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Review Article

Mitochondrial destabilization in tendinopathy and potential therapeutic strategies

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ABSTRACT

Tendinopathy is a prevalent aging-related disorder characterized by pain, swelling, and impaired function, often resulting from micro-scarring and degeneration caused by overuse or trauma. Current interventions for tendinopathy have limited efficacy, highlighting the need for innovative therapies. Mitochondria play an underappreciated and yet crucial role in tenocytes function, including energy production, redox homeostasis, autophagy, and calcium regulation. Abnormalities in mitochondrial function may lead to cellular senescence. Within this context, this review provides an overview of the physiological functions of mitochondria in tendons and presents current insights into mitochondrial dysfunction in tendinopathy. It also proposes potential therapeutic strategies that focus on targeting mitochondrial health in tenocytes. These strategies include: (1) utilizing reactive oxygen species (ROS) scavengers to mitigate the detrimental effects of aberrant mitochondria, (2) employing mitochondria-protecting agents to reduce the production of dysfunctional mitochondria, and (3) supplementing with exogenous normal mitochondria. In conclusion, mitochondria-targeted therapies hold great promise for restoring mitochondrial function and improving outcomes in patients with tendinopathy.

The translational potential of this article: Tendinopathy is challenging to treat effectively due to its poorly understood pathogenesis. This review thoroughly analyzes the role of mitochondria in tenocytes and proposes potential strategies for the mitochondrial treatment of tendinopathy. These findings establish a theoretical basis for future research and the clinical translation of mitochondrial therapy for tendinopathy.

1. Introduction

Tendons connect muscles and bones, and function in conveying muscle-generated contractile force unto the skeletal framework for facilitating body movement [1,2]. These anatomical entities primarily comprise meticulously arrayed strands of collagen fibers with a finite complement of cellular entities. The high density of collagen fibers significantly contributes to the tendon's exceptional mechanical robustness [3]. It is widely recognized that aging is a major risk factor for the development of tendinopathy, which acts as diffused or localized edema, pain, compromised structural soundness of tissue, and hindered physical prowess [4]. Tendinopathy is characterized by distortions in the microstructural composition and cellular constituency of tendon [3]. Research suggests that the pervasiveness of tendinopathy in the lower extremities could attain an incidence as elevated as 10.52 per thousand individuals [5].

Rehabilitation strategies for managing tendinopathy encompass various approaches, which can be broadly categorized into two modalities: passive and active. Passive modalities include pharmacotherapy [6], injection therapy [7], orthosis [8], extracorporeal shock wave therapy [9], therapeutic ultrasound [10], and low-level laser [11]. On the other hand, active modalities comprise tendon loading exercises

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[12], patient education, and load management [13]. When non-surgical treatments fail for tendinopathy, surgical intervention is required. The aim of tendon surgery is to promote regenerative healing by initiating repair processes in the matrix environment. Surgical procedures involve excising degenerated tendons, removing peritendinous adhesions, and performing tendon decompression and/or multiple longitudinal tenotomies [13]. Recent years have seen the exploration of novel treatments such as gene therapy [14] and stem cell therapy [15,16] for tendinopathy. Despite the array of available treatment options, the effectiveness of tendinopathy interventions remains unsatisfactory [6]. Certain patients continue to experience persistent pain even following treatment, significantly compromising their quality of life and imposing substantial economic burdens [3].

Mitochondria represent indispensable organelles accountable for energy metabolism within eukaryotic cells, assuming a pivotal responsibility in sustaining vital life processes [17]. Apart from adenosine triphosphate (ATP) generation through nutrient sources, mitochondria also orchestrate fundamental processes such as apoptosis [18], cell signaling [19], calcium homeostasis [20], innate immunity [21], and phospholipid synthesis [22]. Recent studies have advanced our understanding and recognition of the pivotal role that mitochondrial dysfunction plays in various human pathologies [23]. An increasing number of studies have indicated the significance of mitochondrial function in the aging process [24]. Restoring mitochondrial function in senescent cells proves to be an effective therapeutic approach for ameliorating aging-related diseases [25]. Consequently, preserving optimal mitochondrial function emerges as an imperative prerequisite for safeguarding cellular and organismal well-being [26].

Mitochondria play a crucial role in facilitating the proliferation and differentiation of stem cells [27]. Within the context of chronic inflammation, malfunctioning mitochondria can detrimentally affect both the differentiation and functionality of mesenchymal stem cells (MSCs). Consequently, the restoration of proper mitochondrial and MSC functionality emerges as a promising therapeutic avenue for mitigating the progression of diseases [28]. Notably, tendon stem/progenitor cells (TSPCs) represent pivotal entities in tendon regeneration and repair processes [29,30]. The senescence of TSPCs is associated with degenerative tendinopathy [31]. Exploring the intricate interplay between TSPC mitochondrial function and the manifestation of tendinopathy as a promising realm of investigation. This comprehensive review delineates the significant role of mitochondria in tendinopathy, elucidates the mechanisms through which mitochondrial destabilization contributes to tendinopathy, and provides insights into mitochondria-targeted therapeutic alternatives for alleviating tendinopathy.

2. The role of mitochondria in tenocytes

A growing body of evidence suggested the pivotal role played by mitochondria in the physiology of tenocytes [32]. Mitochondria within tenocytes fulfill diverse functions, including ATP production, regulation of redox status, engagement in mitophagy, and preservation of calcium homeostasis. Maintaining proper mitochondrial physiology stands as a prerequisite for cellular viability. Additionally, the normative physiological operation of mitochondria holds indispensable importance in upholding the internal organismal equilibrium [33]. Tenocytes, when exposed to stress and metabolic fluctuations, can modulate the structure, quantity, and function of their mitochondria in response [34]. The instability of mitochondrial homeostasis can lead to a reduction in ATP production, excessive oxidative stress, and subsequent cell death, as well as a range of abnormal cellular processes. Consequently, unraveling the precise mechanisms governing mitochondrial activities and their intricate links to tendon ailments assumes paramount significance. This endeavor facilitates a comprehensive comprehension of tendon disorder etiology and the formulation of tailored, precision-oriented remedies (Fig. 1).

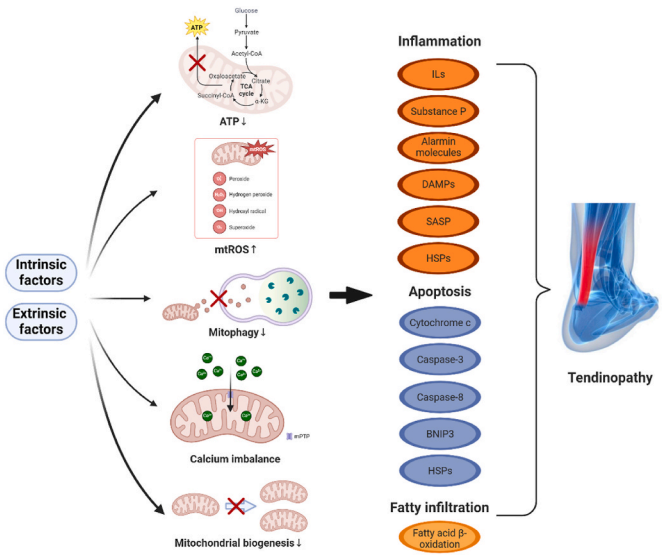

Figure 1. Mitochondrial-associated induction of tendinopathy. Multiple intrinsic and extrinsic factors can damage tenocyte mitochondria to perturb cell metabolism and cause tendinopathy via decreased levels of adenosine triphosphate (ATP) levels, increased levels of mitochondrial reactive oxygen species (mtROS), decreased mitophagy, calcium imbalance, and decreased levels of mitochondrial biogenesis. Reduced mitochondrial adenosine triphosphate (ATP) production capacity leads to inadequate energy supply. Also, elevated levels of mtROS disrupt normal mitochondrial function and accelerate apoptosis. Impaired mitophagy impedes the removal of abnormal mitochondria, while increased inward flow of mitochondrial calcium ions results in elevated oxidative stress levels within the cells. Furthermore, decreased mitochondrial biogenesis hinders the renewal process. These mitochondria-related factors collectively contribute to the development of tendinopathy.

2.1. Energy production

Mitochondria serve as the principal energy source in eukaryotic cells, accounting for 90% of cellular energy supply [35]. They assume a pivotal function in upholding intracellular homeostasis, cellular operation, and the regulation of cell viability [36]. Substantial evidence has emerged connecting mitochondrial dysfunction to a range of degenerative disorders, encompassing lung diseases, cardiomyopathies, and brain injuries [37–40]. Given its association with the aging process, the significance of mitochondria in tendinopathy becomes undeniable [41].

Oxidative phosphorylation (OXPHOS) assumes a pivotal function in the synthesis of ATP and the provision of energy [42,43]. Enzyme complexes housed in the inner mitochondrial membrane (IMM) participate in electron transfer within the respiratory chain [44]. ATP synthesis occurs through the conversion of adenosine diphosphate (ADP) to ATP by ATP synthase, located at the end of the electron transport chain (ETC) [45]. Synergistic interactions between respiratory chain complexes during the OXPHOS process generate ATP, which serves as an energy source for cells. Tendons, characterized by avascularity and lack of innervation, contain tenocytes within a relatively hypoxic extracellular matrix [46]. Studies have convincingly showcased the indispensable role of OXPHOS in the energy metabolism of tenocytes [47]. Mitochondrial dysfunction possesses the potential to disrupt the equilibrium between glycolysis and oxidative phosphorylation, precipitating a substantial reduction in ATP generation within tenocytes [48]. Impaired ATP synthesis in tenocytes could potentially exert a ripple effect on the production of extracellular proteins and undermine matrix stability, ultimately contributing to the genesis of tendon disorders [28].

2.2. Redox regulation

Reactive oxygen species (ROS) encompass a cluster of reactive

molecules intricately involved in diverse biological processes that contribute to the etiology of tendinopathy [3]. Within tenocytes, mitochondria constitute the principal wellspring of ROS generation [49]. ETC can yield ROS via proton leakage, commonly termed as mtROS [50,51]. Incomplete oxidative phosphorylation in mitochondria, as well as the involvement of NADPH oxidase and xanthine oxidase, are significant sources of ROS production [52]. Significantly, mitochondrial electron transfer stands out as a physiologically substantial process propelling ROS production [53]. Ordinarily, oxygen molecules accept electrons relayed by the respiratory chain, resulting in their reduction and consequent water molecule formation. However, sites of instability within the ETC, exemplified by Fe-S clusters, flavins, or quinones, can trigger single-electron oxidation due to proximate oxygen molecules. This phenomenon culminates in the genesis of superoxide anion (O_2-) radicals during the course of mitochondrial electron transport. Spontaneous or enzymatic decomposition of O_2- produces hydrogen peroxide (H_2O_2), further promoting the generation of hydroxyl radicals (•OH) [54].

ROS have conventionally been perceived as agents that induce cellular dysfunction and contribute to pathological processes by inflicting oxidative harm upon intracellular constituents [55]. Nonetheless, contemporary investigations have unveiled a paradigm shift, elucidating that modest ROS concentrations play an indispensable and advantageous role in sustaining fundamental cellular functions including but not limited to proliferation, differentiation, and survival. Notably, stem cells exemplify this phenomenon, characterized by low ROS levels that escalate upon differentiation. This increment in ROS content actively contributes to the initiation of transcriptional mechanisms governing the modulation of gene expression patterns [56].

Mitochondria harbor an adept antioxidant defense system, meticulously preserving comparatively modest levels of ROS. Within typical tenocytes, only a fraction of the ROS generated by mitochondria is released into the cytoplasm. ROS additionally engage in intricate interactions with various mitochondrial components, impeding the escape of mitochondrial ROS (mtROS). The superoxide scavenging system encompasses vital entities like superoxide dismutase (SOD), cytochrome c, α-tocopherol or α-tocopherol radical, and ionic ligands. H_2O_2 functions as a less reactive yet pivotal mediator of redox signaling. Nevertheless, an excessive H_2O_2 yield can culminate in oxidative damage to proteins, lipids, and DNA. The quenching of H_2O_2 hinges on glutathione peroxidase, leveraging reduced glutathione for the breakdown of H_2O_2 [53]. Moreover, mitochondria possess the capability to neutralize ROS generated by alternative cellular sources, encompassing cytoplasmic enzymes and diverse oxidative enzymes [54]. In specific pathological conditions, such as ischemia-reperfusion, the mitochondrial antioxidant defense system further endeavors to eliminate excess O_2 and H_2O_2 [57].

Furthermore, mitochondria, replete with DNA, proteins, and lipids, are susceptible to assault by mtROS [58]. Heightened mtROS levels correlate with an elevated susceptibility to mtDNA mutations, compromised ATP synthesis, and ensuing mitochondrial malfunction [59]. The mitochondrial theory of aging posits mitochondria as pivotal sources and targets of oxygen radicals, intricately intertwined with the aging trajectory. Escalated ROS levels instigate mtDNA impairment, thereby fostering mutations in mitochondrial proteins, ultimately escalating the generation of oxygen radicals [60,61].

2.3. Mitophagy

Mitophagy plays a crucial role in coordinating the apoptosis of dysfunctional cells, and its significance is particularly prominent in challenging cellular repair environments. This degradation process involves the enclosure of mitochondria within double-membrane structures known as autophagosomes, followed by their fusion with lysosomes for organelle breakdown [62]. The activation of autophagy bestows a protective influence upon tenocytes, underscoring the pivotal contribution of mitophagy to cell survival [63,64]. Given their pivotal role in aerobic respiration and cellular energy provisioning, mitochondria remain susceptible to impairment. Impaired mitochondria are immobilized within bilayer membrane structures and fuse with lysosomes, culminating in the formation of autophagosomes that are subsequently broken down by enzymes [65]. The genesis of mitochondrial autophagosomes constitutes a critical juncture within mitochondria-mediated autophagy, facilitating the expeditious removal of damaged or surplus mitochondria. This autophagic process allows for the continuation of normal cellular functions and intracellular homeostasis [66].

Mitophagy can be categorized into three types: proteins situated within the outer mitochondrial membrane (OMM), lipid moieties of the OMM, and those linked with ubiquitinated mitochondrial proteins [33]. Among the extensively studied mitochondrial autophagic pathways are those orchestrated by phosphatase and tensin homolog-induced Parkin and kinase 1 (PINK1) [67]. Under physiological circumstances, mitochondrial processing peptidase cleaves PINK1, releasing it into the cytoplasm [68]. The resulting PINK1 fragment directly binds to the E3 ubiquitin ligase Parkin, impeding its relocation and stabilization within the OMM. This interaction acts as a suppressor of mitophagy [69]. However, upon disruption of the mitochondrial membrane potential (ΔΨm), PINK1 undergoes activation and localizes to the OMM, subsequently enlisting and activating Parkin. Parkin selectively recruits autophagy receptors to instigate mitophagy [70]. An additional autophagy marker, outer mitochondrial membrane 20 translocase (TOMM20), is subject to degradation during the autophagic process [71]. Parkin and TOMM20 exhibit affirmative and negative associations with mitophagy, respectively [72]. Furthermore, when mitochondria are compromised, lipids located in the OMM interact with lipidated LC3 (LC3-II), triggering mitophagy [73].

Recent studies have revealed that mitochondrial Ca^{2+} functions as a potential specific signal governing mitophagy. Mitochondrial AMPK-dependent mechanisms can enhance mitochondrial Ca^{2+} uptake, thereby attenuating excessive autophagy flux [74]. Consequently, the regulation of mitophagy is partially contingent upon the modulation of mitochondrial Ca^{2+} levels. Moreover, an overabundance of ROS can also precipitate mitophagy. Excess ROS triggers the disintegration of oxidized mtDNA through autolysis enzymes orchestrated by DNase II in vivo. Oxidative harm can disrupt mitophagy, contributing to the release of oxidized mtDNA, thereby potentially triggering inflammatory signaling [75].

Moreover, the dynamic processes of mitochondrial fusion and fission tightly intertwine with mitophagy. Through the fission and ejection of impaired mitochondria from elongated counterparts, cells uphold the integrity of its function and structure, sequestering the damaged organelles within autophagosomes for subsequent degradation [76].

However, mitophagy is a dual-faceted mechanism. It comes into play when oxidative stress damage exceeds the threshold of IMM potential, leading to the disposal of dysfunctional mitochondria through this autophagic process. While this action clears impaired mitochondria and safeguards cells against apoptosis, excessive mitophagy may result in the depletion of vital cellular constituents and eventual cell death.

2.4. Calcium homeostasis

Calcium homeostasis holds pivotal significance in cellular metabolism within the realm of medical science. Calcium-mediated signaling, particularly in the context of ATP synthesis regulation, assumes a critical role in mitochondrial operations. Elevated mitochondrial Ca^{2+} levels culminate in cell death, whereas diminished calcium ion concentrations disrupt cellular energy metabolism [77,78]. Ordinarily, Ca^{2+} is released from the endoplasmic reticulum (ER) and subsequently shuttled to the mitochondrial matrix. Within this matrix, Ca^{2+} activates the TCA cycle, thereby stimulating ATP production [79]. Overabundant Ca^{2+} causes mitochondrial calcium overload, triggering the mitochondrial permeability transition pore (PTP) opening, and ensuing tenocytes apoptosis

[80]. Conversely, Ca^{2+} deficiency can impede ATP generation and disrupt metabolic processes. Moreover, Ca^{2+} serves as a stimulus for mitochondrial enzymes that modulate TCA cycle. Dysregulation of mitochondrial Ca^{2+} diminishes ATP production and influences ATP-related metabolic activities [78]. While the mechanism transduction of Ca^{2+} might be intertwined with mitochondrial polarization or depolarization, elucidating the precise mechanism necessitates further exploration [81].

The regulation of calcium homeostasis by mitochondria involves the mitochondria-associated endoplasmic reticulum membranes (MAMs), which facilitate the transport and regulation of Ca^{2+} between the ER and mitochondria [82]. Upon Ca^{2+} release from the ER, specific regions of mitochondrial surface exhibit significantly higher Ca^{2+} concentrations compared to the cytoplasm. Functioning as a channel for calcium transfer, MAMs establish a buffering system between the ER and mitochondria [72]. It is worth noting that the inositol 1,4,5-trisphosphate receptor (IP3R) serves as a crucial calcium channel located in the ER, responsible for controlling the release of calcium ions (Ca^{2+}). On the other hand, voltage-dependent anion channel 1 (VDAC1) is a calcium-related protein located in the OMM, which mediates the uptake of Ca^{2+} by mitochondria [83,84]. The IP3R-VDAC1 complex represents a key structure within MAMs for calcium transport [85]. Upon stimulation of tenocytes, Ca^{2+} is released from the ER via IP3R, and subsequently transported into mitochondria via the highly conductive protein VDAC1. The resulting high concentration of Ca^{2+} activates the mitochondrial calcium uniporter (MCU) complex on the mitochondrial membrane [86]. MCU facilitates Ca^{2+} transport across IMM, enabling Ca^{2+} entry into the mitochondrial matrix. Consequently, Ca^{2+} plays a crucial role in various metabolic reactions, such as cytoplasmic Ca^{2+} signal transduction, energy production, cell death, and extracellular matrix calcification.

2.5. Mitochondrial biogenesis

Mitochondria are dynamic organelles displaying various morphologies, including small spheres, short or elongated tubules, and interconnected structures. The regulation of their number, morphology, and positioning within cells is achieved through a coordinated cycle of fission and fusion. For instance, short tubule-like mitochondria can merge into elongated forms, while tubule-like mitochondria can undergo fission to generate smaller spherical mitochondria. This balance between mitochondrial fusion and fission governs mitochondrial size, quantity, shape, membrane and content mixing, maintenance of mtDNA, and promotion of mitophagy [87]. These dynamic changes critically impact mitochondrial function and cellular metabolism [88]. Mitochondrial biogenesis, in turn, influences the quantity, distribution, and shape of mitochondria. The delicate interplay between fission and fusion acts as a fundamental mechanism for regulating mitochondrial structure and function, thereby ensuring cellular homeostasis [89].

Extensive research has aimed to uncover the molecular mechanisms underlying mitochondrial fission and fusion processes [88,90]. In mammalian cells, the primary orchestrators of mitochondrial fission are proteins such as cytoplasmic dynamin guanosine triphosphatase (GTPase), dynamin-related protein 1 (Drp1), mitochondrial fission protein 1 (Fis1), and dynamin2 (Dnm2) [91]. Drp1 operates in both mitochondrial and peroxisomal fission. It is dynamically recruited to future fission sites on the OMM where it forms cyclic structures, leading to GTP-dependent membrane constriction [92,93]. Dnm2 is attracted to the site of Drp1-mediated mitochondrial constriction, triggering the scission of the mitochondrial membrane [94]. Fis1 influences mitochondrial fission by interacting with Dnm2 and Drp1 [95,96]. This process facilitates the elimination of damaged mitochondria through autophagy and facilitates mitochondrial redistribution in tenocytes in response to ATP demand [97].

Mitochondrial fusion, in contrast, is regulated by optic atrophy 1 (Opa1) and two highly homologous GTPases mitofusins (Mfn1 and Mfn2) [98]. Mfn1 and Mfn2 play a crucial role in coordinating the fusion of OMM, followed by Opa1, which facilitates fusion of IMM [99]. The interaction between the OMMs of two mitochondria occurs through trans interactions involving Mfns. GTP induce conformational changes in Mfns, promoting mitochondrial docking and facilitating membrane contact sites [100,101]. Subsequent to OMM fusion, Opa1 interacts with cardiolipin, linking the two IMMs, and GTP hydrolysis by Opa1 drives IMM fusion [102]. By enabling the exchange of crucial components, especially mtDNA, between mitochondria, mitochondrial fusion plays a vital role in maintaining the uninterrupted functionality of mitochondria [103].

Mitochondrial mobility and morphodynamics are closely intertwined with the Ca^{2+} homeostasis [104], energy metabolism, and cytoskeletal proteins [105]. Aberrations in proteins associated with mitochondrial dynamics have been documented in numerous pathologies, including insulin resistance [106], cancer [107], and cardiovascular diseases [108]. Dynamic changes in mitochondria play a critical role in facilitating efficient energy production, preserving the integrity of mtDNA, and regulating essential cellular functions such as calcium signaling and apoptosis.

In summary, mitochondria play a crucial role in the normal physiological processes of cells. Mitochondrial abnormalities are the key factor that leads to tenocytes dysfunction, resulting in tendinopathy.

3. Mitochondrial abnormalities observed in tendinopathy

Tendinopathy has a complex, multifactorial pathogenesis. Tendon tissues primarily consist of type I collagen, alongside proteoglycans, glycosaminoglycans, glycoproteins, and other collagen subtypes like types III, V, and XII [109,110]. In tendinopathy, the issue matrix changes involve a loss of collagen structural organization and alterations in fibrocartilage composition, leading to the deposition of additional matrix proteins such as glycosaminoglycans [111]. Initially, type III collagen is rapidly produced in response to tendon injury to provide temporary protection despite its weak mechanical properties [112,113]. However, this repair mechanism is compromised in tendinopathy, resulting in an increased accumulation of type III collagen [3].

Cytologically, tendinopathy is often associated with inflammation and oxidative stress in tenocytes, both believed to be related to cellular mitochondrial function [114,115]. Recent studies utilizing single-cell and spatial omics techniques have unveiled that during tendinopathy, there is a notable infiltration of inflammatory cells, concomitant with chondrogenesis and intrachondral ossification [116]. The primary pathological process in tendinopathy is apoptosis, which is manifested by tendon collagen degeneration, impaired fiber orientation, and increased mucus matrix [117]. Apoptosis leads to a progressive decline in intrinsic tenocytes, further hindering the tissue's repair capacity [118]. Samples from patients with degenerative rotator cuff tendinopathy and a rat model of overuse tendinopathy showed elevated expression of caspase 3 and caspase 8, which are important mediators of apoptosis [119,120].

Mitochondrial dysfunction plays a crucial role in the development of tendinopathy. Mitochondria, being both the primary source and target of ROS, have a significant impact on mitochondrial function [121]. Previous studies have shown that elevated ROS production by tenocytes during tendinopathy, highlighting the involvement of mitochondrial dysfunction and increased ROS levels [122–124]. Mitochondria contribute to tendinopathy through processes like inflammation, apoptosis, and fatty infiltration of tenocytes [117]. Mitochondria-associated molecules such as heat shock proteins (HSPs) can activate innate immune response and responding to tissue stress [125]. Under stress conditions, tenocytes release HSP70 to maintain repair-degeneration balance [126]. In addition, inflammatory cytokines and mediators, such as interleukins (ILs), substance P and alarmin molecules and damage-associated molecular patterns (DAMPs) such as HMGB1, HIF1α and IL-33 are also upregulated in degenerative

tendinopathy [127,128]. Recent studies revealed that mitochondrial function influences inflammatory signaling, with oxidized mitochondria initiating chronic inflammation, disrupting tendon homeostasis, and promoting tendinopathy [129]. Decreased mitochondrial function correlates with elevated senescence-associated secretory phenotype (SASP) expression in tenocytes, while enhanced mitochondrial function can decrease SASP levels [130]. Apoptosis is a characteristic feature of tendinopathy and involves the mitochondrial pathway [119]. Oxidative stress induces apoptosis in human tenocytes via mitochondrial cytochrome c release and caspase-3 activation. ROS act as key mediators in tendinopathy [118], potentially inducing apoptosis and regulating pro-apoptotic factors like BNIP3, leading to mitochondrial depolarization, dysfunction, and subsequent cell death [131]. The HSP family also influences the apoptotic cascade [132]. Fatty infiltration is a feature of degenerative tendinopathy, with mitochondria serving as the primary site for fatty acid β-oxidation [133]. Mitochondrial dysfunction can impede this process, resulting in decreased fatty acid oxidation rates. This disruption contributes to the pathogenesis of tendinopathy [134]. In summary, tendinopathy is multifactorial, with mechanisms involving inflammation, apoptosis, and fatty infiltration related to mitochondrial processes requiring further investigation to fully comprehend their role in tendinopathy development.

The majority of studies on mitochondrial abnormalities in tendinopathy exist at the molecular level and are mostly conducted in vitro. Currently, there is limited research on the influence of mitochondria on tendinopathy in vivo. However, there are still articles available that explore this topic.

To explore mitochondrial alterations in tendinopathy, Zhang et al. conducted a study employing a mouse model of supraspinatus tendinopathy [135]. Their investigation encompassed mitochondrial structure, activity, and function changes, revealing a connection between clip-induced tendinopathy and mitochondrial dysfunction. Remarkably, the removal of the clips resulted in an enhancement of mitochondrial activity. Structural modifications associated with tendinopathy encompassed reduced intracellular mitochondrial count and an increased number of cristae per mitochondrion. Notably, these changes exhibited partial reversal upon clip removal. At the genetic level, the study disclosed diminished expression of genes related to mitochondrial iron transport, respiration, ATP synthase, and mitophagy subsequent to clip insertion, thereby confirming the relationship between mitochondrial dysfunction and tendinopathy progression. Additionally, the levels of SOD, an enzyme countering highly reactive superoxide radicals, demonstrated a significant decrease in tendinopathy, contributing to ROS accumulation. Remarkably, SOD levels experienced a substantial rebound after clip removal, further substantiating the presence of mitochondrial dysfunction in tendinopathy development (Fig. 2).

In another investigation conducted by Lee et al., intact exogenous mitochondria were effectively transplanted into compromised tenocytes within a rat model of tendinopathy [28]. The study revealed that this transplantation exerted protective effects against tenocyte injuries induced by TNF-α and a collagenase-induced tendinopathy model. Furthermore, the transplantation of mitochondria substantially elevated the expression levels of specific tenocyte markers, including tenomodulin (TNMD) and collagen type I (COL1), while concurrently diminishing the expression of matrix metalloproteinase-1 (MMP1) and tenascin-C (TNC), which are associated with the tendon's response to compression.

In conclusion, mitochondrial dysfunction and abnormalities significantly influence tendinopathy, affecting both its progression and healing. Further clarification of the mechanisms through which mitochondria contribute to tendinopathy, coupled with the formulation of targeted interventions, represents a promising avenue for future research.

4. Potential therapeutic approaches targeting mitochondria

The etiology of tendinopathy remains largely elusive, resulting in a dearth of effective treatment options [136]. Existing management approaches primarily prioritize pain alleviation, while the formidable task of reinstating the tendon to its original healthy state persists as a significant challenge [3]. In recent years, researchers have increasingly recognized the crucial role of mitochondria in various diseases, including chronic metabolic disorders like obesity [137] and type 2 diabetes [138], as well as degenerative conditions such as intervertebral disc degeneration [139] and osteoarthritis [140]. In view of this insight, investigators have delved into diverse therapeutic avenues targeting mitochondria for disease intervention. Broadly, mitochondrial therapy can be categorized into the following core components: (1) Mitigating the adverse impacts of mitochondrial dysfunction such as ROS reduction. (2) Restoring mitochondrial function via chemical drugs and biologics. (3) Exogenous mitochondrial replenishment from healthy donor cells. Restoring mitochondrial function can be further divided into two approaches: direct targeting of mitochondria and indirect modulation of mitochondrial function.

4.1. Mitigating the adverse impacts of mitochondrial dysfunction

Mitochondrial dysfunction frequently results in an overproduction of

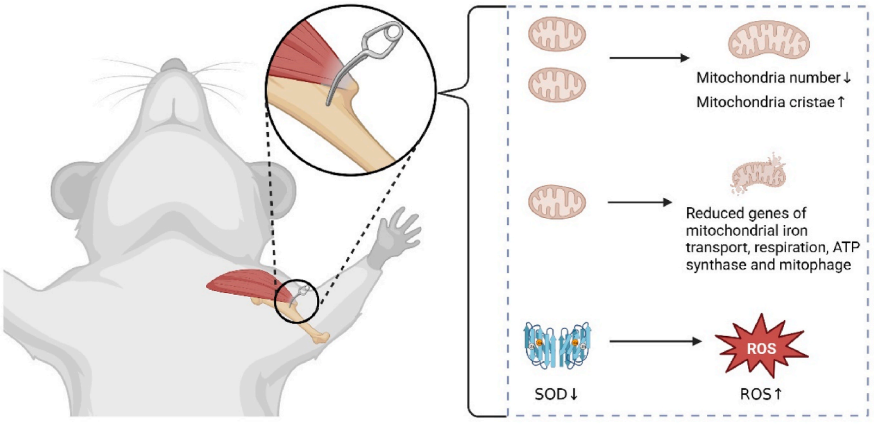

Figure 2. Mitochondrial abnormalities in tendinopathy. Tendinopathy is characterized by a decrease in the number of intracellular mitochondria and an increase in the number of cristae per mitochondrion. Additionally, the expression of genes associated with mitochondrial iron transport, respiration, ATP synthase, and mitophagy is reduced. Tendinopathy leads to a significant decrease in superoxide dismutase (SOD) levels, resulting in the accumulation of reactive oxygen species (ROS).

ROS, which detrimentally impacts cellular functions. Growing evidence indicates that countering the heightened ROS generation during tendinopathy holds promise as an efficacious strategy for alleviating its symptoms [117]. Numerous therapeutic approaches have been explored within this context (Fig. 3).

Growth hormone-releasing hormone (GHRH) is a neuropeptide derived from the hypothalamus that triggers the release of growth hormone and demonstrates beneficial effects in various diseases [141]. Synthetic GHRH agonists [142] have shown efficacy in animal models of diabetes [143], myocardial infarction [144], lung injury [145], and disc degeneration [146]. Controlled-release GHRH agonists exhibit ROS scavenging properties [147], hinder tendon calcification, reinstate tendon function, and enhance collagen synthesis, thus mitigating tendinopathy [122].

Proanthocyanidins (PC), potent natural antioxidants found in plants [148], showcases robust capabilities in scavenging free radicals [149, 150]. Moreover, it demonstrates anti-inflammatory effects and the ability to impede cardiac ossification. Researchers have harnessed mesoporous silica nanocomposites as carriers for PC, enabling controlled release directly to injured tendons in a mouse model. This targeted delivery proficiently mitigated ROS and suppressed abnormal tendon calcification [151].

OP2113, a synthetic drug recognized for its choleretic and anti-inflammatory properties, effectively curtails mitochondrial ROS production while leaving mitochondrial oxidative phosphorylation unimpeded [152]. Yet, a more comprehensive inquiry is warranted to unveil OP2113's precise mode of action. These revelations underscore the therapeutic potential of quelling surplus mitochondrial ROS production as a viable strategy for mitigating tendinopathy. Prospects for the future include the development of biomaterials tailored to precisely target afflicted regions and efficiently neutralize ROS, holding significant promise for enhancing tendinopathy treatment.

4.2. Restoring mitochondrial function

Mitochondria play a pivotal role in governing intracellular calcium ion levels. Elevated calcium concentrations within mitochondria can induce the formation of mitochondrial permeability transition pore (mPTP) complexes, which are implicated in cellular demise, diminished membrane potential, and apoptosis [153]. An mPTP inhibitor, cyclosporin A (CsA), a cyclic peptide, has been identified as capable of averting cell death triggered by oxidative stress [154]. CsA's potential shines through in its ability to rectify mitochondrial dysfunction and apoptosis across diverse experimental models, encompassing ischemia-reperfusion injury [155], collagen VI myopathy [156], and traumatic brain injury [157], suggesting a prospective avenue where CsA might emerge as a therapeutic agent for managing tendinopathy (Fig. 4).

SS-31, or elamipretide, stands out as a synthetic tetrapeptide with the remarkable capacity to rejuvenate mitochondrial function. It achieves this by precisely targeting the inner mitochondrial membrane, inhibiting the production of harmful ROS and enhancing the stability of cardiolipin, a pivotal constituent of mitochondrial membranes [158, 159]. SS-31's interactions are selective, centering on cardiolipin, which leads to the stabilization of mitochondrial cristae architecture, enhanced electron transfer, and the prevention of cytochrome c from converting into a peroxidase [160,161]. This protective effect upholds mitochondrial integrity, amplifies ATP synthesis and oxidative phosphorylation, diminishes ROS concentrations, and serves as a deterrent against apoptosis and inflammation [162]. Convincing preclinical studies have showcased SS-31's prowess in countering oxidative stress [163], guarding against ischemia-reperfusion injury [164], and refining mitochondrial efficiency [165]. Presently, clinical trials are in progress to assess its potential in managing heart failure, primary mitochondrial myopathy, and stent revascularization in atherosclerotic renal artery stenosis [166–168]. In a further dimension, SS-31 demonstrates the ability to mend compromised mitochondria [169], exhibiting lasting benefits even post-treatment, thus spotlighting its potential to ameliorate mitochondrial function in degenerative tendons and reinstate homeostasis to tenocytes (Fig. 4).

In chronic inflammation, an upsurge of calcium ions from the endoplasmic reticulum to mitochondria triggers mitochondrial calcium overload, instigating subsequent damage. In parallel, chronic inflammation prompts activation of the Wnt/β-linked protein pathway, curbing mitophagy and culminating in the accumulation of impaired mitochondria and compromised cellular function. Recent advancements introduce a transformative solution in the form of METP/siβ-linked protein nanoparticles. These nanoparticles exhibit a distinctive configuration, comprising a positively charged mesoporous silica nanoparticle core (TMA-MSN) engorged with siRNA, embraced by a shell formed by the intricate coupling of ethylene glycol tetraacetic acid (EGTA, a calcium chelator) and triphenyl phosphate (TPP, a mitochondrial targeting agent). The resultant METP NPs adeptly sequester mitochondrial-associated calcium. Remarkably, these nanoparticles additionally disperse siRNA, effectively suppressing the Wnt/β-linked protein pathway and thereby rejuvenating intracellular mitochondrial function [170]. This innovative approach heralds a fresh and promising avenue for the restoration of mitochondrial functionality within tendinopathy-affected tenocytes (Fig. 4).

Nicotinamide mononucleotide (NMN), a precursor to nicotinamide

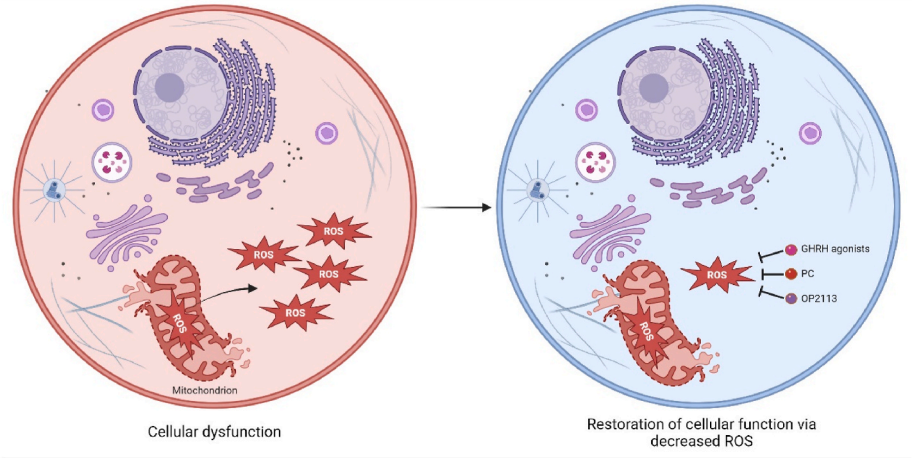

Figure 3. Mitigating the adverse impacts of mitochondrial dysfunction via ROS reduction. Growth hormone-releasing hormone (GHRH agonists), proanthocyanidins (PCs), and small molecule drugs such as OP2113 are utilized to scavenge excessive ROS produced by dysfunctional mitochondria, thereby restoring cellular function.

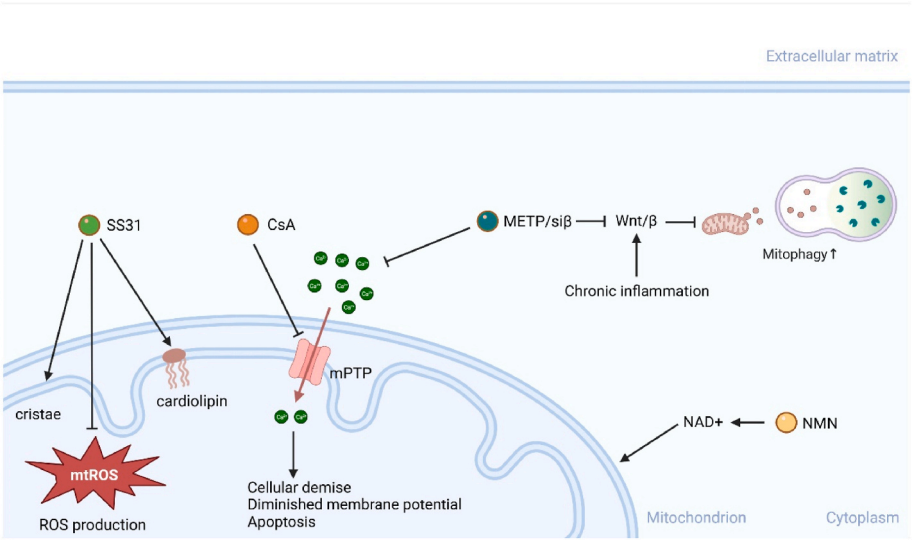

Figure 4. Restoring normal mitochondrial function via chemical drugs and biologics. Cyclosporin A (CsA) inhibits mitochondrial permeability transition pore (mPTP) complex, preventing cell death and restoring normal mitochondrial function. Elamipretide (SS-31) interacts with cardiolipin, stabilizing cristae morphology and protecting mitochondrial structure. Nicotinamide mononucleotide (NMN) promotes the biosynthesis of nicotinamide adenine dinucleotide (NAD+), enhancing mitochondrial function. METP/siβ binds excess calcium ions and initiates mitophagy to remove dysfunctional mitochondria.

adenine dinucleotide (NAD+), assumes a pivotal role in cellular energy metabolism. Through revitalizing the NAD+ recycling pathway, NMN augments NAD+ availability, thereby promoting oxidative phosphorylation, amplifying physiological reserves, and improving survival, observed both in aged mice and models of severe shock [171]. Notably, NMN exhibits efficacy in reinstating cardiac function in murine heart failure models. Unlike SS-31, NMN emphasizes NAD+ biosynthesis to fortify mitochondrial function [172]. Remarkably, a combination of SS-31 and NMN have synergistic potential in ameliorating cardiac dysfunction, suggesting the potential of mitochondria protection via NAD+ synthesis as a promising avenue in tendinopathy treatment (Fig. 4).

4.3. Mitochondrial replenishment

Given the pivotal role of mitochondrial function in tendinopathy, direct supplementation of mitochondria to tenocytes presents a promising avenue (Fig. 5). Lee et al. demonstrated the protective potential of intact exogenous mitochondrial transplantation against TNF-α-induced tenocyte injury and collagenase-induced tendinopathy in an animal model (Fig. 6A) [28]. Employing centrifugation and activation of damaged tenocytes, successful integration of mitochondria into tenocytes was achieved. Post-mitochondrial transplantation, alterations in TNMD, COL1, MMP1, and TNC levels were evident, accompanied by diminished pro-inflammatory markers. Exogenous mitochondria hold the potential to complement or supplant endogenous mitochondrial activity, with the presence of viable and healthy mitochondria proving pivotal in inducing favorable impacts on collagen production, oxidative stress, ATP content, and cell viability. However, the direct transfer of mitochondria encounters notable constraints, including the limited ability of tenocytes to directly access exogenous mitochondria. Substantial mitochondrial injections might be necessary, potentially fostering escalated production of mitochondrial DAMPs (damage-associated molecular patterns) that could counteract the advantageous consequences of mitochondrial transplantation. Consequently, enhancing the efficacy of mitochondrial transfer remains an imperative

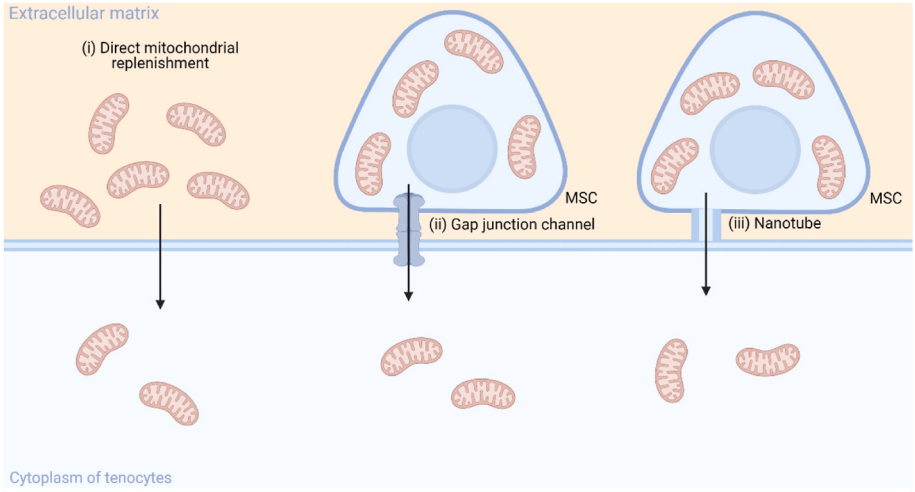

Figure 5. Mitochondrial-based therapy to restore tenocyte function. Exogenous mitochondrial supplementation methods, including (i) direct supplementation, (ii) gap junctions of mesenchymal stem/stromal cells (MSCs) and (iii) nanotube-mediated transfer from MSCs, have the potential to provide functional mitochondria to tendon cells.

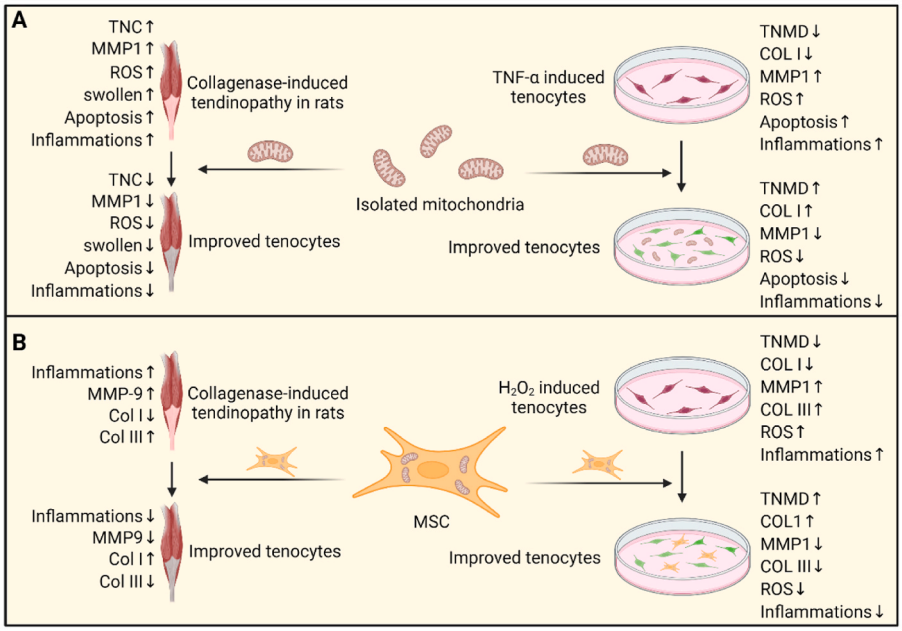

Figure 6. Existing work of Mitochondrial replenishment therapy for tendinopathy. (A) Topical injection of extracted mitochondria effectively alleviated tendinopathy in a rat tendinopathy model in vivo and in vitro; (B) Bone marrow-derived mesenchymal stromal cells (BMSCs) are effective in mitigating tendinopathy in rats through mitochondrial delivery, both in vivo and in vitro.

concern.

Stem cells are emerging as potential mitochondrial donors [37,173], partly due to the lower energy requirements of MSCs in the glycolytic state, facilitating mitochondrial transfer to energy-demanding diseased cells [174]. Furthermore, MSCs possess notable homing capabilities toward diseased tissues [175], presenting an avenue for targeted mitochondrial delivery. These cells also exhibit immune-modulatory properties and minimal oxidative damage, amplifying their appeal. Recent studies have shown that bone marrow-derived mesenchymal stromal cells (BMSC) have been effective in mitigating tendinopathy in rats through mitochondrial delivery (Fig. 6B) [176]. Notably, augmenting stem cells' capacity for mitochondrial transfer becomes crucial in this context. Huang et al. proposed the use of iron oxide nanoparticles (IONP) to engineer MSCs, with the aim of enhancing intercellular mitochondrial transfer. This approach involves the controlled release of iron ions within stem cells and the upregulation of Cx43, a pivotal protein governing intercellular gap junction channels, via the JNK pathway (Fig. 5). Elevated Cx43 expression fosters the transfer of functional mitochondria from stem cells to injured cells in vivo through gap junctions [177]. This innovative strategy presents an efficient means of bolstering mitochondrial infusion into compromised cells, particularly pertinent to tendinopathy. Recently, Huang et al. further discovered that pioglitazone can promote mitochondrial regeneration in MSCs [173]. This technique is also expected to promote mitochondrial regeneration in tenocytes, facilitating mitochondrial homeostasis and oxidative metabolism to aid in tendinopathy healing.

In 2004, Rustom et al. unveiled the phenomenon of organelle transfer between mammalian cells through tunneling nanotubes (TNTs, Fig. 5) [178]. These nanotubes, formed by microtubules and widely prevalent in vivo, play a pivotal role in facilitating mitochondrial transport. Notably, recent investigations have found that nanotubes enable tumor cells to acquire mitochondria from immune cells, enhancing their metabolic prowess while impeding immune cells' capacities—culminating in immune evasion. Furthermore, in the context of acute myeloid leukemia (AML), cancerous cells acquire mitochondria from neighboring mesenchymal stem cells via nanotubes, thus sustaining their expansion capabilities [179]. Within the skeletal motor system, Gao et al. illuminated the significance of ER-mitochondrial connections in orchestrating mitochondrial transfer amid osteoblasts [180]. Noteworthy also is the pivotal role of microtubule organization, dictating astrocytomas' heightened resistance to chemotherapy and radiotherapy compared to oligodendrocytes [181]. Nanotubes, as swift and efficient intercellular channels, emerge as potential channels for mitochondrial transport. Augmenting structural integrity of stem cell nanotubes and enhancing mitochondrial migration through these intercellular channels presents an enticing avenue for tendinopathy intervention.

5. Conclusion

Tendinopathy represents a multifaceted aging-related pathological progression in which mitochondrial dysfunction assumes a pivotal role. Mitochondria emerge as prominent generators of reactive oxygen species (ROS) within degenerative tendons, their activity tightly governed by stress-induced pathways [182]. Recent investigations have underscored the compelling relationship between mitochondrial dysfunction and tendinopathy [135]. Hence, unraveling the impact of mitochondrial dysfunction on the initiation and progression of tendinopathy holds paramount significance in elucidating the fundamental mechanisms at play.

Addressing tendinopathy remains a challenge due to the lack of effective solutions, despite the array of current available treatments that primarily target symptom relief. Tendon tissue, characterized by poor vascularity [183], often suffers from fibrosis and abnormal regenerative differentiation during injury healing [122,123], culminating in tendon disorders and clinical challenges. Therefore, it is crucial to target the underlying causes of tendon regeneration and restore cellular homeostasis during tendinopathy. Mitochondrial restoration/supplementation is believed to enhance cellular oxidative respiratory capacity, support normal cellular differentiation, and maintain homeostasis [36], presenting a promising solution for tendinopathy. Recent studies have shown that topical injection of mitochondria in a rat model of tendinopathy has yielded significant results [28], and BMSC have been effective in mitigating tendinopathy in rats through mitochondrial delivery [176]. These findings highlight the potential of mitochondrial therapy in addressing tendinopathy and signify a promising direction for future

treatments.

Macrophage mitochondrial dysfunction is known to be associated with various diseases, including tendinopathy. Research indicates that M1-type macrophages transfer damaged mitochondria to mesenchymal stem cells (MSC), leading to osteoporosis [184]. Additionally, dysfunctional macrophage mitochondria can exacerbate inflammation and impair myocardial repair [185]. As mentioned above, Mitochondrial protective strategies can mitigate mitochondrial stress and reduce cellular inflammation. Notably, a study utilizing energy-Supporting enzyme-mimic Nanoscaffold for tendons, focusing on mitochondrial protection and microenvironmental remodeling, effectively reduced SASP levels and modulated macrophage polarization, rebalancing repair signals and immune microenvironment dysregulation. This suggests that the efficacy of mitochondria-targeted therapy may be beneficial not only for tenocytes but also for macrophages in pathological processes [130].

Tendinopathy exert far-reaching repercussions, exacting a toll on mental health, life quality, professional engagements, physical activities, and social engagement. Current therapeutic avenues encompass a spectrum of approaches, spanning physical therapy to surgical interventions. Although diverse in mechanisms, these strategies converge in their pursuit to alleviate symptoms—primarily pain—expedite tendon recovery, and restore patient functionality. Yet, the regenerative capacities of tendons remain constrained by their limited vascularization, posing formidable obstacles to effective healing upon injury. Recognizing the paramount role of mitochondria harbors the potential for unveiling novel therapeutic modalities aimed at reinstating tendons to their inherent integrity. Insights into the healing trajectory of tendinopathy reveal promising targets through increased mitochondrial activity [135]. Notably, the emergence of mitochondria-targeted agents like SS-31, currently in clinical trials for mitochondria-linked ailments, holds the promise of decelerating tendinopathy progression and catalyzing tendon recuperation both in animal models and anticipated clinical investigations. Augmenting the efficiency of exogenous mitochondrial supplementation to ailing tenocytes carries the potential to amplify oxidative metabolism and effectively fulfill their physiological requisites. Capitalizing on distinct mitochondrial pathways further augments the therapeutic repertoire for tendinopathy, embarking on a course to identify innovative treatment strategies rooted in ameliorating mitochondrial malfunction.

Mitochondria have been widely studied for the treatment of various diseases due to their potent metabolic functions. In a study focusing on tendinopathy, local injection of extracted mitochondria successfully alleviated tendinopathy in a rat model [28], paving the way for potential clinical applications. Beyond local injections, systemic administration via intravenous delivery has shown promise in treating localized diseases. Researchers have developed mitochondria-encapsulated carrier proteins that efficiently target the liver when injected intravenously in mice [186], and have demonstrated successful mitochondrial transplantation through intra-arterial injection for treating acute kidney injury in pigs [187]. In addition to mitochondrial injection, intercellular mitochondrial transfer has emerged as a promising approach for disease treatment, ensuring the quality, functionality, and targeted delivery of transferred mitochondria. For example, studies have shown that BMSCs can alleviate rat tendinopathy through mitochondrial transfer [176]. To address potential limitations in donor cell mitochondrial quantity for disease correction, direct in vitro replenishment of MSCs with mitochondria before in vivo implantation appears to be a viable option, as described in a recent publication in *Nature* [188].

Mitochondrial therapy holds promise for treating tendinopathy, yet faces challenges in precise targeting. Mitochondrial dysfunction, often linked with aging, does not follow a specific pattern in conditions such as tendinopathy. One key challenge in targeting mitochondria for therapeutic purposes is the risk of unintended consequences and complications due to their ubiquitous and essential nature. Because mitochondria are present in nearly every cell in the body, any manipulation or intervention that affects their function could have far-reaching and unpredictable effects. This makes it difficult to design therapies that are both specific and safe. Furthermore, the mechanisms underlying mitochondrial dysfunction in different diseases and conditions can vary significantly. While tendinopathy may involve alterations in mitochondrial bioenergetics, oxidative stress, or dynamics, these changes may not be the same as those observed in other age-related conditions or diseases. Therefore, therapies that target mitochondria in a general sense may not be effective or may even be harmful in specific contexts. Consequently, more precise mitochondria-targeted therapies are required in clinical practice, and this is what researchers are working towards. Currently, artificially supplementing normal mitochondria into diseased tenocytes, or even normal tenocytes, is an interesting and promising strategy to maintain or enhance intracellular mitochondrial function. This strategy offers a substantial quantity of mitochondria for therapy within a specific timeframe and avoids the systemic issues associated with pharmacological treatments [189]. However, challenges persist with this approach, including the acquisition and maintenance of isolated mitochondria's integrity and functionality. Actually, transferring mitochondria with compromised quality may worsen disease progression [189,190]. Additionally, effectively targeting mitochondrial transport to specific damaged cells poses significant challenges [177]. As an alternative approach, intercellular mitochondrial transfer has been considered [191]. It has been observed that mitochondria are actively delivered from healthy to damaged cells under disease stress, indicating directional transfer [37,38]. However, the limited quantity of mitochondria in healthy cells often proves insufficient for effective disease treatment, significantly impacting treatment outcomes [173]. To achieve more effective mitochondrial transfer, one promising direction is the development of synthetic cell membranes capable of interacting with tenocytes to facilitate the efficient delivery of a large quantity of mitochondria into diseased cells [192]. Another feasible approach involves enhancing the mitochondrial amplification capacity of normal tenocytes or TSPCs to ensure adequate mitochondrial transfer [173].

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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References

[1] Andarawis-Puri N, Flatow EL, Soslowsky LJ. Tendon basic science: development, repair, regeneration, and healing. J Orthop Res : official publication of the Orthopaedic Research Society 2015;33(6):780–4.
[2] Thorpe CT, Screen HR. Tendon structure and composition. Advances in experimental medicine and biology 2016;920:3–10.
[3] Millar NL, Silbernagel KG, Thorborg K, Kirwan PD, Galatz LM, Abrams GD, et al. Tendinopathy. Nat Rev Dis Prim 2021;7(1):1.
[4] Kwan KYC, Ng KWK, Rao Y, Zhu C, Qi S, Tuan RS, et al. Effect of aging on tendon biology, biomechanics and implications for treatment approaches. Int J Mol Sci 2023;24(20).
[5] Albers IS, Zwerver J, Diercks RL, Dekker JH, Van den Akker-Scheek I. Incidence and prevalence of lower extremity tendinopathy in a Dutch general practice population: a cross sectional study. BMC Muscoskel Disord 2016;17:16.
[6] Aicale R, Bisaccia RD, Oliviero A, Oliva F, Maffulli N. Current pharmacological approaches to the treatment of tendinopathy. Expet Opin Pharmacother 2020;21(12):1467–77.
[7] Zhang YJ, Xu SZ, Gu PC, Du JY, Cai YZ, Zhang C, et al. Is platelet-rich plasma injection effective for chronic achilles tendinopathy? A meta-analysis. Clin Orthop Relat Res 2018;476(8):1633–41.
[8] Wilson F, Walshe M, O'Dwyer T, Bennett K, Mockler D, Bleakley C. Exercise, orthoses and splinting for treating Achilles tendinopathy: a systematic review with meta-analysis. Br J Sports Med 2018;52(24):1564–74.

[9] Auersperg V, Trieb K. Extracorporeal shock wave therapy: an update. EFORT open reviews 2020;5(10):584–92.
[10] Smallcomb M, Khandare S, Vidt ME, Simon JC. Therapeutic ultrasound and shockwave therapy for tendinopathy: a narrative review. American journal of physical medicine & rehabilitation 2022;101(8):801–7.
[11] Haslerud S, Magnussen LH, Joensen J, Lopes-Martins RA, Bjordal JM. The efficacy of low-level laser therapy for shoulder tendinopathy: a systematic review and meta-analysis of randomized controlled trials. Physiother Res Int : the journal for researchers and clinicians in physical therapy 2015;20(2):108–25.
[12] Murphy M, Travers M, Gibson W, Chivers P, Debenham J, Docking S, et al. Rate of improvement of pain and function in mid-portion achilles tendinopathy with loading protocols: a systematic review and longitudinal meta-analysis. Sports Med 2018;48(8):1875–91.
[13] Andres BM, Murrell GA. Treatment of tendinopathy: what works, what does not, and what is on the horizon. Clin Orthop Relat Res 2008;466(7):1539–54.
[14] Ilaltdinov AW, Gong Y, Leong DJ, Gruson KI, Zheng D, Fung DT, et al. Advances in the development of gene therapy, noncoding RNA, and exosome-based treatments for tendinopathy. Ann N Y Acad Sci 2021;1490(1):3–12.
[15] Yin Z, Hu JJ, Yang L, Zheng ZF, An CR, Wu BB, et al. Single-cell analysis reveals a nestin(+) tendon stem/progenitor cell population with strong tenogenic potentiality. Sci Adv 2016;2(11):e1600874.
[16] Zhang YJ, Chen X, Li G, Chan KM, Heng BC, Yin Z, et al. Concise review: stem cell fate guided by bioactive molecules for tendon regeneration. Stem cells translational medicine 2018;7(5):404–14.
[17] Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. Nat Rev Mol Cell Biol 2020;21(2):85–100.
[18] Schapira AH. Mitochondrial diseases. Lancet (London, England) 2012;379(9828):1825–34.
[19] Chakrabarty RP, Chandel NS. Mitochondria as signaling organelles control mammalian stem cell fate. Cell Stem Cell 2021;28(3):394–408.
[20] Szymański J, Janikiewicz J, Michalska B, Patalas-Krawczyk P, Perrone M, Ziółkowski W, et al. Interaction of mitochondria with the endoplasmic reticulum and plasma membrane in calcium homeostasis, lipid trafficking and mitochondrial structure. Int J Mol Sci 2017;18(7).
[21] Weinberg SE, Sena LA, Chandel NS. Mitochondria in the regulation of innate and adaptive immunity. Immunity 2015;42(3):406–17.
[22] Tamura Y, Kawano S, Endo T. Lipid homeostasis in mitochondria. Biol Chem 2020;401(6–7):821–33.
[23] Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell 2012;148(6):1145–59.
[24] Son JM, Lee C. Aging: all roads lead to mitochondria. Semin Cell Dev Biol 2021;116:160–8.
[25] Victorelli S, Salmonowicz H, Chapman J, Martini H, Vizioli MG, Riley JS, et al. Apoptotic stress causes mtDNA release during senescence and drives the SASP. Nature 2023;622(7983):627–36.
[26] Akbari M, Kirkwood TBL, Bohr VA. Mitochondria in the signaling pathways that control longevity and health span. Ageing Res Rev 2019;54:100940.
[27] Zhang H, Menzies KJ, Auwerx J. The role of mitochondria in stem cell fate and aging. Development (Cambridge, England) 2018;145(8).
[28] Lee JM, Hwang JW, Kim MJ, Jung SY, Kim KS, Ahn EH, et al. Mitochondrial transplantation modulates inflammation and apoptosis, alleviating tendinopathy both in vivo and in vitro. Antioxidants 2021;10(5).
[29] Wang Y, Jin S, Luo D, He D, Shi C, Zhu L, et al. Functional regeneration and repair of tendons using biomimetic scaffolds loaded with recombinant periostin. Nat Commun 2021;12(1):1293.
[30] Chen Y, Xie Y, Liu M, Hu J, Tang C, Huang J, et al. Controlled-release curcumin attenuates progression of tendon ectopic calcification by regulating the differentiation of tendon stem/progenitor cells. Mater Sci Eng C Mater Biol Appl 2019;103:109711.
[31] Cai Z, Zhang Y, Liu S, Liu X. Celecoxib, beyond anti-inflammation, alleviates tendon-derived stem cell senescence in degenerative rotator cuff tendinopathy. Am J Sports Med 2022;50(9):2488–96.
[32] Lowes DA, Wallace C, Murphy MP, Webster NR, Galley HF. The mitochondria targeted antioxidant MitoQ protects against fluoroquinolone-induced oxidative stress and mitochondrial membrane damage in human Achilles tendon cells. Free Radic Res 2009;43(4):323–8.
[33] Ploumi C, Daskalaki I, Tavernarakis N. Mitochondrial biogenesis and clearance: a balancing act. FEBS J 2017;284(2):183–95.
[34] Thankam FG, Chandra IS, Kovilam AN, Diaz CG, Volberding BT, Dilisio MF, et al. Amplification of mitochondrial activity in the healing response following rotator cuff tendon injury. Sci Rep 2018;8(1):17027.
[35] Oyewole AO, Birch-Machin MA. Mitochondria-targeted antioxidants. Faseb J : official publication of the Federation of American Societies for Experimental Biology 2015;29(12):4766–71.
[36] Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. Science (New York, NY) 2012;337(6098):1062–5.
[37] Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, et al. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. Nature medicine 2012;18(5):759–65.
[38] Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, et al. Transfer of mitochondria from astrocytes to neurons after stroke. Nature 2016;535(7613):551–5.
[39] Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, et al. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat Neurosci 2019;22(3):401–12.
[40] Nicolás-Ávila JA, Lechuga-Vieco AV, Esteban-Martínez L, Sánchez-Díaz M, Díaz-García E, Santiago DJ, et al. A network of macrophages supports mitochondrial homeostasis in the heart. Cell 2020;183(1):94–109.e23.
[41] Zhou B, Zhou Y, Tang K. An overview of structure, mechanical properties, and treatment for age-related tendinopathy. J Nutr Health Aging 2014;18(4):441–8.
[42] Balogh E, Veale DJ, McGarry T, Orr C, Szekanecz Z, Ng CT, et al. Oxidative stress impairs energy metabolism in primary cells and synovial tissue of patients with rheumatoid arthritis. Arthritis Res Ther 2018;20(1):95.
[43] Kowaltowski AJ, de Souza-Pinto NC, Castilho RF, Vercesi AE. Mitochondria and reactive oxygen species. Free radical biology & medicine 2009;47(4):333–43.
[44] Polo CC, Fonseca-Alaniz MH, Chen JH, Ekman A, McDermott G, Meneau F, et al. Three-dimensional imaging of mitochondrial cristae complexity using cryo-soft X-ray tomography. Sci Rep 2020;10(1):21045.
[45] Maneiro E, Martín MA, de Andres MC, López-Armada MJ, Fernández-Sueiro JL, del Hoyo P, et al. Mitochondrial respiratory activity is altered in osteoarthritic human articular chondrocytes. Arthritis Rheum 2003;48(3):700–8.
[46] Rodrigues MT, Reis RL, Gomes ME. Engineering tendon and ligament tissues: present developments towards successful clinical products. Journal of tissue engineering and regenerative medicine 2013;7(9):673–86.
[47] Gelberman RH, Lane RA, Sakiyama-Elbert SE, Thomopoulos S, Shen H. Metabolic regulation of intrasynovial flexor tendon repair: the effects of dichloroacetate administration on early tendon healing in a canine model. J Orthop Res : official publication of the Orthopaedic Research Society 2023;41(2):278–89.
[48] Kalghatgi S, Spina CS, Costello JC, Liesa M, Morones-Ramirez JR, Slomovic S, et al. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in Mammalian cells. Sci Transl Med 2013;5(192):192ra85.
[49] Qing J, Zhang Z, Novák P, Zhao G, Yin K. Mitochondrial metabolism in regulating macrophage polarization: an emerging regulator of metabolic inflammatory diseases. Acta biochimica et biophysica Sinica 2020;52(9):917–26.
[50] Zhong H, Yin H. Role of lipid peroxidation derived 4-hydroxynonenal (4-HNE) in cancer: focusing on mitochondria. Redox Biol 2015;4:193–9.
[51] Phull AR, Nasir B, Haq IU, Kim SJ. Oxidative stress, consequences and ROS mediated cellular signaling in rheumatoid arthritis. Chem Biol Interact 2018;281:121–36.
[52] Akuri MC, Barbalho SM, Val RM, Guiguer EL. Reflections about osteoarthritis and curcuma longa. Phcog Rev 2017;11(21):8–12.
[53] Lambert AJ, Brand MD. Reactive oxygen species production by mitochondria. Methods Mol Biol 2009;554:165–81.
[54] Venditti P, Di Stefano L, Di Meo S. Mitochondrial metabolism of reactive oxygen species. Mitochondrion 2013;13(2):71–82.
[55] Mao XY, Zhou HH, Jin WL. Redox-related neuronal death and crosstalk as drug targets: focus on epilepsy. Front Neurosci 2019;13:512.
[56] Khacho M, Harris R, Slack RS. Mitochondria as central regulators of neural stem cell fate and cognitive function. Nat Rev Neurosci 2019;20(1):34–48.
[57] Yu BP. Cellular defenses against damage from reactive oxygen species. Physiol Rev 1994;74(1):139–62.
[58] Panieri E, Santoro MM. ROS homeostasis and metabolism: a dangerous liaison in cancer cells. Cell Death Dis 2016;7(6):e2253.
[59] Nissanka N, Moraes CT. Mitochondrial DNA damage and reactive oxygen species in neurodegenerative disease. FEBS Lett 2018;592(5):728–42.
[60] Payne BA, Chinnery PF. Mitochondrial dysfunction in aging: much progress but many unresolved questions. Biochim Biophys Acta 2015;1847(11):1347–53.
[61] Ziegler DV, Wiley CD, Velarde MC. Mitochondrial effectors of cellular senescence: beyond the free radical theory of aging. Aging Cell 2015;14(1):1–7.
[62] Youle RJ, Narendra DP. Mechanisms of mitophagy. Nat Rev Mol Cell Biol 2011;12(1):9–14.
[63] Li K, Deng Y, Deng G, Chen P, Wang Y, Wu H, et al. High cholesterol induces apoptosis and autophagy through the ROS-activated AKT/FOXO1 pathway in tendon-derived stem cells. Stem Cell Res Ther 2020;11(1):131.
[64] Montagna C, Svensson RB, Bayer ML, Rizza S, Maiani E, Yeung CC, et al. Autophagy guards tendon homeostasis. Cell Death Dis 2022;13(4):402.
[65] Wauer T, Simicek M, Schubert A, Komander D. Mechanism of phospho-ubiquitin-induced PARKIN activation. Nature 2015;524(7565):370–4.
[66] Ni HM, Williams JA, Ding WX. Mitochondrial dynamics and mitochondrial quality control. Redox Biol 2015;4:6–13.
[67] Truban D, Hou X, Caulfield TR, Fiesel FC, Springer W. PINK1, Parkin, and mitochondrial quality control: what can we learn about Parkinson's disease pathobiology? J Parkinsons Dis 2017;7(1):13–29.
[68] Greene AW, Grenier K, Aguileta MA, Muise S, Farazifard R, Haque ME, et al. Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment. EMBO Rep 2012;13(4):378–85.
[69] Fedorowicz MA, de Vries-Schneider RL, Rüb C, Becker D, Huang Y, Zhou C, et al. Cytosolic cleaved PINK1 represses Parkin translocation to mitochondria and mitophagy. EMBO Rep 2014;15(1):86–93.
[70] Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature 2015;524(7565):309–14.
[71] Chan NC, Salazar AM, Pham AH, Sweredoski MJ, Kolawa NJ, Graham RL, et al. Broad activation of the ubiquitin-proteasome system by Parkin is critical for mitophagy. Hum Mol Genet 2011;20(9):1726–37.
[72] Yang M, Li C, Yang S, Xiao Y, Xiong X, Chen W, et al. Mitochondria-associated ER membranes - the origin site of autophagy. Front Cell Dev Biol 2020;8:595.
[73] Li XX, Tsoi B, Li YF, Kurihara H, He RR. Cardiolipin and its different properties in mitophagy and apoptosis. J Histochem Cytochem : official journal of the Histochemistry Society 2015;63(5):301–11.

[74] Granatiero V, Giorgio V, Calì T, Patron M, Brini M, Bernardi P, et al. Reduced mitochondrial Ca(2+) transients stimulate autophagy in human fibroblasts carrying the 13514A>G mutation of the ND5 subunit of NADH dehydrogenase. Cell Death Differ 2016;23(2):231–41.
[75] Ding Z, Liu S, Wang X, Dai Y, Khaidakov M, Deng X, et al. LOX-1, mtDNA damage, and NLRP3 inflammasome activation in macrophages: implications in atherogenesis. Cardiovasc Res 2014;103(4):619–28.
[76] Jiang Y, Krantz S, Qin X, Li S, Gunasekara H, Kim YM, et al. Caveolin-1 controls mitochondrial damage and ROS production by regulating fission - fusion dynamics and mitophagy. Redox Biol 2022;52:102304.
[77] Vakifahmetoglu-Norberg H, Ouchida AT, Norberg E. The role of mitochondria in metabolism and cell death. Biochemical and biophysical research communications 2017;482(3):426–31.
[78] Rossi A, Pizzo P, Filadi R. Calcium, mitochondria and cell metabolism: a functional triangle in bioenergetics. Biochimica et biophysica acta Molecular cell research 2019;1866(7):1068–78.
[79] Hurst S, Hoek J, Sheu SS. Mitochondrial Ca(2+) and regulation of the permeability transition pore. J Bioenerg Biomembr 2017;49(1):27–47.
[80] Fraysse B, Liantonio A, Cetrone M, Burdi R, Pierno S, Frigeri A, et al. The alteration of calcium homeostasis in adult dystrophic mdx muscle fibers is worsened by a chronic exercise in vivo. Neurobiol Dis 2004;17(2):144–54.
[81] Lv M, Zhou Y, Chen X, Han L, Wang L, Lu XL. Calcium signaling of in situ chondrocytes in articular cartilage under compressive loading: roles of calcium sources and cell membrane ion channels. J Orthop Res : official publication of the Orthopaedic Research Society 2018;36(2):730–8.
[82] Rizzuto R, Pinton P, Carrington W, Fay FS, Fogarty KE, Lifshitz LM, et al. Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca2+ responses. Science (New York, NY) 1998;280(5370):1763–6.
[83] Kania E, Roest G, Vervliet T, Parys JB, Bultynck G. IP(3) receptor-mediated calcium signaling and its role in autophagy in cancer. Frontiers in oncology 2017;7:140.
[84] Valladares D, Utreras-Mendoza Y, Campos C, Morales C, Diaz-Vegas A, Contreras-Ferrat A, et al. IP(3) receptor blockade restores autophagy and mitochondrial function in skeletal muscle fibers of dystrophic mice. Biochimica et biophysica acta Molecular basis of disease 2018;1864(11):3685–95.
[85] Lipper CH, Stofleth JT, Bai F, Sohn YS, Roy S, Mittler R, et al. Redox-dependent gating of VDAC by mitoNEET. Proceedings of the National Academy of Sciences of the United States of America 2019;116(40):19924–9.
[86] Fan M, Zhang J, Tsai CW, Orlando BJ, Rodriguez M, Xu Y, et al. Structure and mechanism of the mitochondrial Ca(2+) uniporter holocomplex. Nature 2020;582(7810):129–33.
[87] Chan DC. Mitochondrial dynamics and its involvement in disease. Annual review of pathology 2020;15:235–59.
[88] Wai T, Langer T. Mitochondrial dynamics and metabolic regulation. Trends in endocrinology and metabolism: TEM (Trends Endocrinol Metab) 2016;27(2):105–17.
[89] Chan DC. Fusion and fission: interlinked processes critical for mitochondrial health. Annu Rev Genet 2012;46:265–87.
[90] Bernhardt D, Müller M, Reichert AS, Osiewacz HD. Simultaneous impairment of mitochondrial fission and fusion reduces mitophagy and shortens replicative lifespan. Sci Rep 2015;5:7885.
[91] Schrader M. Shared components of mitochondrial and peroxisomal division. Biochim Biophys Acta 2006;1763(5–6):531–41.
[92] Smirnova E, Griparic L, Shurland DL, van der Bliek AM. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Mol Biol Cell 2001;12(8):2245–56.
[93] Fröhlich C, Grabiger S, Schwefel D, Faelber K, Rosenbaum E, Mears J, et al. Structural insights into oligomerization and mitochondrial remodelling of dynamin 1-like protein. The EMBO journal 2013;32(9):1280–92.
[94] Lee JE, Westrate LM, Wu H, Page C, Voeltz GK. Multiple dynamin family members collaborate to drive mitochondrial division. Nature 2016;540(7631):139–43.
[95] Yoon Y, Krueger EW, Oswald BJ, McNiven MA. The mitochondrial protein hFis1 regulates mitochondrial fission in mammalian cells through an interaction with the dynamin-like protein DLP1. Molecular and cellular biology 2003;23(15):5409–20.
[96] Yu T, Fox RJ, Burwell LS, Yoon Y. Regulation of mitochondrial fission and apoptosis by the mitochondrial outer membrane protein hFis1. J Cell Sci 2005;118(Pt 18):4141–51.
[97] Thomas KJ, Jacobson MR. Defects in mitochondrial fission protein dynamin-related protein 1 are linked to apoptotic resistance and autophagy in a lung cancer model. PLoS One 2012;7(9):e45319.
[98] Koshiba T, Detmer SA, Kaiser JT, Chen H, McCaffery JM, Chan DC. Structural basis of mitochondrial tethering by mitofusin complexes. Science (New York, NY) 2004;305(5685):858–62.
[99] Tilokani L, Nagashima S, Paupe V, Prudent J. Mitochondrial dynamics: overview of molecular mechanisms. Essays Biochem 2018;62(3):341–60.
[100] Ishihara N, Eura Y, Mihara K. Mitofusin 1 and 2 play distinct roles in mitochondrial fusion reactions via GTPase activity. J Cell Sci 2004;117(Pt 26):6535–46.
[101] Brandt T, Cavellini L, Kühlbrandt W, Cohen MM. A mitofusin-dependent docking ring complex triggers mitochondrial fusion in vitro. Elife 2016;5.
[102] Ban T, Ishihara T, Kohno H, Saita S, Ichimura A, Maenaka K, et al. Molecular basis of selective mitochondrial fusion by heterotypic action between OPA1 and cardiolipin. Nat Cell Biol 2017;19(7):856–63.
[103] Chen H, Vermulst M, Wang YE, Chomyn A, Prolla TA, McCaffery JM, et al. Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. Cell 2010;141(2):280–9.
[104] Rossignol R, Gilkerson R, Aggeler R, Yamagata K, Remington SJ, Capaldi RA. Energy substrate modulates mitochondrial structure and oxidative capacity in cancer cells. Cancer Res 2004;64(3):985–93.
[105] Anesti V, Scorrano L. The relationship between mitochondrial shape and function and the cytoskeleton. Biochim Biophys Acta 2006;1757(5–6):692–9.
[106] Dubé JJ, Collyer ML, Trant S, Toledo FGS, Goodpaster BH, Kershaw EE, et al. Decreased mitochondrial dynamics is associated with insulin resistance, metabolic rate, and fitness in african Americans. The Journal of clinical endocrinology and metabolism 2020;105(4):1210–20.
[107] Srinivasan S, Guha M, Kashina A, Avadhani NG. Mitochondrial dysfunction and mitochondrial dynamics-The cancer connection. Biochimica et biophysica acta Bioenergetics 2017;1858(8):602–14.
[108] Dai DF, Rabinovitch PS, Ungvari Z. Mitochondria and cardiovascular aging. Circ Res 2012;110(8):1109–24.
[109] Riley G. Tendinopathy–from basic science to treatment. Nat Clin Pract Rheumatol 2008;4(2):82–9.
[110] Wu YT, Wu YT, Huang TC, Su FC, Jou IM, Wu CC. Sequential inflammation model for Achilles tendinopathy by elastin degradation with treadmill exercise. Journal of orthopaedic translation 2020;23:113–21.
[111] Kannus P, Józsa L. Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. J Bone Jt Surg Am Vol 1991;73(10):1507–25.
[112] Maffulli N, Barrass V, Ewen SW. Light microscopic histology of achilles tendon ruptures. A comparison with unruptured tendons. Am J Sports Med 2000;28(6):857–63.
[113] Maffulli N, Ewen SW, Waterston SW, Reaper J, Barrass V. Tenocytes from ruptured and tendinopathic achilles tendons produce greater quantities of type III collagen than tenocytes from normal achilles tendons. An in vitro model of human tendon healing. Am J Sports Med 2000;28(4):499–505.
[114] Weidinger A, Kozlov AV. Biological activities of reactive oxygen and nitrogen species: oxidative stress versus signal transduction. Biomolecules 2015;5(2):472–84.
[115] Dakin SG, Buckley CD, Al-Mossawi MH, Hedley R, Martinez FO, Wheway K, et al. Persistent stromal fibroblast activation is present in chronic tendinopathy. Arthritis Res Ther 2017;19(1):16.
[116] Fu W, Yang R, Li J. Single-cell and spatial transcriptomics reveal changes in cell heterogeneity during progression of human tendinopathy. BMC Biol 2023;21(1):132.
[117] Zhang X, Eliasberg CD, Rodeo SA. Mitochondrial dysfunction and potential mitochondrial protectant treatments in tendinopathy. Ann N Y Acad Sci 2021;1490(1):29–41.
[118] Yuan J, Murrell GA, Trickett A, Wang MX. Involvement of cytochrome c release and caspase-3 activation in the oxidative stress-induced apoptosis in human tendon fibroblasts. Biochim Biophys Acta 2003;1641(1):35–41.
[119] Yuan J, Murrell GA, Wei AQ, Wang MX. Apoptosis in rotator cuff tendonopathy. J Orthop Res : official publication of the Orthopaedic Research Society 2002;20(6):1372–9.
[120] Millar NL, Wei AQ, Molloy TJ, Bonar F, Murrell GA. Cytokines and apoptosis in supraspinatus tendinopathy. The Journal of Bone and Joint Surgery British 2009;91(3):417–24.
[121] Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat Rev Neurosci 2019;20(3):148–60.
[122] Shen H, Cheng L, Zheng Q, Liu W, Wang Y. Scavenging of reactive oxygen species can adjust the differentiation of tendon stem cells and progenitor cells and prevent ectopic calcification in tendinopathy. Acta Biomater 2022;152:440–52.
[123] Liu RC, Zhou B, Zhang H, Chen YW, Fan CM, Zhang T, et al. Inhibition of ROS activity by controlled release of proanthocyanidins from mesoporous silica nanocomposites effectively ameliorates heterotopic ossification in tendon. Chem Eng J 2021;420.
[124] Liu A, Wang Q, Zhao Z, Wu R, Wang M, Li J, et al. Nitric oxide nanomotor driving exosomes-loaded microneedles for achilles tendinopathy healing. ACS Nano 2021;15(8):13339–50.
[125] Grazioli S, Pugin J. Mitochondrial damage-associated molecular patterns: from inflammatory signaling to human diseases. Front Immunol 2018;9:832.
[126] Millar NL, Murrell GA. Heat shock proteins in tendinopathy: novel molecular regulators. Mediators Inflamm 2012;2012:436203.
[127] Tang C, Chen Y, Huang J, Zhao K, Chen X, Yin Z, et al. The roles of inflammatory mediators and immunocytes in tendinopathy. Journal of orthopaedic translation 2018;14:23–33.
[128] Zhang Y, Deng XH, Lebaschi AH, Wada S, Carballo CB, Croen B, et al. Expression of alarmins in a murine rotator cuff tendinopathy model. J Orthop Res : official publication of the Orthopaedic Research Society 2020;38(11):2513–20.
[129] Mills EL, Kelly B, Logan A, Costa ASH, Varma M, Bryant CE, et al. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell 2016;167(2). 457-70.e13.
[130] Wang S, Yao Z, Zhang X, Li J, Huang C, Ouyang Y, et al. Energy-supporting enzyme-mimic Nanoscaffold facilitates tendon regeneration based on a mitochondrial protection and microenvironment remodeling strategy. Adv Sci 2022;9(31):e2202542.
[131] Gustafsson AB. Bnip3 as a dual regulator of mitochondrial turnover and cell death in the myocardium. Pediatr Cardiol 2011;32(3):267–74.
[132] Xu Y, Murrell GA. The basic science of tendinopathy. Clin Orthop Relat Res 2008;466(7):1528–38.

[133] Pingel J, Petersen MC, Fredberg U, Kjær SG, Quistorff B, Langberg H, et al. Inflammatory and metabolic alterations of kager's fat pad in chronic achilles tendinopathy. PLoS One 2015;10(5):e0127811.
[134] Glick D, Zhang W, Beaton M, Marsboom G, Gruber M, Simon MC, et al. BNip3 regulates mitochondrial function and lipid metabolism in the liver. Mol Cell Biol 2012;32(13):2570–84.
[135] Zhang X, Wada S, Zhang Y, Chen D, Deng XH, Rodeo SA. Assessment of mitochondrial dysfunction in a murine model of supraspinatus tendinopathy. J Bone Jt Surg Am Vol 2021;103(2):174–83.
[136] Aicale R, Oliviero A, Maffulli N. Management of Achilles and patellar tendinopathy: what we know, what we can do. J Foot Ankle Res 2020;13(1):59.
[137] Brestoff JR, Wilen CB, Moley JR, Li Y, Zou W, Malvin NP, et al. Intercellular mitochondria transfer to macrophages regulates white adipose tissue homeostasis and is impaired in obesity. Cell Metabol 2021;33(2). 270-82.e8.
[138] Apostolova N, Iannantuoni F, Gruevska A, Muntane J, Rocha M, Victor VM. Mechanisms of action of metformin in type 2 diabetes: effects on mitochondria and leukocyte-endothelium interactions. Redox Biol 2020;34:101517.
[139] Kang L, Liu S, Li J, Tian Y, Xue Y, Liu X. The mitochondria-targeted anti-oxidant MitoQ protects against intervertebral disc degeneration by ameliorating mitochondrial dysfunction and redox imbalance. Cell Prolif 2020;53(3):e12779.
[140] Yu M, Wang D, Chen X, Zhong D, Luo J. BMSCs-derived mitochondria improve osteoarthritis by ameliorating mitochondrial dysfunction and promoting mitochondrial biogenesis in chondrocytes. Stem cell reviews and reports 2022;18(8):3092–111.
[141] Ma Q, Xia X, Tao Q, Lu K, Shen J, Xu Q, et al. Profound actions of an agonist of growth hormone-releasing hormone on angiogenic therapy by mesenchymal stem cells. Arterioscler Thromb Vasc Biol 2016;36(4):663–72.
[142] Gomes SA, Rangel EB, Premer C, Dulce RA, Cao Y, Florea V, et al. S-nitrosoglutathione reductase (GSNOR) enhances vasculogenesis by mesenchymal stem cells. Proceedings of the National Academy of Sciences of the United States of America 2013;110(8):2834–9.
[143] Zhang X, Cui T, He J, Wang H, Cai R, Popovics P, et al. Beneficial effects of growth hormone-releasing hormone agonists on rat INS-1 cells and on streptozotocin-induced NOD/SCID mice. Proceedings of the National Academy of Sciences of the United States of America 2015;112(44):13651–6.
[144] Kanashiro-Takeuchi RM, Tziomalos K, Takeuchi LM, Treuer AV, Lamirault G, Dulce R, et al. Cardioprotective effects of growth hormone-releasing hormone agonist after myocardial infarction. Proceedings of the National Academy of Sciences of the United States of America 2010;107(6):2604–9.
[145] Czikora I, Sridhar S, Gorshkov B, Alieva IB, Kasa A, Gonzales J, et al. Protective effect of Growth Hormone-Releasing Hormone agonist in bacterial toxin-induced pulmonary barrier dysfunction. Front Physiol 2014;5:259.
[146] Feng ZY, Hu XJ, Zheng QQ, Battié MC, Chen Z, Wang Y. Cartilaginous endplate avulsion is associated with modic changes and endplate defects, and residual back and leg pain following lumbar discectomy. Osteoarthritis Cartilage 2021;29(5):707–17.
[147] Katsumi H, Nishikawa M, Nishiyama K, Hirosaki R, Nagamine N, Okamoto H, et al. Development of PEGylated serum albumin with multiple reduced thiols as a long-circulating scavenger of reactive oxygen species for the treatment of fulminant hepatic failure in mice. Free radical biology & medicine 2014;69:318–23.
[148] Rauf A, Imran M, Abu-Izneid T, Iahtisham Ul H, Patel S, Pan X, et al. Proanthocyanidins: a comprehensive review. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2019;116:108999.
[149] Torres JL, Varela B, García MT, Carilla J, Matito C, Centelles JJ, et al. Valorization of grape (Vitis vinifera) byproducts. Antioxidant and biological properties of polyphenolic fractions differing in procyanidin composition and flavonol content. J Agric Food Chem 2002;50(26):7548–55.
[150] Dong C. Protective effect of proanthocyanidins in cadmium induced neurotoxicity in mice. Drug research 2015;65(10):555–60.
[151] Liu RC, Zhou B, Zhang H, Chen YW, Fan CM, Zhang T, et al. Inhibition of ROS activity by controlled release of proanthocyanidins from mesoporous silica nanocomposites effectively ameliorates heterotopic ossification in tendon. Chem Eng J 2021;420:12.
[152] Detaille D, Pasdois P, Sémont A, Dos Santos P, Diolez P. An old medicine as a new drug to prevent mitochondrial complex I from producing oxygen radicals. PLoS One 2019;14(5):e0216385.
[153] Chan DC. Mitochondrial fusion and fission in mammals. Annu Rev Cell Dev Biol 2006;22:79–99.
[154] Weissig V. Mitochondrial-targeted drug and DNA delivery. Crit Rev Ther Drug Carrier Syst 2003;20(1):1–62.
[155] Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, et al. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med 2008;359(5):473–81.
[156] Merlini L, Angelin A, Tiepolo T, Braghetta P, Sabatelli P, Zamparelli A, et al. Cyclosporin A corrects mitochondrial dysfunction and muscle apoptosis in patients with collagen VI myopathies. Proceedings of the National Academy of Sciences of the United States of America 2008;105(13):5225–9.
[157] Chen L, Song Q, Chen Y, Meng S, Zheng M, Huang J, et al. Tailored reconstituted lipoprotein for site-specific and mitochondria-targeted cyclosporine A delivery to treat traumatic brain injury. ACS Nano 2020;14(6):6636–48.
[158] Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. Br J Pharmacol 2014;171(8):2029–50.
[159] Chavez JD, Tang X, Campbell MD, Reyes G, Kramer PA, Stuppard R, et al. Mitochondrial protein interaction landscape of SS-31. Proceedings of the National Academy of Sciences of the United States of America 2020;117(26):15363–73.
[160] Birk AV, Liu S, Soong Y, Mills W, Singh P, Warren JD, et al. The mitochondrial-targeted compound SS-31 re-energizes ischemic mitochondria by interacting with cardiolipin. J Am Soc Nephrol : JASN (J Am Soc Nephrol) 2013;24(8):1250–61.
[161] Birk AV, Chao WM, Bracken C, Warren JD, Szeto HH. Targeting mitochondrial cardiolipin and the cytochrome c/cardiolipin complex to promote electron transport and optimize mitochondrial ATP synthesis. Br J Pharmacol 2014;171(8):2017–28.
[162] Birk AV, Chao WM, Liu S, Soong Y, Szeto HH. Disruption of cytochrome c heme coordination is responsible for mitochondrial injury during ischemia. Biochim Biophys Acta 2015;1847(10):1075–84.
[163] Hou Y, Li S, Wu M, Wei J, Ren Y, Du C, et al. Mitochondria-targeted peptide SS-31 attenuates renal injury via an antioxidant effect in diabetic nephropathy. Am J Physiol Ren Physiol 2016;310(6):F547–59.
[164] Cai J, Jiang Y, Zhang M, Zhao H, Li H, Li K, et al. Protective effects of mitochondrion-targeted peptide SS-31 against hind limb ischemia-reperfusion injury. J Physiol Biochem 2018;74(2):335–43.
[165] Chiao YA, Zhang H, Sweetwyne M, Whitson J, Ting YS, Basisty N, et al. Late-life restoration of mitochondrial function reverses cardiac dysfunction in old mice. Elife 2020;9.
[166] Daubert MA, Yow E, Dunn G, Marchev S, Barnhart H, Douglas PS, et al. Novel mitochondria-targeting peptide in heart failure treatment: a randomized, placebo-controlled trial of elamipretide. Circulation Heart failure 2017;10(12).
[167] Saad A, Herrmann SMS, Eirin A, Ferguson CM, Glockner JF, Bjarnason H, et al. Phase 2a clinical trial of mitochondrial protection (elamipretide) during stent revascularization in patients with atherosclerotic renal artery stenosis. Circulation Cardiovascular interventions 2017;10(9).
[168] de Barcelos IP, Emmanuele V, Hirano M. Advances in primary mitochondrial myopathies. Curr Opin Neurol 2019;32(5):715–21.
[169] Szeto HH. Pharmacologic approaches to improve mitochondrial function in AKI and CKD. J Am Soc Nephrol : JASN (J Am Soc Nephrol) 2017;28(10):2856–65.
[170] Zhai Q, Chen X, Fei D, Guo X, He X, Zhao W, et al. Nanorepairers rescue inflammation-induced mitochondrial dysfunction in mesenchymal stem cells. Adv Sci 2022;9(4):e2103839.
[171] Sims CA, Guan Y, Mukherjee S, Singh K, Botolin P, Davila Jr A, et al. Nicotinamide mononucleotide preserves mitochondrial function and increases survival in hemorrhagic shock. JCI insight 2018;3(17).
[172] Whitson JA, Bitto A, Zhang H, Sweetwyne MT, Coig R, Bhayana S, et al. SS-31 and NMN: two paths to improve metabolism and function in aged hearts. Aging Cell 2020;19(10):e13213.
[173] Huang T, Lin R, Su Y, Sun H, Zheng X, Zhang J, et al. Efficient intervention for pulmonary fibrosis via mitochondrial transfer promoted by mitochondrial biogenesis. Nat Commun 2023;14(1):5781.
[174] Chen CT, Shih YR, Kuo TK, Lee OK, Wei YH. Coordinated changes of mitochondrial biogenesis and antioxidant enzymes during osteogenic differentiation of human mesenchymal stem cells. Stem cells (Dayton, Ohio) 2008;26(4):960–8.
[175] Zhang TY, Huang B, Wu HB, Wu JH, Li LM, Li YX, et al. Synergistic effects of co-administration of suicide gene expressing mesenchymal stem cells and prodrug-encapsulated liposome on aggressive lung melanoma metastases in mice. J Contr Release : official journal of the Controlled Release Society 2015;209:260–71.
[176] Wei B, Ji M, Lin Y, Wang S, Liu Y, Geng R, et al. Mitochondrial transfer from bone mesenchymal stem cells protects against tendinopathy both in vitro and in vivo. Stem Cell Res Ther 2023;14(1):104.
[177] Huang T, Zhang T, Jiang X, Li A, Su Y, Bian Q, et al. Iron oxide nanoparticles augment the intercellular mitochondrial transfer-mediated therapy. Sci Adv 2021;7(40):eabj0534.
[178] Rustom A, Saffrich R, Markovic I, Walther P, Gerdes HH. Nanotubular highways for intercellular organelle transport. Science (New York, NY) 2004;303(5660):1007–10.
[179] Marlein CR, Zaitseva L, Piddock RE, Robinson SD, Edwards DR, Shafat MS, et al. NADPH oxidase-2 derived superoxide drives mitochondrial transfer from bone marrow stromal cells to leukemic blasts. Blood 2017;130(14):1649–60.
[180] Gao J, Qin A, Liu D, Ruan R, Wang Q, Yuan J, et al. Endoplasmic reticulum mediates mitochondrial transfer within the osteocyte dendritic network. Sci Adv 2019;5(11):eaaw7215.
[181] Osswald M, Jung E, Sahm F, Solecki G, Venkataramani V, Blaes J, et al. Brain tumour cells interconnect to a functional and resistant network. Nature 2015;528(7580):93–8.
[182] Murrell GA. Oxygen free radicals and tendon healing. J Shoulder Elbow Surg 2007;16(5 Suppl):S208–14.
[183] Chen Y, Shen W, Tang C, Huang J, Fan C, Yin Z, et al. Targeted pathological collagen delivery of sustained-release rapamycin to prevent heterotopic ossification. Sci Adv 2020;6(18):eaay9526.
[184] Cai W, Zhang J, Yu Y, Ni Y, Wei Y, Cheng Y, et al. Mitochondrial transfer regulates cell fate through metabolic remodeling in osteoporosis. Adv Sci 2023;10(4):e2204871.
[185] Cai S, Zhao M, Zhou B, Yoshii A, Bugg D, Villet O, et al. Mitochondrial dysfunction in macrophages promotes inflammation and suppresses repair after myocardial infarction. The Journal of clinical investigation 2023;133(4).
[186] Liu X, Khouri-Farah N, Wu CH, Wu GY. Targeted delivery of mitochondria to the liver in rats. J Gastroenterol Hepatol 2020;35(12):2241–7.
[187] Doulamis IP, Guariento A, Duignan T, Kido T, Orfany A, Saeed MY, et al. Mitochondrial transplantation by intra-arterial injection for acute kidney injury. Am J Physiol Renal Physiol 2020;319(3). F403-f13.

[188] Lin RZ, Im GB, Luo AC, Zhu Y, Hong X, Neumeyer J, et al. Mitochondrial transfer mediates endothelial cell engraftment through mitophagy. Nature 2024;629 (8012):660–8.
[189] Caicedo A, Aponte PM, Cabrera F, Hidalgo C, Khoury M. Artificial mitochondria transfer: current challenges, advances, and future applications. Stem Cell Int 2017;2017:7610414.
[190] Picard M, Taivassalo T, Ritchie D, Wright KJ, Thomas MM, Romestaing C, et al. Mitochondrial structure and function are disrupted by standard isolation methods. PLoS One 2011;6(3):e18317.
[191] Li H, Wang C, He T, Zhao T, Chen YY, Shen YL, et al. Mitochondrial transfer from bone marrow mesenchymal stem cells to motor neurons in spinal cord injury rats via gap junction. Theranostics 2019;9(7):2017–35.
[192] Wu Z, Chen L, Guo W, Wang J, Ni H, Liu J, et al. Oral mitochondrial transplantation using nanomotors to treat ischaemic heart disease. Nat Nanotechnol 2024;19(9):1375–85.