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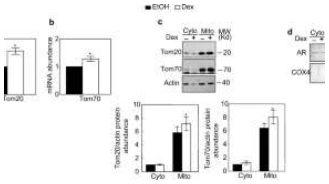

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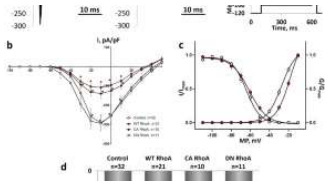

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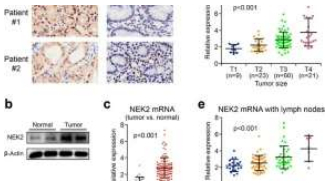

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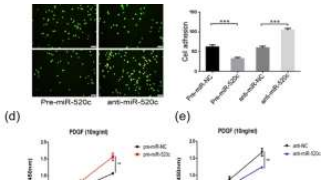

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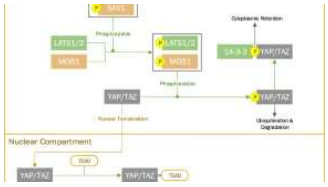

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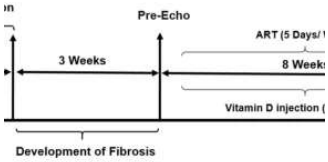

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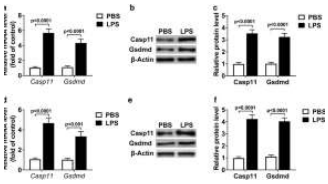

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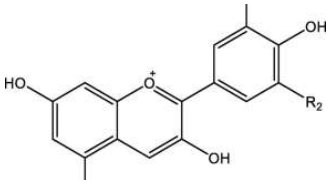

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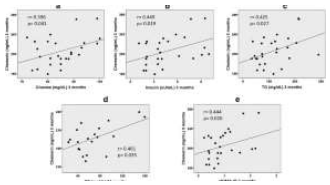

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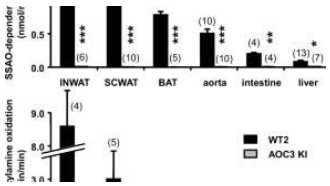

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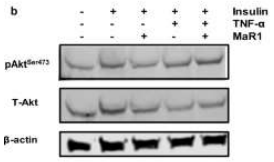

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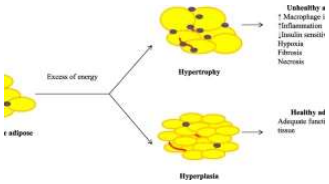

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REVIEW

Hippo pathway effectors YAP and TAZ and their association with skeletal muscle ageing

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Abstract

Skeletal muscle atrophy commonly occurs during ageing, thus pathways that regulate muscle mass may represent a potential therapeutic avenue for interventions. In this review, we explored the Hippo signalling pathway which plays an essential role in human oncogenesis and the pathway's influence on myogenesis and satellite cell functions, on supporting cells such as fibroblasts, and autophagy. YAP/TAZ was found to regulate both myoblast proliferation and differentiation, albeit with unique roles. Additionally, YAP/TAZ has different functions depending on the expressing cell type, making simple inference of their effects difficult. Studies in cancers have shown that the Hippo pathway influenced the autophagy pathway, although with mixed results. Most of the present researches on YAP/TAZ are focused on its oncogenicity and further studies are needed to translate these findings to physiological ageing. Taken together, the modulation of YAP/TAZ or the Hippo pathway in general may offer potential new strategies for the prevention or treatment of ageing.

Keywords Yes-associated protein · Sarcopenia · Ageing · Skeletal muscle · Cell signalling

Iwan Setiawan and Ardo Sanjaya contributed equally to this work.

Key points

- Skeletal muscle mass is regulated through YAP/TAZ effect on myoblast proliferation and differentiation which is altered in aging.
- Ageing is associated with low physical activity which may alter YAP/TAZ levels in myoblasts.
- Ageing causes stiff extracellular matrix and induces further fibrosis through YAP/TAZ.
- YAP has been shown to promote stemness of satellite cells and may be beneficial in ageing.

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Introduction

The Hippo pathway is best known for its regulation and control of cell proliferation and organ size. Although the Hippo pathway consists of many proteins, the core components of this pathway consist of two kinases and two adaptor proteins. The kinases are large tumour suppressor 1 and 2 (LATS1/2), and mammalian sterile-20 like kinase 1 and 2 (MST1/2) and the adaptor proteins are Salvador (SAV) and Mps one binder (MOB1) [1]. Their functions have been elucidated, and their roles in Hippo signalling have been confirmed using knockouts or overexpression in mice. The final effectors of the pathway are the transcription factors, Yes-associated protein (YAP) and its homologue, transcriptional co-activator with PDZ-binding motif (TAZ or *WWTR1*).

Sarcopenia is a term originating from the Greek word, which roughly translates to the deficiency or loss of flesh. At first, the term sarcopenia is reserved for age-related changes in muscle mass [2]. However, this definition has evolved multiple times to accommodate the incorporation of new knowledge and findings in this area [3–5]. The latest recommendation updated by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) defined probable sarcopenia as the presence of low muscle strength [6]. The diagnosis is confirmed if low muscle quantity or quality is also found. However, these diagnostic criteria reflect the fact that the identification of muscle weakness is more practical in clinical settings than assessment of muscle quantity or quality. Two types of sarcopenia are classified according to their cause [7]. Primary sarcopenia is sarcopenia caused by the ageing process (sarcopenia of ageing). In contrast, secondary sarcopenia is due to an underlying disease(s) that causes the loss of muscle mass. Multiple factors have been identified that are associated with the development of sarcopenia of ageing. Notable examples are decreasing physical activity and neuronal motor units, satellite cell failure, and dysfunctional protein synthesis [7–9]. The factors mentioned above are of interest since they may be affected by YAP/TAZ. Therefore, elucidating the relationship between the Hippo pathway effectors, YAP/TAZ, and skeletal muscle during ageing may provide new insights into how this pathway may be involved in sarcopenia.

The ability of YAP/TAZ to pervasively control multiple aspects of cell growth has made them the subject of many cancer studies. Their effects range from control of tissue growth, cell fate, regeneration, metastasis, and also cell competition [10]. Several recent reviews of this pathway have explored the relationship of YAP/TAZ and specific types of cancers and as potential targets for drug developments [10–14]. Researchers have identified that YAP/TAZ mutations confer different effects depending on the specific types of cancers [10, 12]. For example, cancers of neuroectodermal origin harbour a greater incidence of mutations in the Hippo pathway [10]. Due to its importance, the Hippo pathway is beginning to become the focus of drug development strategies in oncology [11, 12]. Although this pathway's role in cancer is well-reviewed, YAP/TAZ is also closely linked with tissue regeneration [12]. Therefore, targeting the Hippo pathway without understanding its regulation may produce deleterious effects. Several recent reviews have explored the Hippo pathway as regulators of muscle size and growth [15–17]. Therefore, as regulators of cell growth and tissue regeneration, it certainly is possible that YAP/TAZ contributes to the ageing phenotype of muscle, most notably the atrophy of skeletal muscles. In this review, the authors use YAP/TAZ to refer to both proteins and only YAP or TAZ if the effects belong to an individual protein.

Overview of the Hippo pathway

The large tumour suppressor (LATS) in human or called warts (Wts) in Drosophila was the first protein of the core Hippo pathway to be identified [18–20]. This enzyme is a serine/threonine kinase and initially was identified as a tumour suppressor during screening for regulators of cell proliferation. Further research found that the loss of function in this protein caused uncontrolled cellular proliferation [18–20], and generated a distinct overgrowth phenotype in Drosophila with a highly folded eye structure that is in common with other loss-of-function mutations of proteins in the Hippo pathway. Another protein, Mps one binder (Mob), was first identified by Lai et al. [21] as a tumour inhibitor. Mob acts together with LATS to stimulate its kinase activity, and both proteins form a complex that phosphorylates YAP/TAZ, leading to their inactivation. Additionally, both proteins are highly conserved across species, and the co-expression of human LATS and MOB can rescue defects in mutant Drosophila [18, 21]. LATS and MOB form a conserved tumour suppressor protein complex in humans. Decreased expression or mutation of either protein is associated with aggressive cancer phenotypes in humans [22].

Hippo (Hpo), the eponymous protein for which the Hippo pathway is named after, was first identified as a gene that regulates proliferation and apoptosis [23–25]. In mammals, the Hippo homologue is called the mammalian sterile-20 like kinase 1 and 2 (MST1/2) [23], and expression of the human MST1/2 kinase in Drosophila rescues the overgrowth phenotype [26], demonstrating that this growth pathway is highly conserved. Harvey et al. [23] first identified the possible interactions between Hpo, LATS, and Sav. Indeed, Mst1/2, LATS, Mob, and Sav were later proven to form a multimeric complex that modulates YAP/TAZ in the Hippo pathway [24, 26].

SAV was identified during a screen for tumour-suppressing genes in Drosophila and is mutated in several human cancer cell lines [27]. Although Sav was first reported to interact with LATS [27], later research suggests that Sav also interacts with Hpo [23]. The interaction of SAV and MST1/2 forms a complex which phosphorylates LATS1/2 and MOB. The phosphorylation results in the activation of

their kinase activity. Similar to other proteins in the Hippo pathway, its loss of function also leads to the same typical overgrowth phenotype in Drosophila.

The last proteins in the core kinase pathway of Hippo are YAP and TAZ. These two proteins are homologous to each other, although they may have distinct but overlapping functions [28]. YAP was initially identified as a transcription factor for Yes-associated Proto-oncogenes [29]. However, it was later shown to be a transcriptional co-activator [30], particularly for the TEA domain (TEAD) family of transcription factors (TEAD1-4) [31]. TEAD transcription factors are one of the best-studied partners of YAP and TAZ and mediate most of their biological effects [32]. Without a co-activator, such as YAP or TAZ, TEAD hardly showed any transcriptional activity [33]. The TEAD transcription factors share a highly conserved TEA/ATTS binding domain, which binds the MCAT element found in the promoter of cardiac, smooth, and skeletal muscle-specific genes [34]. TEAD also regulates genes associated with cell growth, proliferation, and homeostasis [32, 35] such as *CTGF* and *CYR61* [36], *MYC* [37], *SLC7A5* [38], and *GLUT3* [39, 40].

YAP contains a small modular protein domain, WW domain, named after two conserved tryptophan residues spaced 20 to 22 residues apart that enables interaction with LATS. YAP is phosphorylated at serine 127 by LATS in the MST1/2, LATS, MOB, and SAV complex, which then enables YAP binding to 14-3-3 protein to sequester YAP in the cytoplasm. YAP then undergoes proteasomal degradation leading to a reduction in YAP activity [41–43]. TAZ, on the other hand, was identified by Kanai et al. [28] during a screening for proteins that were bound to the 14-3-3 protein. Similar to YAP, the cytoplasmic sequestration and degradation of TAZ are regulated by binding to the 14-3-3 protein [28, 41]. TAZ protein also contains a WW binding domain that enables interaction with the core kinase protein of the hippo pathway, LATS. Indeed, LATS directly phosphorylates both YAP and TAZ [43–45], to inhibit their function as transcriptional activators (Fig. 1). Therefore, LATS phosphorylation and the Hippo pathway in general negatively regulate YAP/TAZ activity by preventing their translocation to the nuclear compartment where they exert their biological activity. It is noteworthy that YAP protein also contains an SH-3 binding region, which allows interactions with specific proteins containing SH-3 regions such as Src [29].

YAP/TAZ is a potent regulator of myogenesis

Although the Hippo pathway is known to regulate growth in other tissues, its function in skeletal muscle tissue is complex and not well understood, as YAP/TAZ have been implicated in proliferation and differentiation [43, 46–49]. However, YAP in particular is well known to induce cellular proliferation as reflected by the many cancer transformation associated with YAP overexpression [43, 45, 47, 50, 51]. YAP is highly expressed during the proliferation of active satellite cells in both in vitro in human satellite cell culture and ex vivo satellite cells from mice muscle tissues [46, 48]. YAP is essential for myoblast proliferation. However, overexpression of YAP inhibits the differentiation of myoblasts and may paradoxically cause atrophy and myopathy in vivo [46, 48]. This inhibition of differentiation can be extreme since YAP can potentially act as an oncogene when overexpressed in muscle satellite cells [51]; thus, YAP expression level and activation needs to be carefully controlled in muscle cells to prevent oncogenesis.

YAP/TAZ induces cellular proliferation and has overlapping actions; however, each protein also has distinct functions. TAZ acts as an inducer of myoblast differentiation, whereas YAP hinders this process [46, 47, 51]. During myoblast proliferation, YAP/TAZ has been shown consistently to be active during myogenesis in C2C12 cells [47, 48]. Transgenic studies using YAP/TAZ overexpression found that both proteins promoted myoblast proliferation. Consistent with this, YAP was found to upregulate *Myf5* expression, which is known to promote myoblast proliferation [48]. Additionally, inhibition of YAP, TAZ, or both proteins decreased *Myf5* expression [47], confirming YAP/TAZ regulatory properties on myoblast proliferation.

However, during differentiation YAP/TAZ shows different functions. Overexpression of YAP has been shown to inhibit the differentiation of myoblasts in vitro and may paradoxically cause atrophy and myopathy in vivo [46, 48]. This inhibition of differentiation can be extreme since YAP can potentially act as an oncogene when overexpressed in muscle satellite cells [51]. This effect is in contrast to TAZ, which were found to promote myogenic differentiation [22, 52–54]. TAZ overexpression in myoblasts was shown to increase the expression of myogenin, which marks myoblasts differentiation [22]. These effects were mediated by TAZ interaction with MyoD. The combination of both TAZ and MyoD cooperatively increases myogenic differentiation, shown by the increased expression of myogenin and MHC, as compared to MyoD alone [52].

After skeletal muscle injury, both genes were found to be highly expressed. However, *TAZ* expression significantly increased more than *YAP* during muscle differentiation [47]. TAZ functions mainly as a transcriptional co-activator of MyoD [52] and TEAD4 [47] that played an essential role in inducing differentiation. The MCAT element that the TEAD family of transcription factors bind to were located in the promoter regions of genes associated with muscle development such as *α-actin* and *β-MHC* (myosin heavy chain) [34]. Confirming this notion, simultaneous silencing of *Tead1*, *Tead2*, and *Tead4* strongly inhibits the differentiation of C2C12 myoblasts in vitro [55]. Thus, the specific expression pattern of YAP/TAZ is carefully controlled during myoblast proliferation and differentiation.

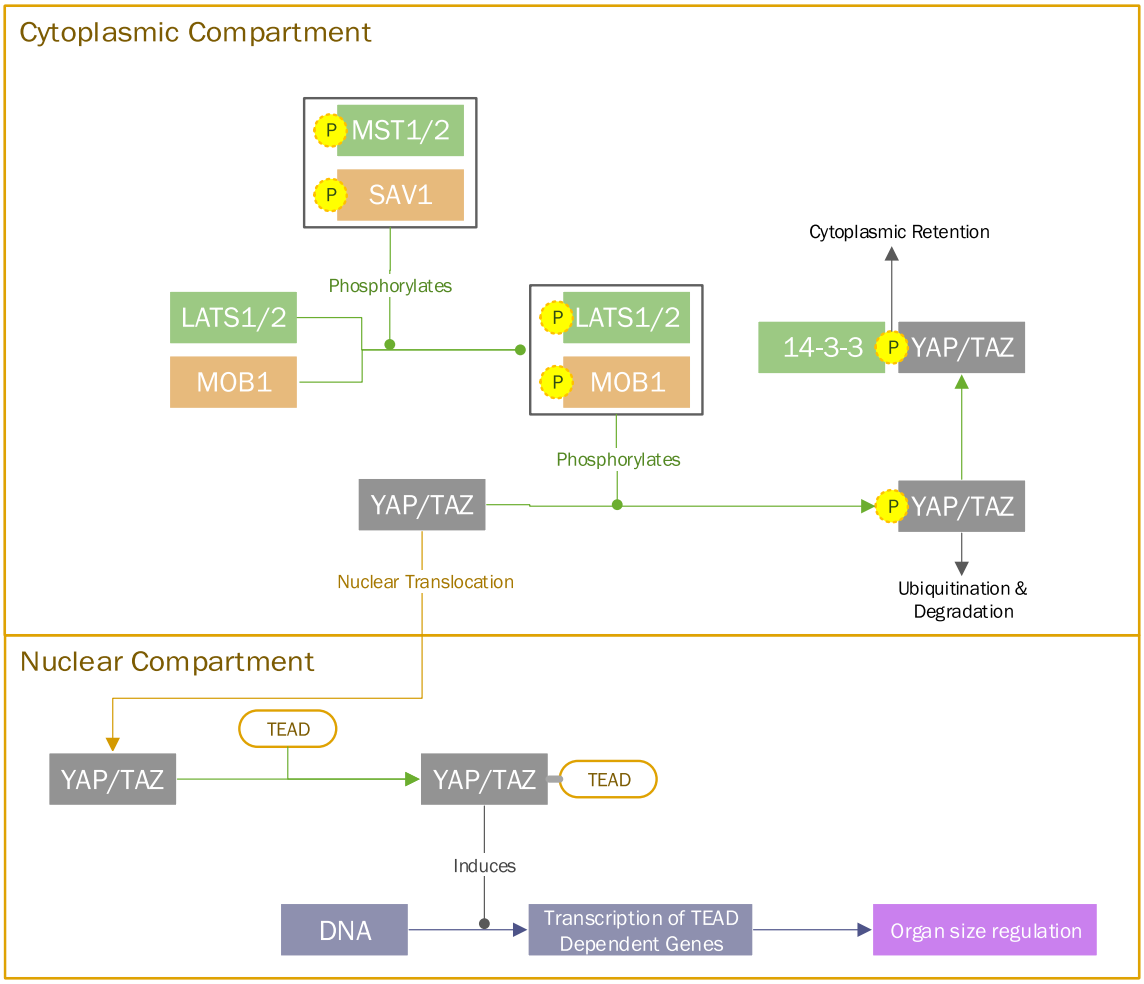

Fig. 1 Central hippo pathway controlling the phosphorylation of YAP/TAZ. Shown below is the protein cascade. Phosphorylation of the proteins involved is directly linked to its activation state. MST1/2, SAV1, LATS1/2, and MOB1 are activated by phosphorylation. Phosphorylated YAP/TAZ is bound by the 14-3-3 protein and cannot translocate to the nucleus. Unphosphorylated YAP/TAZ is translocated into the nucleus where they bind with TEAD and induce gene transcription to regulate organ size. YAP/TAZ had also been found to bind with many different transcription factors besides TEAD (not shown). Black box delineating MST1/2 with SAV1 and LATS1/2 with MOB1 denotes the complex formation of the proteins. MST1/2, mammalian sterile-20 like kinase 1 and 2; SAV1: Salvador 1; LATS1/2: large tumour suppressor 1 and 2; MOB1: Mps one binder 1; YAP: Yes-associated protein; TAZ: transcriptional co-activator with PDZ-binding motif; TEAD: TEA domain transcription factors

The role of YAP/TAZ in skeletal muscle ageing

During ageing, skeletal muscle can undergo atrophy [56]. Since the hippo effectors, YAP/TAZ, regulate myogenesis, it is appealing to hypothesise that lack of them may lead to the development of muscle atrophy. However, it is currently unknown whether YAP/TAZ levels are decreased during ageing.

Other studies suggested that YAP may have a more complicated role in skeletal muscle ageing and atrophy [54, 57–59]. These studies show that although YAP is involved in muscle regeneration and control of muscle mass [43, 46–49], its overactivity can contribute to the ageing phenotype and muscle atrophy [57, 58]. Additionally, YAP/TAZ can act as inducers or inhibitors of ageing in other tissues, including bone and cardiac muscles [54, 60]. However, the functions of YAP/TAZ in ageing may be tissue-dependent, and findings in other tissues may not apply to skeletal muscle. Another complicating issue is the fact that almost every cell type expresses YAP/TAZ. Studies examining YAP/TAZ as regulators of muscle size [43, 46–49] did not take into account the extracellular milieu secreted by fibroblasts, since they also express YAP/TAZ. Transgenic studies in mice and cell culture systems have found that YAP/TAZ expression in fibroblasts promotes fibrosis in the lung, kidney, liver, and skeletal muscle tissues [12, 59, 61–63]. Therefore, their overexpression in fibroblasts may be deleterious to organ health and contribute to ageing. However, YAP/TAZ that was expressed in different cells, such as muscle satellite cells, cardiomyocytes, was also implicated in tissue regeneration, proliferation, and differentiation [17, 46, 47, 49, 54, 60, 64]. These findings reflect the complexities of YAP/TAZ in regulating cellular growth and ageing and are illustrated in Fig. 2. Thus, reducing muscle

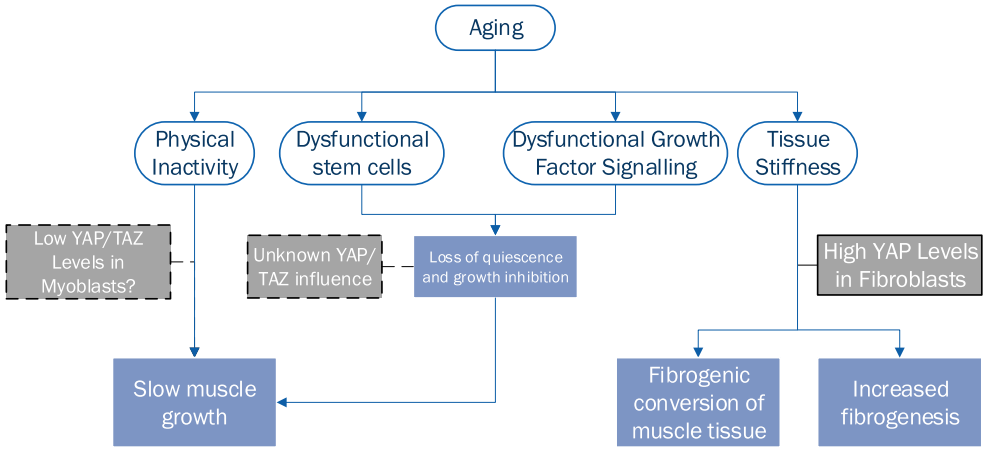

Fig. 2 Overview of the relationship of YAP with features of ageing in skeletal muscle. Ageing has been known to be associated with low levels of physical activity, dysfunctional stem cells and growth factor signalling, and tissue stiffness. Physical inactivity may reduce YAP/TAZ levels in muscles and, therefore, may account for slow muscle growth. Ageing muscles also exhibit dysfunctional stem cells with loss of quiescence and a lower number of satellite cells. It is unknown if YAP/TAZ exerts any influence on this phenomenon. However, high levels of YAP protein levels were found in supporting fibroblasts. Increased YAP in fibroblasts has been shown to induce fibrosis and fibrogenic conversion of muscle cells. Grey box with a dashed black outline represents hypothetical or unknown YAP influence. Grey box with solid black outline represents proven influence of YAP

atrophy may not be as simple as stimulating the activity of YAP/TAZ pharmacologically since there may be different tissue-dependent effects. Further research on the levels and effects of YAP/TAZ in muscle satellite cells, supporting fibroblasts, and differentiated muscle fibre cells will help elucidate their role(s) in ageing.

Another factor influencing ageing and atrophy is the autophagy mechanism. Autophagy is defined as the cellular recycling mechanism which provides additional energy and building blocks for homeostasis [65]. Autophagy has been found to regulate skeletal muscle ageing, either by maintaining muscle mass or promoting regeneration through its effects on satellite cells [66, 67]. Therefore, it is interesting to explore whether YAP/TAZ have a role(s) in influencing this biological process.

Although at first glance, inducing autophagy seemed deleterious to the tissue, this recycling process helps eliminate misfolded proteins, damaged mitochondria, and other cellular waste, which improves the tissue as a whole. Studies exploring the role of autophagy have yielded promising results. The induction of FOXO/4E-BP1 protein expression, a signalling pathway in autophagy, has been shown to improve lifespan and measures of skeletal muscle ageing in flies [68] and mouse models [69]. Additionally, autophagy has been shown to improve satellite cell function. Restoration of autophagy using rapamycin treatment to block mammalian Target of Rapamycin (mTOR) signalling allowed aged satellite cells proliferation to match those of young control cells [70] as well as showed a significant restoration of function. Autophagy was also shown to be essential in satellite cell differentiation. A study using C2C12 cells in vitro showed that inhibition of autophagy using 3-methyladenine or *Atg7* disruption causes impaired myoblast fusion [71]. Hence, ample evidence supports the beneficial effect of autophagy in the prevention of ageing and the promotion of regeneration in skeletal muscle.

Although YAP/TAZ also support muscle mass gain and stem cell function, their relationship with autophagy is not as straightforward as it seems. Studies exploring the role of autophagy and YAP have been focused on cancer cells in various tissues. The effects of autophagy in cancer cells are much more complex, with both beneficial effects in reducing tumour mass and deleterious effects due to tumour growth enhancement [65, 72]. Therefore, the relationship between autophagy and YAP/TAZ in these contexts may not translate well to ageing conditions. However, these studies showed that autophagy and YAP operate as inhibitors of each other's function. Activation of autophagy through the administration of rapamycin has been shown to consistently reduce the levels of YAP protein and also inhibits cancer growth [53, 73, 74]. Transgenic studies using mice models showed that YAP was degraded by autophagy [73]. However, several proteins of the Hippo pathway also showed inhibitory activity towards many autophagy proteins. LATS1, one of the core kinase of the Hippo pathway, was shown to ubiquitinate Beclin-1, which inactivates the protein and therefore, negatively regulates autophagy. YAP was shown to affect autophagy through several mechanisms [75]. YAP overexpression in hepatocellular carcinoma cell lines has been shown to inhibit reactive oxygen species production, which in turn inhibits RAC-1 mediated autophagy on the mTOR pathway [76]. YAP also regulates the expression of *SLC7A5,* which stimulates mTOR activity and thus negatively regulates autophagy [38]. These studies have shown that the Hippo pathway and autophagy negatively regulate each other, and their main outcome depends on the

balance of these two pathways. However, it remains to be seen whether this relationship also exists in physiological conditions; and if so, which path is more beneficial in the prevention of ageing in skeletal muscle.

Murgia et al. [77] used a proteomic approach to find protein expression differences between young and aged people. Although their research did not specifically explore the effects of YAP protein expression, they identified a change in glycolytic enzymes protein expression between aged and young muscle fibres. Previous research using cancer cells in vitro have shown that YAP regulates the protein and mRNA expression of several critical glycolytic enzymes such as *HK1* (hexokinase 1), *GPI* (glucose-6-phosphate isomerase), *ALDOA* (aldolase A), *PGK1* (phosphoglycerate kinase 1), and *LDHA1* (lactate dehydrogenase A) [78, 79]. Therefore, further analysis may be able to explore whether YAP/TAZ has any role in the changes in metabolic enzyme expressions in ageing.

The role of YAP and TAZ in the cellular microenvironment of skeletal muscle during ageing

A critical aspect of ageing that is likely mediated by YAP/TAZ is the role of muscle stem cell microenvironment or niche of aged muscle. Mashinchian et al. [80] classified the regulation of muscle stem cell growth into two main types, intrinsic and extrinsic regulation. Intrinsic regulation originates from the mechanisms preprogrammed into muscle stem cells such as epigenetic adaptations, telomerase activity, and activated or repressed signalling loops. Extrinsic regulation of the skeletal muscle stem cells is due to the stem cell niche, which consists of the extracellular matrix, growth factors and cytokines, and cell to cell interactions. In this segment, we are going to focus on extrinsic regulations of stem cells in ageing conditions. For a comprehensive review of the effects of the stem cell niche on muscle ageing, the reader is referred to reviews by Mashinchian et al. [80] and Hwang and Brack [81].

The earliest evidence for the role of the stem cell niche in muscle ageing was shown by Carlson and Faulkner [82], who cross-transplanted muscles between aged and young mice. They showed that in aged mice, muscle regenerates slowly regardless of the age of the transplanted muscle [82]. These findings paved the way for subsequent experiments validating the role of the extracellular niche, specifically the surrounding growth factors and cytokines, in influencing muscle stem cell activity [83–85]. Growth factors and cytokines are critical during satellite cell proliferation and differentiation. During muscle healing due to injury, inflammatory mediators released by the surrounding tissue are able to induce the muscle stem cells to proliferate [80]. However, in ageing, cytokines and growth factors may instead induce loss of quiescence and regenerative capability of muscle stem cells. Several investigators have found that defective signalling of the fibroblast growth factors (FGF) ligands cause impaired proliferation of muscle stem cells in ageing conditions [83, 84]. However, it is not known whether YAP/TAZ plays any role in the regulation of these cytokines.

The extracellular matrix of skeletal muscle has been shown to influence muscle stem cell proliferation. Muscle stem cells grown in vitro on stiff medium lose proliferative capability compared to the elastic medium [86, 87]. With ageing, the muscle's extracellular matrix becomes stiffer due to extensive collagen crosslinking compared to young muscles [88]. Since YAP/TAZ acts as mechanoreceptors [89], increased stiffness of the extracellular matrix due to ageing may influence their expression and ability to support fibroblasts and muscle stem cells. In this connection, the stiff extracellular matrix increased the expression of YAP in the nuclear compartment of the fibroblasts [59]. The expression of YAP in fibroblasts, in turn, promoted the fibrogenic conversion of the skeletal muscle and thus created a feedback loop in which fibrogenic conversion causes further stiffening of the extracellular matrix. Additionally, when *LATS1/2* was deleted in fibroblasts, the increased expression of YAP increased fibrogenesis and slowed the healing process in cardiac and skeletal muscle tissue [59, 64]. Satellite cells have been shown to regulate extracellular matrix production by fibroblasts [90]. Although there may be reduced amounts of satellite cells in skeletal muscle during ageing, they still may be sufficient to increase extracellular matrix production and stiffness [81]. However, it is currently not known whether substrate stiffness affects YAP levels in muscle stem cells. However, aged muscle stem cells undergo a loss of focal adhesion formation that altered cytoskeletal properties of muscle in conjunction with increased YAP nuclearization [57]. These findings demonstrate a complicated relationship among YAP, satellite cells, and fibroblasts in the extracellular matrix. Current data suggest that they can interact with each other and regulate each other's functions. Although YAP expression enables muscle stem cells to proliferate, it also promotes fibrogenesis in fibroblasts, so the net benefit of increasing YAP expression may depend upon the cell type.

YAP/TAZ act as mechanoreceptors to mediate the effects of ageing and exercise

Distefano and Goodpaster [91] characterize the age-related changes during muscle ageing as not only due to the ageing process per se but also due to the decline in physical activity. They conclude that physical inactivity is especially deleterious in the ageing population and can cause long-lasting impairment. Furthermore, resistance exercise can improve muscle strength and performance [91]. Gabriel et al. [92] have described the links between the Hippo pathway and exercise. However, in this review, we will focus on several mechanisms related to the relationship between YAP/TAZ and physical activity/exercise.

YAP/TAZ in skeletal muscle can be regulated by cell geometry, extracellular matrix stiffness, cytoskeletal tension, stretching, and cell density [89, 93, 94]. Thus, YAP/TAZ may modulate the effects of exercise and physical activity on muscle growth through mechanical signalling. Interestingly, mechanical overload on mouse muscle tissue increases skeletal muscle mass as well as total YAP protein levels (both phosphorylated and unphosphorylated) [95]. In fact, the increased YAP expression is enough to induce hypertrophy of the muscles [95]. However, other research has shown that exercise did not increase YAP expression in skeletal muscles [96]. Further studies are needed to determine whether exercise produces similar effects with mechanical stretching and whether ageing influences the response of YAP/TAZ as mechanoreceptors.

YAP also is induced during satellite cell activation [97], and its overexpression is associated with an increase in satellite cell proliferation [46]. Increased YAP expression in satellite cells occurs during mechanical stretching and may induce hypertrophy of muscles. Thus, it possible that changes in YAP/TAZ expression may mediate some of the effects on exercise-induced hypertrophy and muscle atrophy. Since ageing is associated with the loss of muscle mass, we postulate that this loss may be mediated by the loss of YAP/TAZ signalling in muscle cells and satellite cells. YAP has been shown to regulate satellite and muscle cells and were able to induce muscular hypertrophy. However, further research is needed to determine if YAP/TAZ levels are altered in ageing and if exercise can modulate YAP/TAZ expression. Additionally, further exploration of whether YAP/TAZ modulation plays a significant role(s) in the prevention of muscle atrophy in ageing is needed.

Another aspect of ageing that influences YAP/TAZ regulation is the loss of motor neurons. Although the loss of motor neurons is a well-documented phenomenon in ageing muscle, there remains debate on whether pathologies in the neuromuscular junction precede or are caused by muscle dysfunction [98]. YAP expression in muscle is elevated following denervation and may be a mechanism to counteract neurogenic atrophy [49]. However, YAP also influences the development of the neuromuscular junction in skeletal muscle [99]. Therefore, the upregulation of YAP due to denervation may serve a dual function: to preserve muscle mass and to regulate neuromuscular junction regeneration.

YAP and TAZ possible roles in reversing senescence in satellite cells

In aged muscle, satellite cells either lose their stem cell properties or decrease in number [81], which then leads to impaired muscle regeneration. During ageing, muscle satellite cells slowly lose their differentiation capabilities and become senescent [100]. In this state, they are no longer able to proliferate, even after an injury. Decreased $p18^{INK4\alpha}$ expression and its dysregulation accelerate ageing in satellite cells by decreasing the number of active self-renewing satellite cells that express $Pax7^{+}Ki67^{-}$ [101].

An exciting recent development regarding YAP/TAZ is their capability to induce mature cells back into a stem cell state. Zhao et al. [102] reported a new method to generate induced Pluripotent Stem Cells (iPS Cells) when they found that activating *Oct4*, *Sox2*, and *Yap* allows amniotic epithelial cells to regain stem cell properties. They speculated that harnessing this ability of YAP to induce senescent satellite cells back into functioning satellite cells could be a viable approach to chronic diseases associated with ageing [102]. Another group found that YAP overexpression allows iPS cells to regain back their potency potentials to a level similar to embryonic stem cells [103]. Thus, YAP helps maintain the characteristics of stem cells [104] and are expressed in almost all progenitor cells, including those within the inner cell mass of embryos. Thus, YAP not only plays important roles in embryonic development but also is needed to maintain stem cell potency [104].

Interestingly, overexpressing YAP increases the number of $Pax7^{+}$ cells and contributes to muscle proliferation [46], potentially opens a therapeutic avenue for increasing satellite cells by inducing YAP expression. However, although YAP activation promotes proliferation, its overexpression alone is not sufficient to activate quiescent satellite cells [51]. Taken together, YAP can convert mature cells back into their pluripotent state in several tissues, including muscle. However, further research needs to be performed to determine the effects of YAP activation in aged skeletal muscle since their activation may help delay progressive muscle atrophy due to ageing.

Conclusions

YAP/TAZ regulates several ageing pathways. Since the Hippo pathway is typically associated with organ size regulation, YAP/TAZ upregulation may decrease muscle atrophy. In addition, their function as mechanoreceptors may provide a unique signalling pathway to influence their expression, especially during exercise, muscle regeneration, and ageing. Autophagy is also a significant pathway implicated in skeletal muscle ageing. However, the influence of YAP/TAZ on this pathway has yet to be fully explored. YAP also plays a significant role in maintaining pluripotency and represents a novel target for improving stem cell therapy. YAP/TAZ also has the potential to prevent atrophy and rejuvenate aged cells; however, inducing YAP needs to be considered with caution since there may be an increased risk for oncogenesis. There is an urgent need for further research in understanding these areas, particularly since the elderly population is increasing rapidly in many countries. Modulating YAP/TAZ function in mature muscle cells, satellite cells, fibroblasts, and surrounding motor neurons offer potential new strategies to prevent or treat skeletal muscle atrophy in those patients.

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