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Review

Aging and Autophagy: Roles in Musculoskeletal System Injury

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ABSTRACT: Aging is a multifactorial process that ultimately leads to a decline in physiological function and a consequent reduction in the health span, and quality of life in elderly population. In musculoskeletal diseases, aging is often associated with a gradual loss of skeletal muscle mass and strength, resulting in reduced functional capacity and an increased risk of chronic metabolic diseases, leading to impaired function and increased mortality. Autophagy is a highly conserved physiological process by which cells, under the regulation of autophagy-related genes, degrade their own organelles and large molecules by lysosomal degradation. This process is unique to eukaryotic cells and is a strict regulator of homeostasis, the maintenance of energy and substance balance. Autophagy plays an important role in a wide range of physiological and pathological processes such as cell homeostasis, aging, immunity, tumorigenesis and neurodegenerative diseases. On the one hand, under mild stress conditions, autophagy mediates the restoration of homeostasis and proliferation, reduction of the rate of aging and delay of the aging process. On the other hand, under more intense stress conditions, an inadequate suppression of autophagy can lead to cellular aging. Conversely, autophagy activity decreases during aging. Due to the interrelationship between aging and autophagy, limited literature exists on this topic. Therefore, the objective of this review is to summarize the current concepts on aging and autophagy in the musculoskeletal system. The aim is to better understand the mechanisms of age-related changes in bone, joint and muscle, as well as the interaction relationship between autophagy and aging. Its goal is to provide a comprehensive perspective for the improvement of diseases of the musculoskeletal system.

Key words: aging, senescence, autophagy, musculoskeletal system

1. Introduction

Aging refers to the inevitable functional deterioration, internal instability, reduced resilience and progressive breakdown of the structure and components of the physiological organs of an organism with age, which leads to irreversible death [1]. It is also one of the major risk factors for human diseases including cancer, cardiovascular disease, diabetes and neurodegenerative diseases. Approximately 150,000 people die each day worldwide, with two-thirds of these deaths attributable to aging [2]. Almost all multicellular organisms show signs of aging over time. The gradual loss or deterioration of tissue and organ function results in many chronic age-related diseases. The underlying basis for these conditions may be shared by some common molecular and cellular mechanisms. Cell senescence is a response of cells to stress that involves irreversible cell cycle arrest and loss of proliferative activity [3]. The phenomenon of cellular senescence was first observed in 1961 by the microbiologists Leonard Hayflick and Paul Moorhead, who observed that fibroblasts in vitro cultures stopped growing after more than 50 passages [4]. Cellular senescence is a prominent manifestation of the aging process and is a driving factor in the development of many age-related diseases. In addition, cellular senescence can

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occur at any stage of life, from the embryonic stage to adulthood [5-6]. It is a highly regulated process, and when any part of this process is disrupted, it can have both positive effects on the body, such as playing an essential role in normal development, maintaining tissue homeostasis, and inhibiting tumor proliferation, as well as negative effects, driving age-related pathological processes [7-8]. Understanding the mechanisms of aging, its effects on organ function, and the prevention or slowing of aging is therefore of paramount importance [9].

This review focuses on aspects of musculoskeletal injuries, summarized with aging and autophagy as the main keywords. The Pubmed and Web of Science websites were then searched using keywords such as aging, autophagy, and musculoskeletal system, and the main scope of the review is shown in Figure 1.

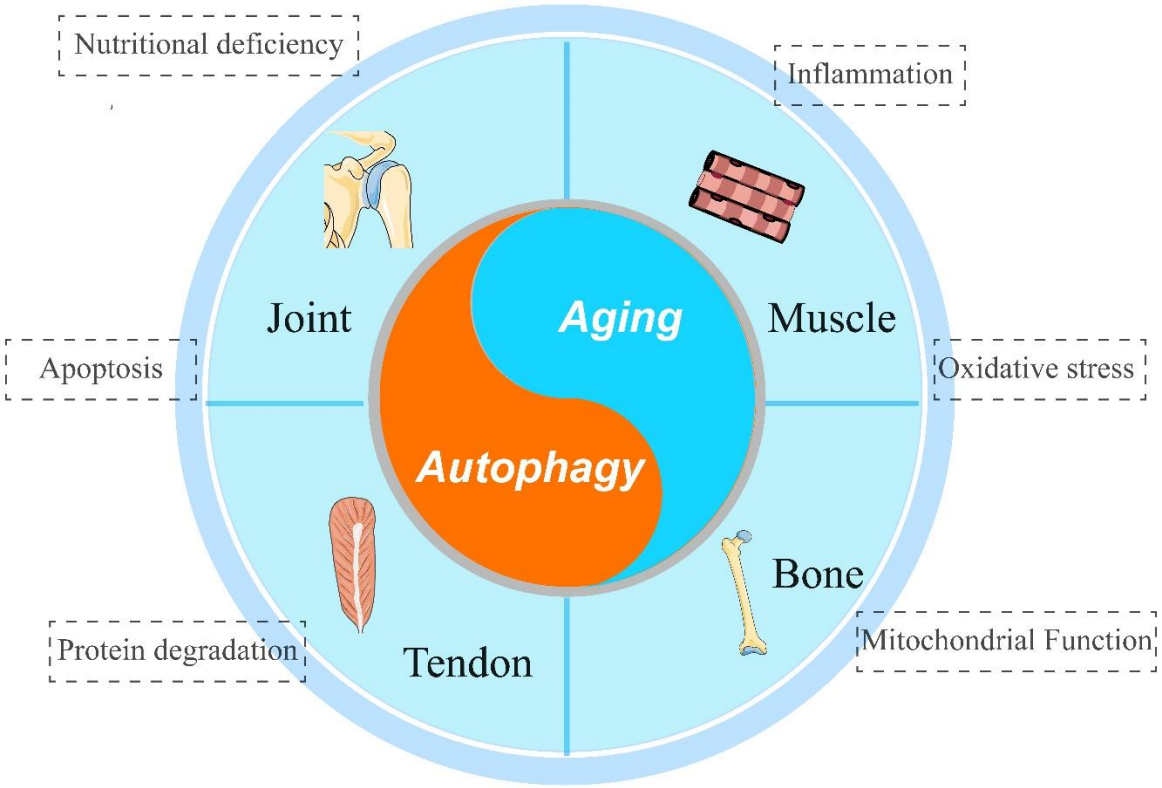

Figure 1. Search for injuries to the musculoskeletal system on the topic of autophagy and aging, including the mechanisms of injury that occur in the bones, muscles, tendons, and joints.

2. Aging involved various physiological mechanisms

The current point of view is that cellular senescence is a self-protective mechanism of the cells in response to endogenous and exogenous stress. It occurs under conditions including DNA damage, telomere shortening, oncogene activation, epigenetic changes, oxidative stress, and others [10]. It is characterized by permanent growth arrest, where the cell cycle stops at G1 or S to prevent the propagation of abnormal genes to the next generation of cells, thereby maintaining organismal homeostasis [11-12]. During cellular senescence, cells undergo changes in their morphology, which typically include enlargement and flattening [13]. Depending on the cause of senescence, it can be classified into replicative senescence and stress-induced premature senescence [14], the latter including various types such as DNA damage senescence, oxidative stress senescence, epigenetic senescence, and inflammatory senescence. Increased expression of the p21, p16 and p53 pathways, enhanced activity of senescence-associated β-galactosidase (SA-β-gal) and high levels of reactive oxygen species (ROS) are typical features of stress-induced premature senescence [15]. In addition, a high level of expression of p19ARF, p53, and plasminogen activator inhibitor-1 (PAI-1) has been observed in senescent cells and has been used as a marker for senescent cells [16]. Although senescent cells stop dividing, they still possess metabolic functions and can secrete a variety of senescence-associated secretory phenotypes (SASP), including matrix metalloproteinases (MMPs), growth factors, pro-inflammatory cytokines, and chemokines. These secretions act through paracrine

pathways to increase local expression levels of inflammatory mediators and matrix-degrading enzymes, thereby affecting surrounding cells and tissues [17]. Acute cellular senescence contributes to the maintenance of organismal homeostasis. Secreted growth factors can promote embryonic development [18-19], wound healing [20], and insulin secretion [21]. However, the persistence of senescent cells accelerates the dysfunction of tissues and organs, leading to the degenerative diseases associated with aging [22].

Cellular senescence is a key mechanism in the pathogenesis of age-related diseases. With increasing age, senescent cells accumulate in a variety of organs and systems and are accompanied by inflammation, oxidative stress, and cell apoptosis [23]. The actual age of an individual is different from his or her biological state of aging [24]. In studies by Giuseppe et al, the number of circulating $CD34^+$ cells have been proposed to be a predictor of life span in the oldest individuals, under the influence of apoptosis, oxidative stress, telomere shortening and inflammation [25]. DNA methylation age is an epigenetic biomarker of aging, more accurate than chronological age in predicting disease incidence and aging status [26]. Aging leads to a decline in a variety of bodily functions, including immune function [27], and is associated with a number of diseases such as cancer, Alzheimer's disease, and a number of musculoskeletal disorders [28]. In the musculoskeletal system in particular, age is manifested in reduced bone mass and microstructural damage. In sarcopenia, where muscle mass and function decline with age, age-related inflammation is a major pathogenic factor [29]. In addition, it contributes to the degeneration of intervertebral discs, senile osteoporosis, and arthritis and tendon disorders caused by the aging of the tendons [30-33].

3. The Physiological Regulation of Autophagy in the Body

Autophagy is a cellular process that involves the engulfment of cellular components and their delivery to the lysosomes for degradation [34]. It plays a regenerative role by recycling and reusing parts of the cell, thereby maintaining the internal stability of the environment and providing a timely response to damaged and aging cells [35]. When autophagy occurs, autophagosomes and lysosomes fuse normally. However, when autophagic flux is inhibited, it reduces the ability to remove cellular waste and exacerbates cell death [36].

Autophagy is initiated by a number of autophagy-related genes. These are mainly classified into macroautophagy, microautophagy, chaperone-mediated autophagy, and selective autophagy [37]. Macroautophagy can be further subdivided into mitophagy, nucleophagy, pexophagy, aggregophagy, and xenophagy [38-39]. The most typical and common form of autophagy is microautophagy, while selective autophagy selectively degrades specific materials such as aging organelles (e.g., mitochondria, endoplasmic reticulum), thereby regulating organelle function. During nutrient deprivation, autophagy can promote cell survival, but excessive activation of the autophagic mechanism can be a cause of cell death [40]. Iron starvation can induce autophagy, as proposed in the study by Liu et al. Transmembrane protein 164 mediates the induction of autophagy, leading to iron accumulation and promoting iron-dependent cell death, a form of autophagy-dependent death [41]. Autophagy can also be induced when exposed to genetic toxic stress [42]. LC3-associated phagocytosis (LAP) and pore-forming toxin-induced non-canonical autophagy (PINCA) are both noncanonical autophagy pathways [42]. These pathways are capable of modification of single membrane vesicles with ATG8 family proteins. To enhance macrophage activity against Listeria, Listeria-containing phagosomes can be targeted by this non-canonical autophagy pathway. However, non-canonical autophagy induced by the pore-forming toxin does not have a clear antimicrobial function. However, it may play a role in the repair of damaged vesicle membranes. Autophagy regulates the body primarily by modulating inflammatory responses and stress resistance, regulating mitochondrial function, and degrading abnormal proteins. In doing so, it maintains environmental homeostasis [43].

3.1 Regulating Inflammation

Decreased cellular autophagy can lead to lysosomal permeabilization, thereby triggering inflammation [44]. Dai et al. found that reduced cellular autophagic capacity promotes the release of inflammatory factors, impairs the function of osteoblasts, and facilitates inflammation in osteoarthritis [45]. In addition, Leena P et al. found that metformin may have an anti-inflammatory effect through an increase in mitochondrial autophagy [46]. In a pulmonary inflammation study, balanced polarization between M1 and M2 macrophages was observed to regulate lung inflammation, with M1 macrophages, typically associated with autophagy inhibition, promoting inflammation, while M2 macrophages, with anti-inflammatory properties, can be polarized via autophagy to ameliorate inflammation [47-48].

3.2 Anti-stress Response

Under conditions of hypoxia or oxidative stress, autophagy can be a cell survival enhancer [49]. In cancer therapy, induction of autophagy in tumor cells can

increase oxidative stress-induced damage, which can lead to tumor cell death. Mfn2, an outer mitochondrial membrane protein, is involved in the regulation of mitochondrial function. Its over-expression induces mitochondrial autophagy, which requires the involvement of reactive oxygen species (ROS), since ROS can activate the PINK1/Parkin signaling pathway and thereby trigger mitochondrial autophagy [50]. Reducing the number of mitochondria helps counteract oxidative stress because mitochondria are the primary site of intracellular ROS generation [51].

3.3 Regulating Mitochondrial Function

Autophagy can regulate the function of organelles, in particular that of the mitochondria. Lysosomes are critical for autophagy, and their dysfunction can cause cellular iron depletion and subsequent mitochondrial dysfunction [52]. Furthermore, proteins involved in mitochondrial autophagy can recruit autophagic factors to damaged mitochondria to promote degradation [53]. Studies in lung fibrosis have shown that BMP4, a multifunctional growth factor, promotes selective mitochondrial autophagy in lung fibroblasts, which restores the balance of mitochondrial dynamics. This prevents sustained activation of lung fibroblasts and improves lung function [54]. Another study suggested that the promotion of mitochondrial autophagy should be considered as a target to counteract cerebral hemorrhage, which is associated with impaired mitochondrial function [55-56].

3.4 Degradation of Abnormal Proteins

In addition to the transport of organelles for degradation within lysosomes, autophagy also plays a similar role in protein degradation and serves as the primary pathway for the turnover of stable and defective proteins within cells [57]. The AGT8 family of proteins has been implicated in autophagy. In a related study, interactions between six homologous human proteins and 67 other proteins were observed, revealing a large degree of overlap between the members of the family and their potential functions [58]. Protein aggregation has been implicated in the pathogenesis of various diseases. The chaperone protein subunit CCT2 functions as an autophagic receptor, facilitating the clearance of aggregating proteins and enhancing the autophagic degradation of less mobile protein aggregates [59]. In addition, autophagy has been implicated in the degradation of abnormal proteins and the maintenance of environmental stability. One study showed that exercise increased autophagosome formation or decreased autophagosome clearance in middle-aged and elderly sprinters, which is beneficial for maintaining muscle protein homeostasis [60-61].

4. The crosstalk between autophagy and aging

Cell senescence can be induced by a variety of external and internal stresses through two main mechanisms, namely the activation of the p53-p21 signaling pathway and/or the activation of the p16INK4a-Rb signaling pathway [62]. Examples of these stresses include telomeric attrition, DNA damage, oxidative stress, mitochondrial dysfunction, and aberrant levels of cellular autophagy [63-64]. Research indicates that decreased levels of cellular autophagy, leading to reduced degradation capacity of damaged organelles and proteins, are often associated with the process of cellular senescence. In addition, reduced levels of cellular autophagy accelerate the aging process. On the other hand, moderately increased levels of autophagy have an anti-aging effect [65]. In mammalian organisms, cellular autophagy is a highly conserved catabolic process. Under stress conditions, such as nutrient deprivation and hypoxia, autophagy is activated. It is finely regulated by the assembly of multiple protein complexes. As a key regulator of autophagy, Beclin-1 is an essential component of the class III PI3K complex required for autophagosome formation [66]. The level of the Beclin-1 protein influences its activity and thus determines, to a certain extent, the level of cellular autophagy [67]. Beclin-1-dependent autophagy is an essential cellular pathway for the extension of the life span of organisms. In addition, Beclin-1 contains a BH3 domain. Through this domain, the anti-apoptotic factor BCL-2 binds to Beclin-1, affecting its activity and suppressing the level of cellular autophagy. Recent studies have confirmed that basal autophagic levels in tissues can be increased, organism lifespan prolonged and cell senescence reversed by inhibiting BCL-2 or interfering with its binding to Beclin-1 [63]. In the meantime, it has also been shown that Beclin-1-dependent cellular autophagy plays an important role in certain age-related degenerative diseases under pathological conditions [68]. In the field of pulmonary fibrosis, numerous studies have shown that autophagy is insufficient in alveolar epithelial cells of IPF (idiopathic pulmonary fibrosis), and that knockout of autophagy-related proteins leads to abnormalities in lamellar bodies and increased endoplasmic reticulum stress, thereby exacerbating cell senescence [69-70]. A down-regulation of the expression of Beclin-1 has also been observed in the fibrotic cells of IPF. In addition, research has shown that Beclin-1-dependent autophagy is involved in the regulation of the anti-fibrotic effects of nintedanib [71-72].

Autophagy is an important cellular quality control mechanism that participates in the degradation and renewal of mitochondria. This improves mitochondrial function and muscle health [73]. The interaction between

autophagy and aging is very close. Autophagy plays a crucial role in the removal of cellular waste products and damaged organelles, thereby contributing to the delay of the aging process. Conversely, the aging process can affect the level and efficiency of autophagy [74]. The ability of autophagy to function decreases with age, and this is a bi-directional regulatory process [75]. The mTOR signal is one of the regulatory factors for autophagy, cellular homeostasis and lifespan [76]. Muscle contraction can induce the production of the endogenous peptide apelin, which is a promoter of mitochondrial biogenesis and autophagy. Muscle aging can be combated by targeting muscle stem cells [77].

4.1 Age-related skeletal diseases

The major age-related skeletal disease is osteoporosis (OP, a condition where bones become thin and lose their strength). In senile osteoporosis, there is a decrease in the activity of autophagy. OPTN is a protein that is involved in selective autophagy, and FABP3 is a novel autophagic substrate of OPTN. Reduced expression of FABP3 results in decreased bone mass, increased adipogenic capacity, decreased osteogenesis and decreased autophagic capacity [78]. The inhibition of mitochondrial autophagy can induce the senescence of bone marrow mesenchymal stem cells, which leads to senile osteoporosis. Aging and the progression of senile osteoporosis can be exacerbated by the deposition of advanced glycation end products. Sirt3 is an enzyme that is a regulator of mitochondrial metabolism and may be an ameliorator of this condition [79] (Figure 2). In the study by Liu et al, it was found that knockdown of LRRc17 activates mitochondrial autophagy by inhibiting the mTOR/PI3K pathway, thereby reducing mitochondrial dysfunction and inhibiting the senescence of bone marrow mesenchymal stem cells by a mechanism similar to that of rapamycin [80]. Rapamycin is an immunosuppressive agent that can regulate the activity of T cells and improve the inflammatory response [81].

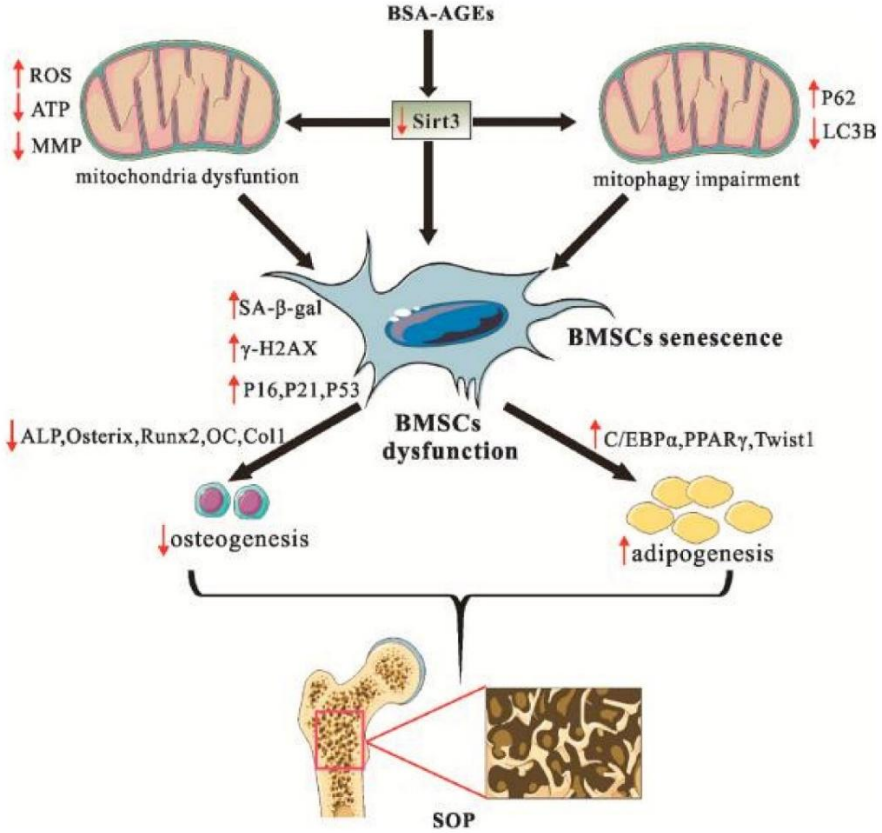

Figure 2. The mechanism of Sirt3-mediated mitophagy regulated AGEs-induced BMSCs senescence and senile osteoporosis [79].

4.2 Age-related Joint Diseases

Osteoarthritis (OA, defined as joint cartilage and underlying bone injury disease) is an age-related disorder. Increased levels of p62 in cartilage and decreased levels of microtubule-associated protein LC3 and beclin-1 suggest reduced autophagic function and increased cell senescence in tissues from osteoarthritis patients [82].

Inhibition of autophagy is associated with activation of the NLRP3 inflammasome, which has an adverse effect on bone cell function [83]. Fibroblast-like synoviocytes from arthritic patients show impaired autophagy leading to upregulated senescence-associated secretory phenotype. An increase in autophagic flux can suppress the expression of this phenotype and thereby inhibit cell aging and consequent cartilage destruction [84]. IL-1β induces inflammation, mitochondrial dysfunction and chondrocyte degeneration, while Sirt3 in arthritis treatment can ameliorate arthritis severity and joint damage through inhibition of the PI3K/Akt/mTOR pathway [85]. Rapamycin in the treatment of arthritis may potentially be a therapeutic strategy through the upregulation of autophagic flux and the targeting of aging pathways. Clinical therapy requires multiple injections over a short period of time. In the study by Kaamini M et al, it was found that rapamycin loaded into poly (lactic-co-glycolic acid) microspheres can promote the function of cellular autophagy in arthritis patients and thus prevent the aging process [86]. In addition to the effect on the joints, autophagy and aging also play a role in the supporting structures of the joints. For example, TBK1, a protein kinase involved in immunity and autophagy, is decreased with the degeneration of the intervertebral disc, while its overexpression can inhibit the apoptosis and aging of the nucleus pulposus cells. TBK1 primarily enhances autophagy by promoting the fusion of autophagosomes and lysosomes, clearance of damaged mitochondria and protein aggregates to maintain cellular homeostasis. The activation of TBK1 is dependent on Parkin, which is a mediator of mitochondrial autophagy [87] (Figure 3). Mitochondrial DNA depletion factor 2 is also required to promote mitochondrial autophagy in intervertebral disc cells through the PINK1/Parkin pathway in order to protect the cells from oxidative stress [88]. The transcription factor EB is the major regulator of autophagy flux by initiating autophagy-related genes and lysosomal biogenesis. It can also regulate senescence and apoptosis of nucleus pulposus cells in intervertebral disc degeneration [89]. Quercetin can protect the nucleus pulposus from apoptosis and prevent ECM degeneration through the p38 MAPK autophagy pathway [90].

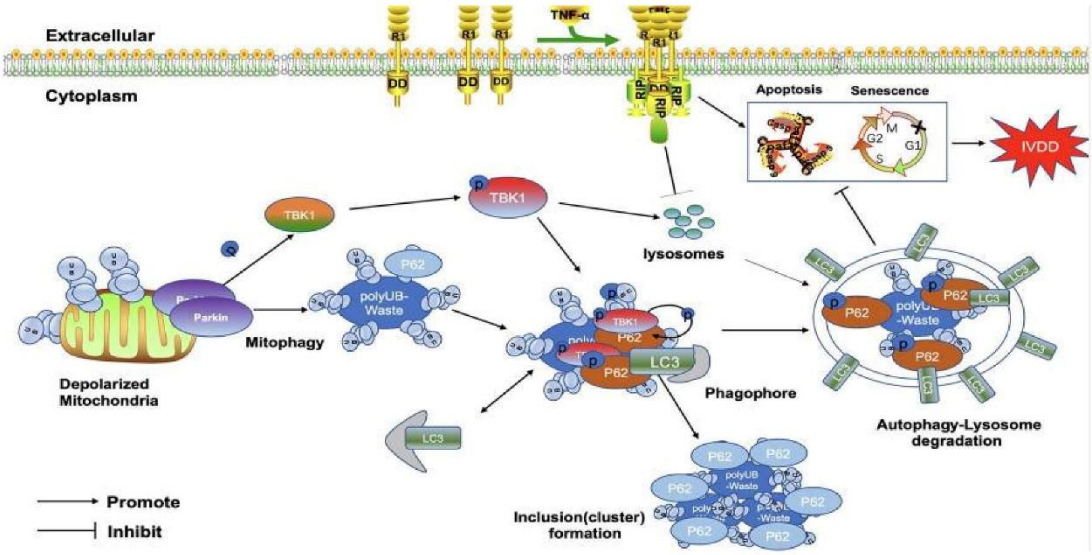

Figure 3. Tank binding kinase 1 (TBK1) in regulating autophagy and this gene protects against intervertebral disc degeneration (IVDD) through affecting autophagy. TBK1 represents a promising avenue for IVDD treatment [87].

4.3 Muscle and Tendon Aging-Related Diseases

Autophagy is a key process in the regulation of muscle mass and function, and muscle aging is one of the causes of muscle atrophy [91]. Studies have shown that oxidative stress can promote muscle atrophy through the autophagy pathway, which may be due to excessive levels of autophagy [92]. Activating defective mitochondria through targeted mitochondrial autophagy can delay muscle atrophy and promote skeletal muscle mitochondrial autophagy [93]. Research has also shown that mitochondrial autophagy may restore skeletal muscle regeneration in aging satellite cells [94]. The ability to form autophagosomes in muscle may be enhanced by exercise training [95]. It has been observed that sedentary elderly individuals have significantly upregulated autophagy genes, whereas the autophagy genes of elderly athletes approach the levels of young athletes. This

suggests that autophagy may act as a mechanism against aging and oxidative stress, and exercise may inhibit excessive autophagy, thereby maintaining skeletal muscle homeostasis and metabolism [96]. Exercise training may increase the ability of autophagosome formation in muscle [97]. Intake of essential amino acids after exercise can reduce autophagy in skeletal muscle and increase muscle protein synthesis after exercise [98]. It shows that appropriate autophagy can maintain the homeostasis of the cell environment, but too much autophagy will affect the homeostasis of the environment.

However, there are fewer studies on the diseases caused by autophagy in the aging of muscle and tendon [99]. Autophagy can prevent the loss of self-renewal capacity and stemness induced by oxidative stress in the aging of human tenocytes [100]. Tenocyte senescence occurs with age. Rapamycin has been shown to ameliorate phenotypes associated with senescence, to increase autophagic activity, and to serve as a marker of autophagy [101]. In tendon-derived stem/progenitor cells (TSPCs), the mTOR pathway plays an important role in regulating autophagy, and activation of the AMPK/mTOR axis is associated with aging. Resveratrol may ameliorate the aging of TSPCs by regulating the AMPK/mTOR axis, thereby delaying the aging of tendons and related diseases [102] (Fig. 4).

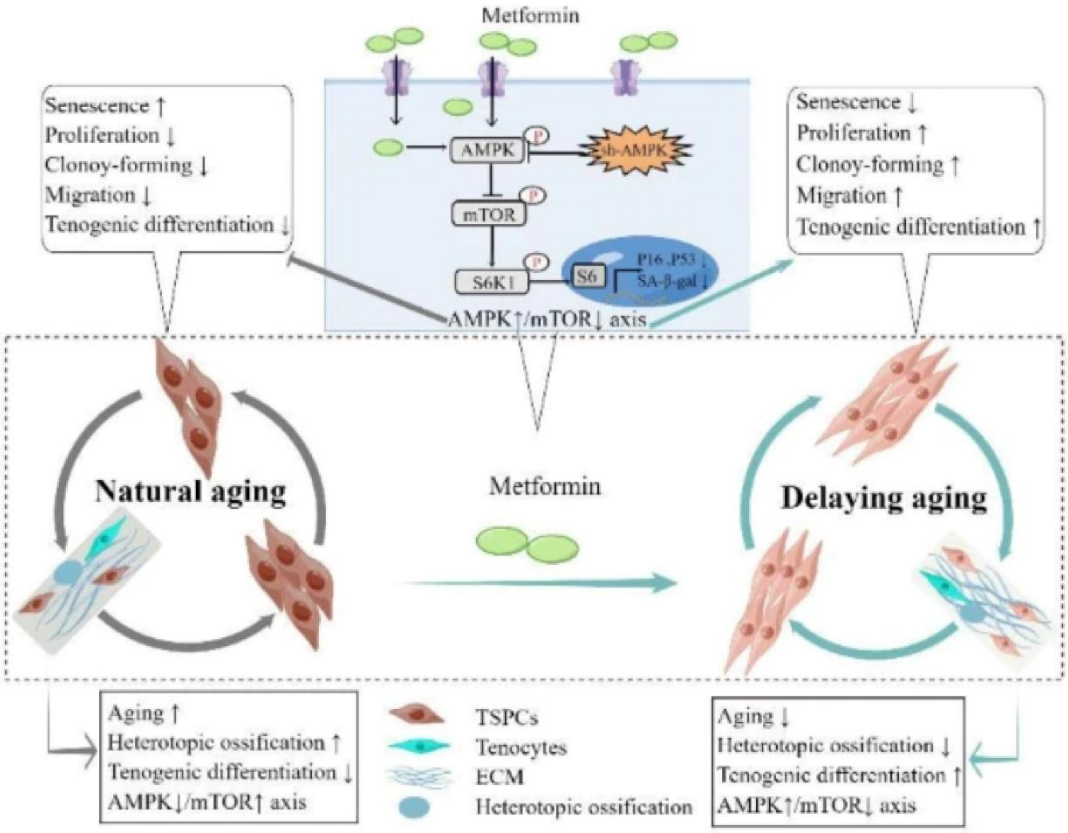

Figure 4. Age-related tendon disorders are closely linked with tendon stem/progenitor cells (TSPCs) senescence. This study revealed new insight into TSPCs senescence and proposed a novel therapeutic treatment for age-related tendon disorders by targeting the AMPK/mTOR axis at the early stage of aging [102].

The decline of various physiological functions is a hallmark of aging. In muscle diseases, aging is often associated with skeletal muscle homeostasis and regeneration. Studies have shown that fibro-adipogenic progenitors (FAPs) represent a cell population that can be therapeutically targeted to improve skeletal health associated with aging, injury and disease [103]. FAPs are a group of muscle progenitor cells that play a critical role in muscle regeneration and maintenance of skeletal muscle fiber size [104]. These pivotal functions of the FAPs are mediated by a complex secretome which acts in a paracrine manner to stimulate muscle satellite cell (SC) division and differentiation. The former are characterized by Pax7 expression and the latter by high PDGFRa expression. Fibrosis, fat infiltration (intramuscular abnormal fat deposition), muscle atrophy and impaired

muscle regeneration result from dysregulation of FAPs differentiation [105]. Recent literature reports that these cells are typically quiescent in the absence of muscle injury. Upon injury, cytokines such as IL-4 and/or IL-15 stimulate FAPs proliferation and migration to the site of injury [106]. In particular, activated FAPs secrete signaling factors that instruct SCs to differentiate and proliferate, and in the absence of FAPs, muscle regeneration is compromised. On the other hand, the aging of FAPs is an essential component that leads to the apoptosis of FAPs and impaired muscle regeneration [107]. FAPs do not undergo senescence and are resistant to apoptosis in chronically injured muscles, such as in myopathies. Muscle degeneration therefore occurs when FAPs senescence is inhibited [108-110]. For example, the high levels of fat infiltration and fibrous deposition that are observed in rotator cuff tears have been attributed to FAPs [111-112]. In a mouse model of rotator cuff tears, the levels of FAPs are increased while the apoptosis index is decreased [113]. TGF-β levels increase after injury to the muscle tendon increase the survival rate of FAPs [112-113]. In comparison to other muscle diseases, muscle tendon injuries have a high and concentrated rate of fat infiltration. Shoulder muscles have a greater potential for adipogenesis and have a higher concentration of FAPs than lower limb muscles [114]. Depending on the specific muscle, the amount of FAPs also varies. For example, the percentage of FAPs is higher in the muscles of the shoulder than in the muscles of the quadriceps [115]. These ratios may be of interest in the study of the role of FAPs in various muscle and skeletal disorders [116].

In addition, research has shown that the interaction between FAPs and inflammatory cells is bidirectional. Following muscle injury, immune cells (neutrophils, pro- and anti-inflammatory macrophages, natural killer cells, B cells, and T cells) rapidly accumulate, leading to changes in the proportion of non-immune cells (endothelial cells, smooth muscle cells, glial cells, tendon cells, and fibro-adipogenic progenitor cells) [117]. For example, macrophage polarization has been observed in muscle injury, including rotator cuff atrophy and fat infiltration after large tendon tears. Muscle-resident FAPs fibro/white fat generation leads to fibrosis and fat infiltration, whereas brown/beige fat generation of FAPs promotes shoulder muscle regeneration. This suggests that the transplantation of M2 macrophages may be able to reduce atrophy and fat infiltration in the supraspinatus muscle. However, the intravenous injection of M2 exosomes directly regulates the differentiation of FAPs and significantly reduces the muscle atrophy and fat infiltration in the supraspinatus muscle, thus providing a new therapeutic option for the muscle atrophy and fat infiltration in the rotator cuff [118]. During muscle injury, for example, activated FAPs upregulate the expression of IL-10. This cytokine acts as a central effector in the induction of the transition of macrophage subtypes to their anti-inflammatory phenotype [119]. During muscle regeneration, there is a transition in macrophage phenotype from pro-inflammatory macrophages to anti-inflammatory macrophages. The former secrete cytokines that promote the proliferation of myoblasts, while the latter secrete factors that stimulate the differentiation and fusion of myoblasts. This suggests that FAPs may play a role in switching macrophage phenotypes [120-121]. Mononuclear cells/macrophages also play a critical role in the regulation of FAPs. Changes in cell apoptosis, rather than proliferation, mediate the effect of mononuclear cell/macrophage depletion on FAPs accumulation It has been shown that TNF-α, which is highly secreted by pro-inflammatory macrophages during acute injury, induces FAPs apoptosis [122]. Another pro-inflammatory factor, IL-1α/β, which is secreted by pro-inflammatory macrophages, has been shown to inhibit the adipogenic differentiation of FAPs [123]. There is a transition in macrophage phenotype to anti-inflammatory macrophages secreting higher levels of TGF-β as the regeneration process progresses. This growth factor competes with TNF-α and promotes FAPs survival. TGF-β also down-regulates the expression of the FAPs markers PDGFRα and TCF7L2/TCF4 as well as their downstream signaling pathways [124-125]. TGF-β influences the fate determination of FAPs through pathways such as increasing the survival of FAPs, promoting their proliferation, inhibiting their adipogenic differentiation, and promoting their differentiation into myofibroblasts [113,126].

New technologies, such as single-cell RNA sequencing, have revealed the cellular heterogeneity of FAPs and the complex regulatory network that regulates them during muscle regeneration. Due to their central role in skeletal muscle pathophysiology, the regulatory mechanisms of FAPs and their cellular and molecular crosstalk with muscle stem cells (MuSCs) have been extensively studied [127] (Figure 5). Recently, the cellular heterogeneity of FAPs and their complex molecular interactions during different stages of muscle regeneration and muscle diseases have been identified by breakthroughs in single-cell sequencing technology. These new insights will play a critical role in the development of novel therapeutic approaches targeting FAPs to limit their accumulation and/or restore their function, thereby reducing fibrofatty deposition and promoting muscle regeneration in muscle diseases.

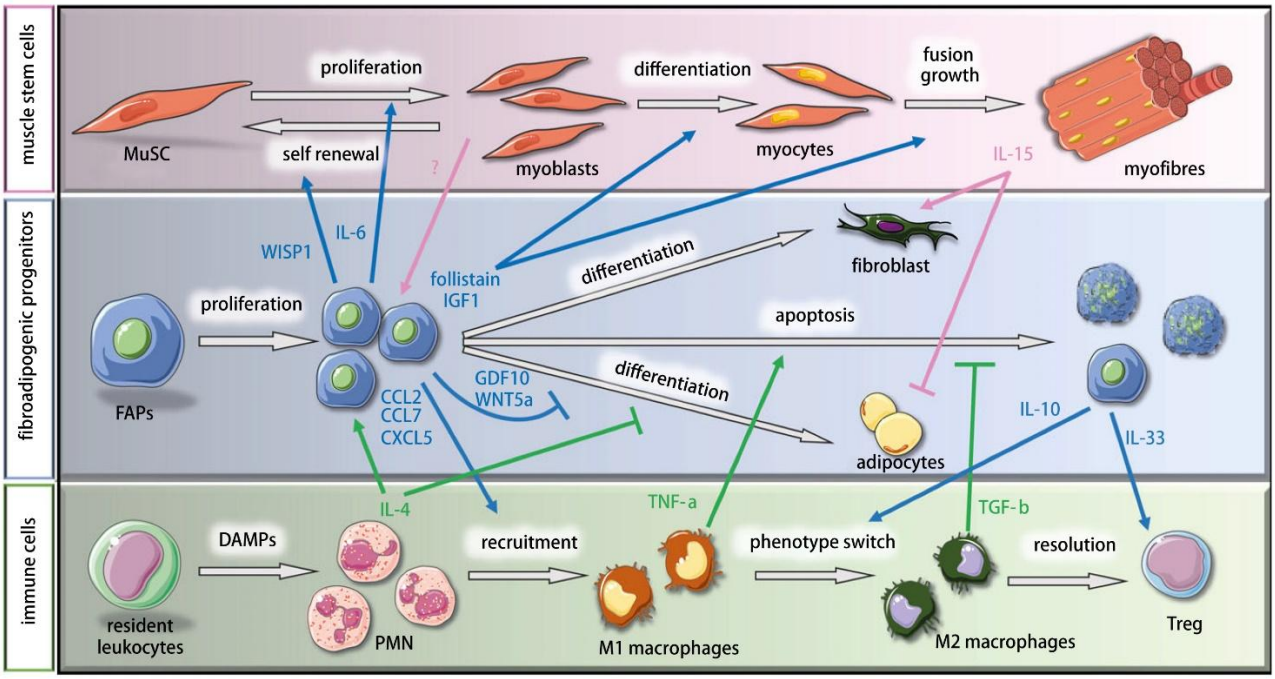

Figure 5. the interaction of FAPs with MuSC and immune cells [127].

5. Conclusions

The onset of various diseases is often associated with the aging process in the human body. Cellular autophagy provides functions such as anti-inflammation, stress resistance, mitochondrial regulation and protein degradation, and has the ability to facilitate self-renewal in aging cells. It is a molecular process necessary for the maintenance of cellular homeostasis and may have a regulatory role in the delay of aging and age-related diseases. However, the capacity of autophagy is reduced with age. Autophagy and aging exist in a dynamic equilibrium. Appropriate levels of autophagy can ameliorate aging and age-related diseases, whereas excessive levels of autophagy can disrupt the internal environment of the organism. This phenomenon is not only evident in diseases associated with aging in general, but it also plays a role in diseases associated with the musculoskeletal system. Studies have shown that many drugs increase autophagy to regulate aging, therefore, novel approaches for the treatment of aging and related diseases may be developed by exploring the molecular mechanisms between autophagy and aging using autophagy-targeted activators or inhibitors for early prevention and intervention of skeletal muscle aging. Obviously, since exercise and glucose and lipid metabolism play a critical role in homeostatic regulation, attention to this field can help improve exercise function and accelerate "healthy aging" in older people.

Removing senescent cells may prevent neighboring healthy cells from entering the vicious cycle of senescence. How to promote repair of existing tissue damage is another important issue that needs to be addressed. In the future, in addition to in-depth studies of the regulatory effects of cells of different origins on the microenvironment of the motor system and the crosstalk mechanisms with different senescent cells, combined with new gene sequencing and bioinformatics analysis technologies, such as single-cell nuclear transcriptome and single-cell nuclear chromatin openome, can be selected to construct a multimodal cell atlas of the aging human skeletal muscle to help further explore the molecular mechanisms of senescence, which may provide new ideas for cellular rejuvenation and in situ repair of tissue damage.

Author Contributions

H.Z. and W.G. proposed the research idea and wrote the original manuscript; H.Z. was responsible for drawing and revising the manuscript; G.W. and Y.Y was responsible for the selection of the topic and revision of the manuscript, and management of resources and project. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

No data were created for this review article. All data analyzed were included in the manuscript. All data or information can be provided on demand by the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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