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Impact of Aging on Tendon Homeostasis, Tendinopathy Development, and Impaired Healing

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Abstract

Aging is a complex and progressive process where the tissues of the body demonstrate a decreased ability to maintain homeostasis. During aging, there are substantial cellular and molecular changes, with a subsequent increase in susceptibility to pathological degeneration of normal tissue function. In tendon, aging results in well characterized alterations in extracellular matrix (ECM) structure and composition. In addition, the cellular environment of aged tendons is altered, including a marked decrease in cell density and metabolic activity, as well as an increase in cellular senescence. Collectively, these degenerative changes make aging a key risk factor for the development of tendinopathies and can increase the frequency of tendon injuries. However, inconsistencies in the extent of age-related degenerative impairments in tendons have been reported, likely due to differences in how “old” and “young” age-groups have been defined, differences between anatomically distinct tendons, and differences between animal models that have been utilized to study the impact of aging on tendon homeostasis. In this review, we address these issues by summarizing data by well-defined age categories (young adults, middle-aged, and aged) and from anatomically distinct tendon types. We then summarize in detail how aging affects tendon mechanics, structure, composition, and the cellular environment based on current data and underscore what is currently not known. Finally, we discuss gaps in the current understanding of tendon aging and propose key avenues for future research that can shed light on the specific mechanisms of tendon pathogenesis due to aging.

Keywords

Tendon; Aging; Tendinopathy; Tendon Healing; Extracellular Matrix; Senescence

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Introduction

Aging results in decline of tissue homeostasis and regenerative capacity after injury. The number of individuals worldwide aged 60 and over is projected to double in the next 35 years [1]. An increasing number of individuals in this population will require healthcare, as adults aged 65 and over are twice as likely to be admitted to a hospital in comparison with adults ages 45-64 [2]. Given these statistics, focus should be placed on understanding the effects of aging on the systemic, tissue, and cellular levels to improve both health span and lifespan of aged individuals.

To better understand the different age-related impairments in the cellular and molecular levels across different organisms and tissues, previous studies have come up with aging hallmarks such as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, dysregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem-cell exhaustion, and altered intercellular communication [3, 4]. Aged tendons are characterized by impairments in homeostasis, acceleration of tendinopathy, and inferior healing outcomes after injury. Specifically, some of the aging hallmarks that have been identified in tendons are cellular senescence, stem/progenitor cell exhaustion, loss of proteostasis, and altered inter-cellular communication [5-13]. In addition, aged tendons exhibit changes in extracellular matrix (ECM) proteins composition and turnover, bulk tissue degeneration, changes in biomechanical properties and, in some cases, increased vascularization and innervation [9, 14-25]. However, in assessing the literature on the tendon response to aging, many inconsistencies or controversies were identified. A primary reason for these discrepancies relates to the different definitions of “aged” and “young”, and the specific model ages that were used. Several studies have used “middle-aged” animals as an “aged” group, or “young” animals as a “middle-aged” group. Second, the effects of aging in anatomically distinct tendons may differ to some extent, although it has not been directly tested. Third, some studies have focused on animal (mouse, rat, rabbit, horse, zebrafish) tendons, while other studies have used human tendons. In this review, we address these issues by collating data using well-defined age categories. We have also separated the results based on both the anatomical positioning of tendons and its source (different animal or human tendons). Therefore, we separated the age-groups into three different categories: the “young adult” group that corresponds to human ages between 20s and 30s, the “middle-age” group, that corresponds to human years between 40s and 50s, and finally, the “aged” group, that corresponds to 65+ year old humans (Table 1) [26-37]. Despite the use of these age brackets, it is important to acknowledge that there is a high level of phenotypic and functional diversity within the ‘aged’ group. However, for the purposes of this review and given that there are insufficient studies that address specific differences between such sub-groups, we have grouped them together.

Tendon response to aging: Biomechanics and function

Tendon mechanical properties are important parameters that define the structural, functional, and material quality of the tissue. Elastic structural mechanical properties such as the peak load and stiffness provide information about the tissue’s structural mechanical integrity and are dependent on the cross-sectional area of the tissue. In contrast, elastic material

properties such as the peak stress and elastic modulus provide information about the intrinsic material quality of the tissue independent of tissue cross-sectional area. Finally, viscoelastic mechanical properties such as percent (%) relaxation, provide information about how viscous or elastic the tendon is in a time-dependent manner. Due to their importance in terms of assessing structure and function, quantification of tendon mechanical properties during aging has been the primary focus of many studies [14-16, 18, 24, 38-52]. Below, we review studies that compare tendon mechanical properties between young adult and middle-aged animals and humans, followed by a comparison of mechanical properties between young adult and aged animals and humans. These findings are summarized in Fig. 1

Tendon biomechanics of middle-aged vs young adults:

Research studies have primarily utilized animal models to understand the effect of aging on tendon biomechanics between middle-aged and young adult subjects. With age, tendon structural mechanics remain similar [15, 24], suggesting that by adulthood tendons have reached their peak structural mechanics values (e.g., stiffness) and are maintained at these levels during the middle-age. For example, both peak load and stiffness of middle-aged rabbit and rat Achilles tendons (ATs) were similar compared to young adult counterparts [15, 24]. In contrast, there seems to be a different story when it comes to tendon material properties. Middle-aged tail tendons (TTs) have increased material properties relative to young adults [38], while middle-aged ATs and supraspinatus tendons (SSTs) from rabbits and mice were found to have similar material properties relative to their young adult littermates [15, 18]. Finally, other studies found that some material properties were decreased, while other remained similar [14, 24]. One potential interpretation of such discrepancies is that anatomically distinct tendons are differentially affected by age. For example, TTs were found to have increased material properties with age [38] in contrast to PTs and ATs where such changes were not consistent [14, 24]. Second, such discrepancies might exist because of a species-specific effect of aging in tendons. For example, middle-aged ATs from rats had a decreased elastic modulus compared to young adult littermates, while ATs from middle-aged rabbits had similar elastic modulus values compared to their young adult littermates [15, 24] (Fig. 1B), suggesting that age-related physiological declines, such as degradation of extracellular matrix (ECM) proteins in the same tendon type, may take place at different rates between species.

In addition to these animal studies, a few studies have assessed human tendon mechanical properties between middle-age and young adults. Both structural (peak load and stiffness) and material properties (peak stress and elastic modulus) were found to decrease with age [39, 40] (Fig. 1B). These data suggest that with increased age, human ATs, and patellar tendons (PTs) have a decrease in the load and stress they can withstand and become less stiff compared to young adult subjects (Fig. 1B).

The above animal and human studies suggest that age has a similar effect on specific tendon types between animals and humans (such as PTs). In contrast, comparing different tendon types between species (TTs in animals and PTs in humans) results in contradicting results. Such differences potentially suggest that anatomically distinct tendons in different species could have a different age-related effect. However, it is important to underscore

the type of mechanical testing protocol used in animals and human subjects. Animal-based mechanical characterization has been primarily performed via a uniaxial tensile stretching at a specific strain rate until tissue failure. In contrast, human-based studies utilized non-invasive methods such as ultrasound and magnetic resonance imaging (MRI) to calculate structural and mechanical properties. Such methods (destructive vs non-invasive) can draw significantly different results, making direct comparison between animals and humans difficult.

Tendon biomechanics of aged vs young adults:

Despite the comparisons between aged and young adult tendons being the most studied aspect of tendon aging, there is not a consensus on the impact of aging on tendon mechanics. With age, some structural mechanical properties are consistently unchanged, while others decrease or increase (Fig. 1B). Peak load values of aged ATs and flexor tendons (FTs) in mice and rats had similar values compared to their young adult counterparts [16, 24, 43], suggesting that independent of tendon type and animal model, aged tendons can withstand similar forces compared to younger counterparts. In contrast, there are conflicting results in terms of how tendon stiffness is altered due to aging. Aging can differentially affect anatomically distinct tendons in the same animal [16]. For example, stiffness of anatomically distinct FTs in aged mice was found to be differentially affected due to age compared to young adults. Flexor digitorum longus (FDL) tendons between aged and young adult mice had similar stiffness values, however, flexor carpi ulnaris (FCU) tendons of aged mice had a decrease in stiffness relative to young adult littermates [16]. Moreover, aging can also differentially affect the stiffness of the same tendon type in different animal models. For example, while aged rat FTs had an increase in stiffness relative to young adult littermates, ATs from aged and young adult rats demonstrated similar stiffness values [24, 42] (Fig. 1B).

The effect of aging on tendon material properties and viscoelastic properties is not clear. Both the peak stress and elastic modulus have been shown to increase, decrease, or remain unchanged. One explanation of the above is that aging might have different effects on the same tendon tissue in different animals. For example, aged FTs in equine, rat, and mouse were found to have a decrease, increase, and unchanged peak stress values relative to young adults [41-43]. Another important aspect is the anatomy and position of the tendon tissue. Aging has different effect on the material properties of different tendons in the same animal model. For example, in rats, aged AT peak stress and elastic modulus were decreased compared to young adults [24], while aged TT peak stress and elastic modulus were increased compared to young adult littermates [38] (Fig. 1B). The stress relaxation between aged and young adult SST tendons in mice was decreased, suggesting that with aging there seems to be an impairment of tendon viscoelastic properties [18, 53]. Similarly, the dynamic modulus and $tan\delta$ viscoelastic properties in rat Achilles tendons were also decreased with aging, further suggesting that independent of tendon or animal type, aging negatively impacts viscoelastic properties [54]. In contrast, when nanoscale, poroviscoelastic mechanical properties of aged and young SST were assessed, results differed based on anatomy [19]. Specifically, low frequency nanoindentation moduli were found to decrease with aging in the insertion site of the SSTs. In contrast, the same property was found to be increased by aging in the midsubstance [19]. Collectively, these studies suggest that the

effect of aging on tendon mechanics is highly complex, and important parameters such as the specific anatomical position of the tissue, the animal model, and the actual lifespan of the species need to be considered.

In human studies, two types of tendons have been assessed, the ATs and PTs. There are consistent age-related decreases of tendon structural mechanical and material properties. ATs of aged human subjects exhibit decreases of both structural mechanical and material properties relative to young adults [39, 44-47]. In contrast, PTs have a different age-related effect. In one study, aged human PTs showed a decrease in the peak load, while there were no changes in stiffness, as well as in material properties, relative to the young adult counterparts [40]. In other studies, peak stress was found to decrease in aged human PTs, while stiffness and elastic modulus were maintained similar, relative to young adults [48, 49]. These studies suggest that although aging impairs human tendon mechanical properties, some tendons appear to be more prone to such impairment (e.g., ATs) relative to other tendons (e.g., PTs) (Fig. 1B). Interestingly, the AT was the only tendon tissue that was studied in both animal and human studies. In both cases, the structural mechanical and material properties of ATs were decreased or remained the same in aged vs young subjects (Fig. 1B).

Given the current research, aging could have different effects on tendon structural mechanical and material properties among different species (e.g., animals versus humans) or among anatomically distinct tendons. Further, these properties might be differentially affected due to the different lifespans of animals or humans. Taken together, all the above parameters need to be taken into consideration.

Tendon response to aging: Structure and composition

Structural and compositional properties of tendons are important parameters that directly impact functionality and overall homeostasis. To better understand structural changes with aging, previous studies have focused on assessing the cross-sectional area (CSA) of the whole bulk tissue, the diameter and density of individual collagen fibrils, and the organization of the collagen fibrils/fibers in both the micro- and macro- scale [15, 18, 22, 24, 43-45, 49, 55-59]. Other studies have focused on identifying potential ECM compositional changes that occur with aging by quantifying differences in the mRNA and protein levels of the different collagen types such as Col I, Col III, and Col V, different proteoglycans (PGs) and glycoproteins (GPs), as well as different matrix metalloproteases (MMPs) [22, 43, 55, 60-64].

Tendon structure and composition of middle-aged vs young adults:

A small number of studies have assessed the effect of aging in tendon structure between middle-aged and young adult animals [15, 23, 24]. CSA of ATs in rabbits [15] and rats [24] increased in middle-aged animals relative to the young adult groups, suggesting that as the tissue increases in age, there may be compositional changes in both rabbits and rats [15, 24]. We recently identified that middle-aged FT in mice had a decreased abundance of PG and GP molecules, molecules that exhibit a high turnover rate, including

cochlin, chondroadherin, thrombospondin 2 and 3, aggrecan, and keratocan. These matrix components are crucial for the maintenance of tendon homeostasis (Fig. 2) [9] and suggests that with age, there is a diminished ability of the tissue to maintain abundance of these ECM proteins.

Tendon structure and composition of aged vs young adults:

A significant body of work has focused on better understanding how the structure and composition of tendons shift between aged vs young adult animals. In terms of tendon structure, both CSA and collagen fibril diameter are increased in aged tendons relative to young adults. Increases have been shown in ATs, FT, maxillary superficial tendons (MSTs), and PTs [22, 24, 55, 57] and multiple animal models (rat, mouse, rabbit, and zebrafish) [22, 24, 55, 57], suggesting that structural changes are conserved between tissue anatomical location and animal model. Finally, with aging, there is also a consistent decrease in collagen fibril organization in anatomically distinct tissues (ATs, FTs, PTs, and SSTs) [17, 18, 22, 43, 55], across different animal models including rabbit and mouse [18, 22, 43, 55]. Aging tendons appear to have multiple impairments including the loss of multiple ECM molecules which results in consistent and universal tendon structural shifts like collagen fibril disorganization and diameter (Fig. 2).

In terms of ECM compositional changes, there is a consistent downregulation of mRNA levels in multiple collagens, PGs, and GPs. At the protein level, there are similar levels of collagens and decreased levels of PGs and GPs in aged tendons relative to young adults. In specific, mRNA levels of Col I, III, V, as well as PGs and GPs were significantly downregulated in aged vs young adult tendons. These decreases are consistent among anatomically distinct tendons such as ATs and FTs [43, 60, 61], as well as between different animal models such as mouse and rat [43, 60, 61]. However, aged tendons between the same animal models (rats) and between different animal models (rats and equines), had similar protein levels of Col I, III, and V [60-62] and decreased protein levels of PGs and GPs [55, 62] compared to young adults, suggesting that PGs and GPs are age-related markers and/or regulators of a healthy homeostatic ECM. Previous *in vivo* and *in vitro* studies have shown that removal of PGs and/or GPs results in substantial fusions of lateral collagen fibrils and impairment of tendon structure and function [65, 66]. Loss of these molecules during aging may result in the fusion of neighbouring collagen fibrils, which may explain, in part, the impaired tissue structure and organization, and subsequently the loss of homeostasis (Fig. 2).

In contrast, there is a limited work assessing the effect of aging in human tendon structure and composition. Only CSA and protein levels of PGs and GPs have been assessed. Aged human ATs exhibit an increase in CSA relative to young adult counterparts [44, 45], while PTs seem to be study-specific, with one study showing an increase of PT CSA with age[48, 58] while another study showing no changes in PT CSA with age [49]. A potential explanation of the discrepancies in PT CSA results might be due to sex differences. While both studies used males and females, there was no data on what proportion of the aged and young adults were male or female. Finally, aged human SSTs have a significant decrease in protein levels of PGs and GPs compared to young adult counterparts [63]. Based on the current limited knowledge, human tendons follow similar age-related structural and

compositional shifts with animal models (e.g., increase in tissue CSA and decrease in the protein levels of GPs and PGs molecules).

Tendon response to aging: Cellular function and morphology

Tenocytes (resident tendon fibroblasts) are the primary architects of tendon tissue formation and maturation, and their function is crucial for the maintenance of tendon homeostasis. Multiple studies have attempted to assess how the density as well as activity (e.g., proliferation, apoptosis, senescence, and migration) of tenocytes shifts due to aging. In general, independent of the different aging groups, tendon types and animal models assessed, there seems to be general impairments in both the density and activity of tendon cells with aging.

Tendon cell density and activity of middle-aged vs young adults:

To date, studies have focused on understanding how proliferation, senescence, and migration of tendon cells is shifted between middle-aged and young adult mice and rats. Independent of tendon type (AT, PT) and animal model (mouse, rat), the proliferation of tendon cells decreases in middle-aged vs young adult animals [67-69]. Rat AT cells have an increase in senescence [67], and a decrease in their ability to migrate based on in vitro wound scratch assays [68]. Recent studies found that cell density of middle-aged mouse FTs and rat ATs was significantly decreased relative to young adults [9, 54]. Taken together, middle-aged tendons exhibit a loss/death of tendon cells coupled with increased senescence and decreased cell proliferation. Although mechanistic studies are lacking to directly explain why such shifts are happening when tendons reach middle-age, it can be speculated that cell-based homeostatic mechanisms might be impaired. For example, age-related cellular stressed such as accumulated mechanical stress, DNA damage, oxidative stress, epigenetic impairments, and mitochondrial disfunction may promote dysregulation of intrinsic apoptotic pathways, and regulate the age-related cellular death. Currently there are no data in terms of how apoptosis and density of tendon cells is regulated between middle-aged and young adult animals. Based on the available published studies, tendon cells of middle-age animals have some functional impairments including proliferation and migration rate, concomitant with an increase in senescence markers [67-69]. Importantly, to our knowledge, no studies have assessed the impact of aging on tendon cell function *in vivo* in human tissue (Fig. 3B).

Tendon cell density and activity of aged vs young adults:

More studies have aimed to decipher how tendon cell density and activity is shifted between aged and young adult animals and humans. Cell density of aged equine and mouse FTs was decreased compared to young counterparts [25, 70]. In addition, aged AT cells exhibited a decreased proliferation rate in both mice and rats [67, 71], and aged mouse AT cell cultures demonstrated phenotypic differences relative to young adults [71], while aged rat AT cells had an increase in senescence markers compared to their young adult littermates [67]. Another study utilized mouse flexor tendon explants from aged and young adult subjects, induced a stress-deprivation environment in the explants for up to one week, and

found that aged explants demonstrated a decreased metabolic activity, viability, proliferation, and biosynthesis [20]. Strikingly, male explants demonstrated increased activity, apoptosis, and ECM remodelling, while female explants demonstrated reduced cell activity and tissue preservation [20]. To mechanistically understand age-related impairments in tendon cells, we recently performed single-cell RNA sequencing of the FT and found that aged FTs demonstrated a significant loss of tenocyte subpopulations annotated as “ECM biosynthetic” cells, while the remaining cells in the aged tissue demonstrated elevated mRNA levels of multiple heat shock proteins (HSP) and IL6, indicating loss of proteostasis and inflammaging [9]. Human studies, also report consistent similarities in terms of age-related impairments in tenocyte density and activity. In specific, aged human AT cells have impaired density [13], as well as activity, such as reduced proliferation and migration and increased apoptosis and senescence rates [12, 13].

Taken together, aged tendon cells, broadly have impairments in both density and activity relative to young adults (Fig. 3). In terms of mechanistic shifts, it seems that with aging there is a major loss of ECM biosynthetic tenocytes, along with retention of functionally impaired and pro-inflammatory tenocytes.

While the primary goal of this review is to summarize and synthesize data from *in vivo* studies of tendon aging, it is important to acknowledge the breadth of *in vitro* and *ex vivo* studies that have examined the impact of aging on tendon cells. Multiple studies have examined how tendon cell activity (e.g., proliferation, apoptosis, senescence, and migration) is altered in aged vs. young tenocytes[9, 12, 13, 16, 25, 54, 67-71]. Importantly, independent of how ‘aged’ tenocytes were defined, the anatomical position that tendon cells were isolated from, and the animal models used, there are consistent impairments in tendon cell activity during aging. In addition, several studies have examined the impact of aging on tendon stem/progenitor cells (TSPCs) *in vitro* and have shown that with aging, there are similar impairments in proliferation, apoptosis, senescence, and migration as shown above with *in vivo* studies on tenocytes. TSPCs have been shown to exhibit marked decrease of differentiation and colony formation with aging[11, 69, 72-79]. For example, it was found that aged TSPCs from both mouse patellar tendons exhibited a decreased proliferation rate and stemness exhaustion as evident by the decreased expression of stem cell markers *Oct-4,* nucleostemin (*NS), Sca-1,* and *SSEA-1* with aging [69]. In addition, TSPCs harvested from rat PT and AT tendons exhibited that with aging, there was a consistent decrease of self-renewal and differentiation capacity, a decrease in the proliferation rate, and a delay in the cell cycle progression [11, 76, 77]. Also, human TSPCs from AT and hamstring tissues exhibited a significant impairment of self-renewal and clonogenicity, while there was an acceleration of cellular senescence in aged TSPCs relative to young samples [12, 73, 74]. Recent studies have identified multiple subpopulations of tenocytes, which seem to have distinct functions in vivo [9, 80, 81]. However, most *in vitro* studies on the age-related effects on tenocytes have treated tenocytes as a homogeneous population. Thus, future work to define the impact of aging on tenocyte and other tendon resident cell subpopulations will be needed to delineate both the conserved and distinct impacts of aging.

Tendon response to aging: healing

Besides the multi-level deficits that non-injured tendons have in terms of mechanics, structure, composition, and cell activity with increasing age, With aging, tendons also exhibit important injury/healing-related deficits such as an increased frequency of tendon injuries and a decreased healing capacity after injury, which have been observed in animals and human studies [16, 82-85].

In terms of animal models, a recent study found that middle-aged rat ATs exhibited inferior healing quality relative to young adult littermates after a unilateral transection of the AT without repair [86]. In the same study, the authors showed that aged rat ATs did not exhibit the healing deficits of the middle-aged group at 6 weeks post-injury, and they suggest this may be due to a lack of blood supply in the aged tendons relative to the other groups during healing, however this was not directly assessed [86]. In another study, aged and young adult mouse FTs were injured via a full transection and repair of the FTs and were directly compared to each other to assess healing [16]. At fourteen days post-surgery, the aged tendons exhibited significant decreases in mechanical properties such as peak load and stiffness, while there were no significant differences in cell proliferation between the aged and young groups *in vivo.* In addition, there was a significant loss of bridging collagen ECM in the aged repairs, suggesting that age-related shifts in ECM production during the healing response might lead to impaired healing in aged vs young adult FTs [16]. In addition, PTs from aged and young samples were injured via removal of ~1 mm in width PT tissue, in the central area, and their healing quality was assessed at two- and four-weeks post-injury. Similar to the previous study, aged PT tendons exhibited impaired healing quality with lower histological score, decreased collagen synthesis, and higher accumulation of adipocytes compared to young adult counterparts [87]. Kietrys *et al.*, utilized a rat model of upper extremity overuse and assessed whether aged FDL and SST tendons exhibited increased impairment in function and inflammation compared to young adult littermates [88]. Here they found that aged tendons SST tendons were significantly more affected by the overuse model than young adult littermates. Moreover, there was increased inflammation coupled with decreased limb agility and a lack of improvement in task success in aged compared to young adult rats [88]. In another study, young, middle-aged, and aged mice PTs were injured via a full thickness, partial width defect using a biopsy punch and the viscoelastic biomechanical properties of the PTs were quantified at three- and six-weeks post-injury [89]. Independent of age group, there were no significant differences in the viscoelastic biomechanical properties, suggesting that after injury, tendons exhibit an inability to resist to strains as well as an increase in dissipated energy [89]. Aging appears to play a significant role in the healing response of tendons. In addition, aged tendons follow a slower and less regenerative healing process compared to younger littermates in rodent models. Although the above studies shed some light on understanding why aged tendons demonstrate impaired healing outcomes, there are remain significant gaps in the underlying mechanisms explaining why this happens.

Human tendons also demonstrate a significant increase in the frequency of both acute injury and tendinopathy development with aging. A cross-sectional study found that the incidence and prevalence of lower extremity tendinopathy in a Dutch general population was

significantly higher among older human subjects [82]. Another study evaluating midportion Achilles tendinopathy in the general population found that middle-aged subjects exhibited a higher prevalence of Achilles tendinopathy relative to young adults [84]. Additionally, the incidence rate of non-sport related AT ruptures was found to continuously increase with age and peaked during the upper mature group (between 50 and 59 years old) [85]. All these studies demonstrate that aged individuals have increased susceptibility and risk to tendinopathy development as well as acute tendon injuries in multiple tendon types [82, 84, 85]. Theories have been developed to explain why older individuals are more prone to the above tendon pathologies compared to young adults. One theory suggests that over time, there is a constant accumulation of small chronic and repetitive damages in the tendon tissue. As damage increases in longevity, size and/or magnitude, they result in significant impairment of tendon homeostasis, and this pathology is observed with aging [90]. Another theory suggests that with aging, there is a decrease in tendon structural and material properties, which in turn diminish both the loading and regenerative capacity of tendons [7]. The above theories try to shed some light on the underlying mechanisms that happen during aging and result in impairments of tendon homeostasis at multiple levels. However, additional mechanism-based studies are needed.

Future perspectives

Aging is a significant risk factor for systemic pathology development including metabolic and immune dysfunction and musculoskeletal disorders. As noted, tenocytes have been largely assumed to be a homogenous cell population. However, recent studies have utilized genetic reporter strains, single cell RNA sequencing (scRNAseq), cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq), and spatial transcriptomics techniques and have consistently demonstrated a high cellular heterogeneity in healthy tendons of different species, and that with progression of tendon disease (e.g., tendinopathy) or injury, such cellular heterogeneity was further increased [80, 81, 91-93]. The application of these innovative technologies will likely be critical to better defining how the cellular landscape shifts during natural aging, age-related degeneration, and healing of acute injuries in the context of aging. In addition, understanding the complexity of the cellular composition in tendons will facilitate the identification of critical cell-cell communication mechanisms that are altered during aging.

Another promising research avenue is rejuvenation of aged cells via complete or partial reprogramming. Although there are no such data in the tendon field, there have been promising results in other fields. In one study, old senescent fibroblasts from a 74-year-old patient were harvested, reprogrammed into induced pluripotent stem cells (iPSCs) which showed a reset in mitochondrial metabolism, oxidative stress, telomere size, and gene expression [94]. Strikingly, those iPSCs as well as iPSCs from young patients were nearly identical in terms of cellular function and activity to embryonic stem cells [94]. In another study of cell reprogramming to ameliorate *in vivo* age-related deficits, the researchers demonstrated two interesting findings. The researchers developed a protocol for short-term cyclic expression of *Oct4, Sox2, Kfl4, and c-Myc* in these mice. They showed that expression of the above factors in a mouse model of premature aging resulted in significant improvements in the skin, spleen, kidney, stomach, and gastro-intestinal tract,

as well as lifespan extension [95]. The results from the above studies provide exciting and promising research avenues in terms of tackling the deleterious effects of aging in tendon homeostasis. However, as noted previously, there is substantial work required to first define the cellular composition and the fundamental shifts in cellularity and ECM that underpin the disrupted tendon homeostasis and impaired healing capacity that occurs with aging.

In addition, development of key model systems to study tendon aging will be crucial for future progress. For example, application of progeria (or accelerated aging) mouse models ($Lmna^{G609G/G609G}$ and $Zmpste24^{-/-}$) [96, 97] or senescence-accelerated mouse models [98] in tendon aging research could be impactful in further increasing our knowledge on the impact of aging in tendon health. Second, a comprehensive understanding of the intrinsic cellular and molecular changes that take place in tendons due to aging is crucial to develop new eloquent and comprehensive key model systems for tendon aging research in the future. Taken together, combining all the above technologies and key model systems will be instrumental to design future therapeutics to improve tendon homeostasis during aging.

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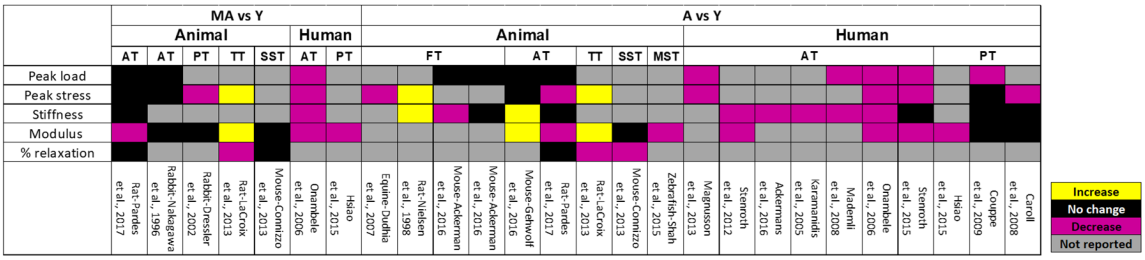

Figure 1.

Effect of aging on tendon mechanical properties. Heatmap showing how age alters tendon structural mechanical and material properties at different aging groups (MA vs Y, A vs Y), on animal or human studies, as well as on different tendon types (AT, PT, TT, etc.,)

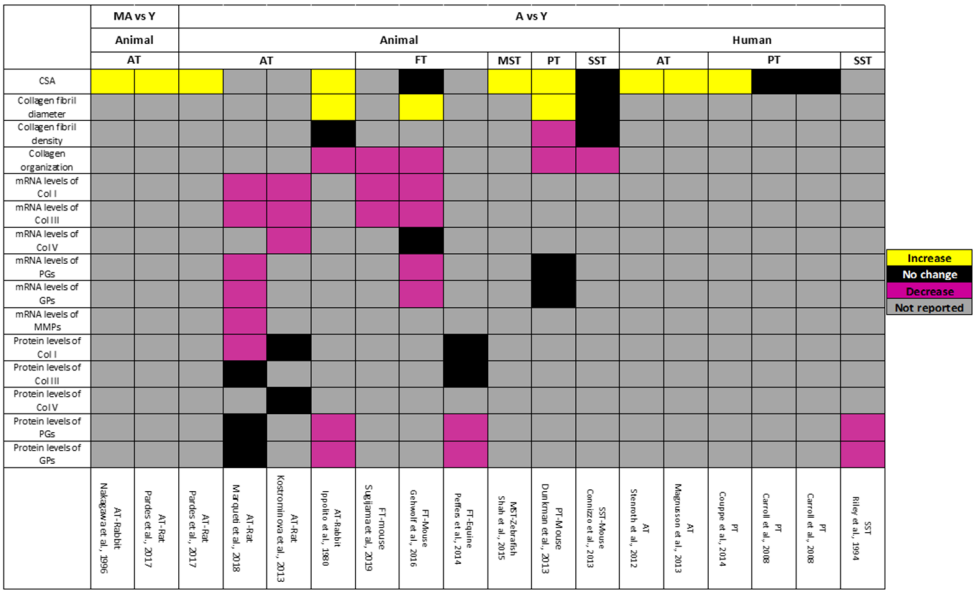

Figure 2.

Effect of aging on tendon structure and composition. Heatmap showing how age alters tendon structure and composition at different aging groups (MA vs Y, A vs Y), on animal or human studies, as well as on different tendon types (AT, PT, TT, etc.,)

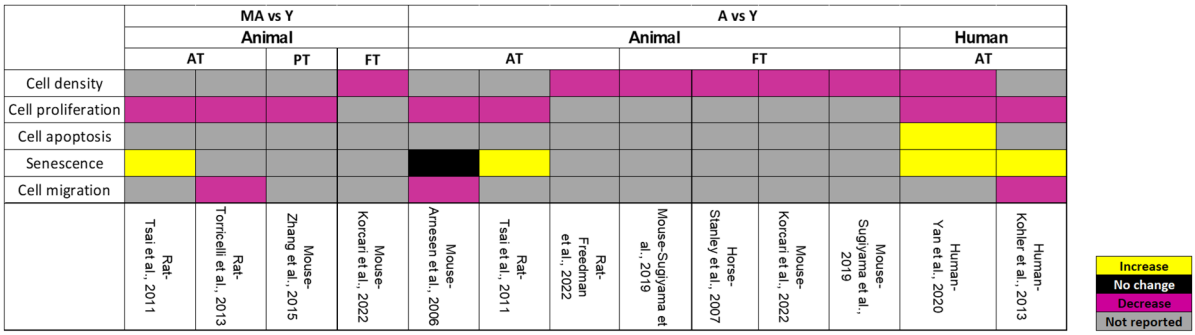

Figure 3.

Effect of aging on tendon cell density and activity. Heatmap showing how age alters tendon cell density and activity at different aging groups (MA vs Y, A vs Y), on animal or human studies, as well as on different tendon types (AT, PT, TT, etc.,)

Table 1.

The relative age ranges of humans and different animal models that resemble the young adults, middle-aged and aged groups. All age ranges are reported in years and months of age [26-37].

	Adults	Middle-aged	Aged
Human	20-39 (240-468 months old)	40-59 (480-708.5 months old)	60+ (720.5 months old +)
Mouse	0.25-0.5 (3-6 months old)	0 83-1.17 (10-14 months old)	1.5+ (18 months old +)
Rat	0.6-1.2 (7.2-14.4 months old)	1.3-2 (15.6-24 months old)	2+ (24 months old +)
Rabbit	2-3.9 (24-47 months old)	4-5.9 (48- 70.8 months old)	6+ (72 months old +)
Equine	6.0-11.0 (72-132 months old)	11.5-17.5 (138.1-210.1 months old)	18+ (216.1 months old +)
Zebrafish	0.66-1 (7.93-12 months old)	1.25-1.67 (15-20 months old)	2+ (24 months old +)