function.
- **Bioactive biomaterials and drug delivery:** As a poorly vascularized tissue, without identified tissue specific surface receptors, systemic delivery of pharmacologic agents to treat tendons is not likely to be efficient or effective. Appropriately timed, locally targeted delivery of pharmacological agents from biomaterial carriers will continue to be a major topic in tendon research for the foreseeable future.

In the section below, we very briefly summarize the main subfields of biomaterial development in the context of tendon disease, and tendon repair. This review is far from comprehensive, and we refer the interested reader to excellent focused reviews [187,211–213].

8.1. Injectable gels for drug delivery (tendinopathy, tendon repair)

Injection of biopolymers, such as collagen or fibrin gels [214,215], provides a potential minimally-invasive technique to locally administer a combination of structural proteins and a plethora of bioactive molecules that can potentially favorably assist in the healing process [187]. Collagen type I is "tissue-mimetic" and may eventually integrate to the host, whereas fibrin should predominantly function as a provisional scaffold and a carrier for bioactive molecules [216,217]. Both collagen [200,218–220] and fibrin [221–223] have been used for tendon healing and ligament fusion with occasionally promising results, however restoring native mechanical properties remains an open challenge [221,223]. One possible hurdle to overcome is the fact that once injected, the materials polymerize into randomly organized scaffolds that may provide a suboptimal, or even scar-inducing, tissue template. Tendon cells from the intrinsic compartment, as well as migrated progenitors from the extrinsic compartment show poorer tenogenic expression when exposed to a randomly organized niche, compared to an aligned niche [224–229,306]. A promising development therefore is the fabrication of aligned collagen constructs [230], which recently have been produced with properties that resemble native tendon tissue [231,232]. A potentially promising future direction may be to engineer injectable gels that adopt an aligned configuration upon administration, providing a tissue template for re-establishing a native tissue multi-scale architecture. Additionally, drugs delivered via such scaffolds may aid in pushing the resident and recruited cells to remodel the ECM into a native-like structure.

8.2. Tissue grafts (tendon repair)

In the case that inadequate native tissue exists to bridge a torn tendon or ligament autografts, allografts or xenografts can be used to bridge such defects [187]. Surgical reconstruction of tendons using grafts often result in suboptimal clinical outcome for various reasons, including donor site morbidity [233,234], immunological rejection [235] and poor graft integration [236,237]. These drawbacks accompany re-tears in 35 to 95% of cases [238,239], although these rates depend highly on the clinical indication and the individual case. Autografts remain the gold-standard, despite inevitable short- and medium-term donor site morbidity that manifests as muscle weakness. Although autograft material immediately provides a well-structured tissue with potentially appropriate material properties, cell-matrix remodeling typically resets the structure of the graft, and can resemble healing stages after tendon injury or even tendinopathy. The result is diminished mechanical properties compared to the initial graft, decreased structural quality of the tissue [240] and occasional adhesion formation [210].

We speculate that graft remodeling involves a high metabolic demand on the resident cells, and may cross the metabolic tipping point - then driving the graft into a potentially adverse response. Excised grafts, irrespective of the source, are completely cut off from an already limited blood supply. Still viable resident cells in an autograft will be exposed to a low-nutrient environment may then potentially recruit participation from the extrinsic compartment. This may plausibly explain why autografts do not generally perform superiorly better than allografts [210,241–243]. A promising approach to promote beneficial graft remodeling may be to functionalize the graft with bioactive molecules [244], however such approaches are still in their very early stages and lack clinical evidence of efficacy.

8.3. Synthetic (Non)-Degradable materials (tendon repair)

In view of the drawbacks associated with tissue grafts, the development of novel biomaterial implants will play an important future role, and the potential range of biomaterials that could be usefully employed is immense. However, the functional requirements on a synthetic tendon graft may provide unifying themes to guide the design of next generation implants: 1) A graft must provide adequate mechanical strength and resistance to mechanical damage until host tissue is able to compensate for degrading implant function over time 2) An implant should provide strong contextual cues (structure, biochemical, mechanical) to guide graft integration in an aggressive biophysical environment (limited baseline regenerative capacity, aberrant mechanical cues, inflammation, predisposition of host tissue toward a net catabolic turnover).

Synthetic grafts have therefore been exploited for repair, as reviewed recently [187,245,246], ranging from grafts based on e.g. polyester [247–251], polypropylene [252,253], polyethelene(-terephthalate) [254–258] and carbon [259,260]. Despite the success reported for these non-degradable scaffold materials, the high mechanical demands on a tendon (or ligament) graft have not resulted in long-term, functional repair [187]. Among the many materials that may potentially bridge between short- and medium-term mechanical stability and longer-term tissue integration – silk has emerged as a potentially interesting candidate material. Because of negligible loss of tensile strength in vivo, silk is considered by many as a non-degradable material. In practice however, silk is enzymatically degradable in vivo, but over an extended period of time [261]. Silk has been used extensively in the repair of tendon ruptures, primarily as suture material [262,263], and has shown tenogenic potential [229,264] and tendon regenerative potential [265,266]. Silk scaffolds have shown promising results when tested in large animal models as candidates for ACL replacement [267]. Silks fibers also are amenable to manufacture in various structures that can capture a range of tissue level mechanical properties. Using various wiring methods, mechanical properties in the range of the native ACL could be attained [268]. Silk grafts have also been successfully combined with osteoconductive biomaterials in large animal models to

achieve native-like histological integration in a bone tunnel [269,270] with adequate mechanical stability up to 6 months after reconstruction [269]. Still, it should be recognized that synthetic grafts for tendon and ligament repair face an uphill climb in terms of convincing clinicians to adopt them into daily practice.

9. Concluding statement

Tendon tissue repair involves a complex coordination between the intrinsic tendon core tissue, and the extrinsic synovial tissues that surround it. In this perspective article, we suggest that metabolic demands on resident tendon cells may play a key role in regulating the interplay between these tissue compartments. We describe a threshold we dub the "metabolic tipping point", which delineates a balance between recruitment and suppression of the extrinsic vascular-nervous system. This in turn may differentially steer tendon towards either functional remodeling or degenerative disease. We believe that future research must focus on better understanding the handshaking between the intrinsic and extrinsic tendon compartments in the disease and repair processes. These efforts will be challenging, but may open paths to better addressing tendon disorders in the clinic.

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