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Research Progress of Hippo-Yap/Taz Signaling in Skeletal Muscle Hypertrophy

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Abstract

The Hippo pathway is an important pathway to control cell proliferation and organ size. By sensing extracellular matrix stiffness and intercellular mechanical force and converting them into molecular signal transduction, through a series of cascade amplification effects of kinases, the final the phosphorylation of YAP/TAZ, the main downstream target of the Hippo pathway, plays a series of regulatory roles. Although many studies have shown that Hippo signaling changes during skeletal muscle hypertrophy, the complex mechanism of Hippo signaling in skeletal muscle hypertrophy remains to be further studied. In this review, we summarize the relationship between Hippo-YAP/TAZ signaling and skeletal muscle hypertrophy and sort out the contribution of the main factors in the process of skeletal muscle hypertrophy.

Keywords: skeletal muscle hypertrophy, Hippo pathway, YAP1, skeletal muscle atrophy, cell proliferation

1. Introduction

Skeletal muscle tissue is a tissue with strong plasticity in the human body. It can undergo skeletal muscle hypertrophy by bearing a gradually increasing load, which is manifested in the increase of skeletal muscle cells, the thickening of skeletal muscle fibers and the increase in the number of skeletal muscle cells. Systemic hypertrophy of skeletal muscle occurs, exercise and growth and development of the body can cause hypertrophy of skeletal muscle cells, this phenomenon is called physiological hypertrophy of skeletal muscle. The hypertrophy process of skeletal muscle involves many biological processes, and many factors and signaling pathways also undergo important changes in the process. The highly conserved Yes-associated protein 1 (Yes associated protein 1, YAP1) used to be an important factor in cancer research and was considered to be one of the key factors promoting cell proliferation. The results of various gene knockout experiments also showed that YAP1 Dysregulation of upstream repression predisposes tissue cells to hyperproliferation. In recent years, the role of YAP1 and its upstream regulatory signal Hippo signal in tissue regeneration has been gradually elucidated. The role of the Hippo-YAP signal transduction system in the process of cardiac regeneration has been widely concerned. It was found that when the upstream inhibition of

YAP1 fails or when nuclear translocation of YAP1 fails to be inhibited, cardiomyocytes will overproliferate and the heart will undergo severe pathological hypertrophy. as has been observed in other organs in the past, so excessive nuclear translocation of YAP1, the induced downstream transcriptional effects are likely to be related to the proliferation of tissue cells. Considering that the hypertrophy of skeletal muscle is also accompanied by the proliferation and differentiation of skeletal muscle cells, it is necessary to further study the physiological role of the Hippo-YAP signal transduction system in the process of skeletal muscle hypertrophy, and to treat diseases related to skeletal muscle atrophy. It has important guiding significance, especially for the prevention and treatment of age-related sarcopenia. This article is based on the review of the regulation of the Hippo-YAP signal transduction system in the process of skeletal muscle hypertrophy, aiming to provide new ideas for exploring the mechanism of skeletal muscle hypertrophy and atrophy, and to provide insights into the prevention and treatment of sports fitness and skeletal muscle atrophy diseases. theoretical basis.

2. Overview of Hippo-YAP/TAZ Signaling Pathway

Several major factors in the Hippo pathway, MST1/2, LATS1/2, and YAP/TAZ, were first identified in Drosophila during the process of identifying a knockout gene that leads to cancer-like overgrowth, the gene Hpo (the homologue of mammalian MST1) named for the overgrowth of the fruit fly's head that resembles hippopotamus skin due to mutations, Hippo (hippo) has since become the name of the pathway in flies and mammals (Huang J, Wu S, Barrera J, Matthews K & Pan D., 2005). Hpo and its downstream target Warts (the homologue of LATS in Drosophila) constitute the core components of the initial Hippo pathway, phosphorylating the main downstream target Yorkie (the homologue of YAP in Drosophila) in a kinase cascade, prevent its excessive cell proliferation caused by nuclear translocation, and then play an anti-tumor role (Dong J, Feldmann G, Huang J, Wu S, Zhang N, Comerford SA, Gayyed MF, Anders RA, Maitra A & Pan D., 2007).

The upstream sensor of the Hippo pathway mainly senses the stiffness of the extracellular matrix (ECM) and the mechanical stress between cells through the transmembrane protein complex or F-actin connected to it, and converts them into biochemical signals. Signaling pathways that bridge mechanical stress signals with intracellular biochemical signals. Experiments have demonstrated that the Hippo pathway is activated under low ECM stiffness, and YAP/TAZ is translocated from the nucleus to the cytoplasm to lose auxiliary transcriptional activity and be degraded by ubiquitination (Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Cordenonsi M, Zanconato F, Le Digabel J, Forcato M, Bicciato S, Elvassore N & Piccolo S., 2011). This phenomenon suggests that the activation of the Hippo pathway depends to some extent on changes in the cytoskeleton or changes in the mechanical load between cells. Experiments have shown that at higher cell densities, the Hippo pathway can be directly activated in response to cell-cell contact to inhibit cell proliferation, which is related to contact inhibition (Calvo F, Ege N, Grande-Garcia A, Hooper S, Jenkins RP, Chaudhry SI, Harrington K, Williamson P, Moeendarbary E, Charras G & Sahai E., 2013). Although it is not yet clear how the Hippo pathway converts intercellular mechanical stress into cellular biochemical signals, a series of evidences show that the Hippo pathway can respond to overloading of mechanical loads, such as resistance training in skeletal muscles or muscle Synergistic ablation-induced mechanical overload induces skeletal muscle hypertrophy by promoting skeletal muscle cell hypertrophy and satellite cell proliferation (Judson RN, Tremblay AM, Knopp P, White RB, Urcia R, De Bari C, Zammit PS, Camargo FD & Wackerhage H., 2012; Goodman CA, Dietz JM, Jacobs BL, McNally RM, You JS & Hornberger TA., 2015; Watt KI, Judson R, Medlow P, Reid K, Kurth TB, Burniston JG, Ratkevicius A, De Bari C & Wackerhage H., 2010). In addition, Hippo signaling is also regulated by some other biological signals, such as the apical-basal cell polarity signal (Marikawa Y & Alarcon VB., 2019), cell adhesion (Kim GJ, Kim H & Park YN., 2013), the stretched state of the actin cytoskeleton (Zhao B, Li L, Wang L, Wang CY, Yu J & Guan KL., 2012; Sansores-Garcia L, Bossuyt W, Wada K, Yonemura S, Tao C, Sasaki H & Halder G., 2011), G protein-coupled receptors (GPCRs) signal transduction (Yu FX, Zhao B, Panupinthu N, Jewell JL, Lian I, Wang LH, Zhao J, Yuan H, Tumaneng K, Li H, Fu XD,

Mills GB & Guan KL., 2012) and mTOR signaling (Verbrugge SAJ, Schönfelder M, Becker L, Yaghoob Nezhad F, Hrabě de Angelis M & Wackerhage H., 2018). And there are cross-links with many other important biological signals such as TGF-β signal, Wnt signal and ErBb signal (Liu H, Du S, Lei T, Wang H, He X, Tong R & Wang Y., 2018), forming a three-dimensional biological information regulation network (Moroishi T, Hansen CG & Guan KL., 2015). In addition, some hormones and neurotransmitters, such as dopamine receptor agonists and epinephrine, can also activate LATS1/2 and prevent YAP/TAZ nuclear translocation (Dethlefsen C, Hansen LS, Lillelund C, Andersen C, Gehl J, Christensen JF, Pedersen BK & Hojman P., 2017). This suggests that Hippo-YAP/TAZ signaling also has the function of sensing endocrine signals and converting them into biochemical signals.

3. Hippo-Yap/Taz Signal Transduction Mechanism

The Hippo pathway is highly conserved in evolution, and there are two highly conserved upstream kinase protein MST1/2 homologues STK3 and STK4 in mammals. In Drosophila, MST1/2 can be activated by the upstream kinase Tao1/2/3 and associate with the important scaffold protein SAV1 (Poon CL, Lin JI, Zhang X & Harvey KF., 2011). There is also evidence shows that MST1/2 is capable of autophosphorylation (Praskova M, Khoklatchev A, Ortiz-Vega S & Avruch J., 2004). The pSTK3/4-pSAV1 kinase complex is formed, which can phosphorylate the downstream scaffold protein MOB1A/MOB1B and recruit LATS1/2 in the cytoplasm. Another key factor in this response is NF2/Merlin, which can directly interact with LATS1/2 interact and promote phosphorylation of LATS1/2 by the MST1/2 – SAV1 complex. In some cases, this phosphokinase dimer is cleaved by the Caspase-3 protein to form another pSTK3/4(1-323/327)-pSAV1 complex variant that has the same regulatory function in this pathway, both can phosphorylate the downstream proteins MOB1A/MOB1B and LATS1/2 and play a downstream regulatory role, but they have different physiological regulation capabilities and other physiological functions (Oh JE, Ohta T, Satomi K, Foll M, Durand G, McKay J, Le Calvez-Kelm F, Mittelbronn M, Brokinkel B, Paulus W & Ohgaki H., 2015). LATS1/2 is phosphorylated into pLATS1/2 and then recruited by phosphorylated MOB1A/MOB1B, and combined to generate pLATS1/2-pMOB1A/B dimer, phosphorylated LATS1/2 can bind YAP/TAZ through its PPxY motif Phosphorylation of serine sites in multiple HXRXXS sequences in YAP/TAZ inactivates YAP/TAZ phosphorylation and retention in the cytoplasm. In this process, another factor that may play an auxiliary role is the AMOT family. It has been reported that AMOT can also bind YAP and promote the phosphorylation of YAP by LATS1/2. When LATS1 phosphorylates YAP or TAZ, a phosphorylated S127 (TAZ is S89) site appears, which can increase the affinity of pYAP/pTAZ to 14-3-3σ protein and cause pYAP/pTAZ to remain in the cytoplasm (Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, Xie J, Ikenoue T, Yu J, Li L, Zheng P, Ye K, Chinnaiyan A, Halder G, Lai ZC & Guan KL., 2007). When LATS1/2 phosphorylates the Ser381 site of YAP1, the phosphorylated YAP1 is recognized and phosphorylated by casein kinase CK1δ or CK1ε, then ubiquitinated by E3 ubiquitin ligases such as SCFβ and TRCP, and finally degraded by the proteasome (Zhao B, Li L, Tumaneng K, Wang CY & Guan KL., 2010). Recent findings indicate that, in addition to the traditional Hippo upstream kinase MST1/2, MAP4K family kinases can also activate LATS1/2 in a non-canonical manner by phosphorylating the hydrophobic motif of LATS1/2, leading to the phosphorylation of YAP/TAZ and cytoplasmic retention (Meng Z, Moroishi T, Mottier-Pavie V, Plouffe SW, Hansen CG, Hong AW, Park HW, Mo JS, Lu W, Lu S, Flores F, Yu FX, Halder G & Guan KL., 2015; Zheng Y, Wang W, Liu B, Deng H, Uster E & Pan D., 2015). This non-canonical MAPK-LATS-YAP/TAZ transduction mechanism is more pronounced when the MAPK signaling pathway is active.

4. Expression of Hippo-Yap/Taz Signaling in Skeletal Muscle

The main function of the Hippo pathway is to sense the mechanical stress between cells and through a series of kinase cascade reactions to regulate cell proliferation and differentiation. It is the main regulatory signal of organ size (Misra JR & Irvine KD., 2018). Deregulation upstream of YAP/TAZ leads to uncontrolled proliferation and development of malignancies in mice or Drosophila organs. As one of the largest organs in the human body, skeletal muscle is not only an important part of the motor system, but also has other functions such

as metabolism and endocrine. Skeletal muscle is a highly plastic tissue, and external intervention (such as exercise training) can promote the hypertrophy of skeletal muscle, which is manifested by an increase in the volume and number of skeletal muscle cells (Joanisse S, Lim C, McKendry J, Mcleod JC, Stokes T & Phillips SM., 2020). The hypertrophy process of skeletal muscle will be accompanied by the increase and enlargement of skeletal muscle cells, and the Hippo-YAP/TAZ signal in skeletal muscle cells will change due to the stimulation of mechanical stress or nutritional level changes between skeletal muscle cells.

5. Skeletal Muscle Hypertrophy

Hypertrophy of skeletal muscle is considered to be a response to physical activity or mechanical load overload, mainly manifested as a marked increase in muscle fiber volume or an increase in the number of myocytes, which can be detected by dual-energy X-ray absorptiometry (DXA), computed tomography (Various imaging techniques such as CT), magnetic resonance imaging (MRI) and ultrasound detection can quantitatively evaluate the hypertrophy of skeletal muscle at the macro level, and can also evaluate the hypertrophy of skeletal muscle through the cross-sectional area (CSA) of muscle fibers at the micro level. The main cause of skeletal muscle hypertrophy is the increase of net protein synthesis, and its two major influencing factors are the increase of skeletal muscle protein synthesis rate and the decrease of skeletal muscle protein degradation. Hypertrophy of skeletal muscle is a very complex process (Schiaffino S, Reggiani C, Akimoto T & Blaauw B., 2021). Many physiological and micropathological responses are involved, in which PI3K-Akt-mTOR signaling plays an important regulatory role, and the expression of many genes undergoes significant changes in these processes, such as Mrf2, Pgc-1α, YAP/TAZ. These factors are also involved in many other biological processes, and cause cascade amplification effects through some signaling pathways, including ErBb pathway, Hippo pathway and SHH pathway, etc., and jointly participate in the regulation of skeletal muscle hypertrophy (Schiaffino S, Reggiani C, Akimoto T & Blaauw B., 2021).

6. The Role and Mechanism of Hippo-Yap/Taz Signaling in Skeletal Muscle Hypertrophy

6.1 Hippo-Yap/Taz Signal Transduction During Skeletal Muscle Hypertrophy

In skeletal muscle cells, in vitro and in vivo experiments have shown that inhibition of the Hippo pathway leads to skeletal muscle hypertrophy. The Hippo pathway is inhibited during resistance training or mechanical overload, and increased nuclear translocation of YAP/TAZ is thought to be necessary for skeletal muscle hypertrophy (Watt KI, Turner BJ, Hagg A, Zhang X, Davey JR, Qian H, Beyer C, Winbanks CE, Harvey KF & Gregorevic P., 2015). When skeletal muscle is overloaded in response to mechanical load, it attenuates the phosphorylation inhibition of YAP/TAZ by LATS1/2 on the one hand by regulating the expression of Hippo upstream kinases MST1/2 and LATS1/2, and on the other hand promotes YAP/TAZ through an unknown mechanism. The synergistic effect of the two leads to the increase of the nuclear level of YAP/TAZ, and YAP/TAZ can up-regulate the expression of myogenic factors such as Myod, Myf5 and Mrf4, which is the reason why YAP/TAZ promotes skeletal muscle hypertrophy one of the mechanisms (Camargo FD, Gokhale S, Johnnidis JB, Fu D, Bell GW, Jaenisch R & Brummelkamp TR., 2007). Studies have shown that phosphorylation of the mTOR pathway-related kinase p70S6k is associated with increased muscle mass, and mTOR and its downstream signals play a key role in the hypertrophy of skeletal muscle (Baar K & Esser K., 1999; Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, Zlotchenko E, Scrimgeour A, Lawrence JC, Glass DJ & Yancopoulos GD., 2001). That is, mTOR signaling can stimulate protein synthesis by sensing nutrient levels and phosphorylating eukaryotic initiation factor 4E-binding proteins (4E-BPs) and ribosomal S6 protein kinase 1 (S6K1). Both Hippo-YAP/TAZ and mTOR are thought to act synergistically through multiple mechanisms during skeletal muscle hypertrophy to precisely control skeletal muscle volume (Rivera-Reyes A, Ye S, E Marino G, Egolf S, E Ciotti G, Chor S, Liu Y, Posimo JM, Park PMC, Pak K, Babichev Y, Sostre-Colón J, Tameire F, Leli NM, Koumenis C, C Brady D, Mancuso A, Weber K, Gladdy R, Qi J & Eisinger-Mathason TSK., 2018). It is suggested that Hippo-YAP/TAZ may also promote protein synthesis by regulating the mTOR pathway in addition to the YAP-c-Myc-ribosome mechanism. In addition, the inhibition of the mTOR pathway on autophagy and protein ubiquitination

degradation makes YAP /TAZ protein degradation decreased (Chiang J & Martinez-Agosto JA., 2012). The protein amount and nuclear export of YAP/TAZ increase, and the three together constitute a positive feedback loop during the hypertrophy of skeletal muscle.

During skeletal muscle hypertrophy, certain hormones or direct mechanical stress signals may induce an upstream inhibitory effect on the Hippo pathway, which may activate YAP/TAZ, both of which have strong pro-proliferative effects and have been described as Genes with strong oncogenic potential (Pan D., 2010; Zhao B, Lei QY & Guan KL., 2008). The pro-proliferation effect of YAP/TAZ makes the abnormal inhibition of the Hippo pathway in some cases lead to hypertrophy of most organs of the animal, such as the liver and heart, and eventually develop into an irresistible malignant tumor phenomenon, so it is speculated that the inhibition of the Hippo pathway. The contribution to skeletal muscle hypertrophy may be mainly realized through the pathway that activated YAP/TAZ promotes the proliferation of myogenic cells.

6.2 Hippo-Yap/Taz Signaling Promotes Skeletal Muscle Hypertrophy Independently of the Mtor Pathway

The traditional idea is that Hippo-YAP/TAZ can sense the mechanical signal of overload during skeletal muscle contraction in a way independent of the mTOR pathway, and the change of intercellular mechanical stress temporarily activates the upstream kinase of the Hippo pathway through the mechanoreceptor protein on the cell membrane. Inhibition, decreased YAP/TAZ phosphorylation, resulting in increased nuclear localization of both (Tipton KD, Borsheim E, Wolf SE, Sanford AP & Wolfe RR., 2003). In the nucleus, YAP/TAZ binds to members of the TEADs family of transcription factors, and the complex of the two can bind multiple skeletons with MCAT (muscle C, A, and T; 5′-CATTCC-3′) motifs in the promoter region. Increase the transcription level of muscle hypertrophy-related genes, such as important myogenesis-related factors MyoD, Myf5 and Mrf4, etc., thereby inducing the proliferation, migration and fusion of satellite cells, increasing the number of skeletal muscle cells, and finally leading to muscle hypertrophy (Huang J, Wu S, Barrera J, Matthews K & Pan D., 2005). And the muscle hypertrophy induced in this way will not be counteracted by the effect of rapamycin, but the process is normally inhibited by VGLL4 upstream of Hippo and in the nucleus (Shi Z, He F, Chen M, Hua L, Wang W, Jiao S & Zhou Z., 2017; Guo T, Lu Y, Li P, Yin MX, Lv D, Zhang W, Wang H, Zhou Z, Ji H, Zhao Y & Zhang L., 2013; Koontz LM, Liu-Chittenden Y, Yin F, Zheng Y, Yu J, Huang B, Chen Q, Wu S & Pan D., 2013). In addition to inducing satellite cell proliferation and promoting skeletal muscle hypertrophy, YAP/TAZ can also up-regulate the mRNA expression of an important cell growth regulator c-Myc. C-Myc is considered to be able to promote the biogenesis of ribosomes in cells, has the physiological function of inhibiting the differentiation of myocytes and promoting the proliferation of myoblasts, and can also increase the rate of protein synthesis (Xiao W, Wang J, Ou C, Zhang Y, Ma L, Weng W, Pan Q & Sun F., 2013). This is an important reason for inducing skeletal muscle hypertrophy. In addition to binding to TEADs family factors, YAP/TAZ also has some other non-canonical pathways, such as the interaction with transcription factors such as NF-kB and STAT1, and promotes the transcription of some downstream genes (Coleman PR, Lay AJ, Ting KK, Zhao Y, Li J, Jarrah S, Vadas MA & Gamble JR., 2020).

6.3 Hippo-Yap/Taz Signaling Cooperates with Mtor to Promote Skeletal Muscle Hypertrophy

The second mechanism is that Hippo-YAP/TAZ signaling works synergistically with the mTOR pathway to induce skeletal muscle hypertrophy: the mTOR pathway is a signaling pathway that plays an important regulatory role in the process of increasing muscle mass, mainly by sensing nutrient levels and by promoting protein synthesis of skeletal muscle hypertrophy. The mTOR pathway is regulated by its upstream PI3K-Akt and IGF1 signaling pathways, and some studies suggest that the mTOR pathway can also be activated in response to mechanical stress. There are complex interactions between mTOR and the Hippo pathway, and these complex interactions jointly regulate skeletal muscle mass through multiple target genes, and the main action sites are still unclear. One point of view is that the Hippo pathway is actually located downstream of the PI3K-Akt-mTOR pathway, which is mainly based on the following points. First, the activation of the mTOR pathway is earlier than the inhibition of the Hippo pathway in time, and they are about 3 days and more than 7 days respectively (Judson RN, Gray SR, Walker C, Carroll AM, Itzstein C,

Lionikas A, Zammit PS, De Bari C & Wackerhage H., 2013). Secondly, Akt can phosphorylate and inactivate Mst1, thereby inhibiting the phosphorylation of LATS1/2 by MST1 and inhibiting Hippo signaling. It has also been reported that Akt can directly phosphorylate YAP1 to inhibit its nuclear translocation, so that YAP1 is retained in the cytoplasm and loses its auxiliary transcription activity, but this has not been confirmed by subsequent studies. In addition, studies have also reported that mTORC1, the main complex of the mTOR pathway, can regulate the protein level of YAP by inhibiting autophagy-mediated degradation, thereby increasing the amount of YAP1 protein in cells, thereby increasing the nuclear export level of YAP1.

There is also a view that both the mTOR pathway and the PI3K-Akt pathway are regulated by the Hippo pathway (Xu W, Yang Z, Xie C, Zhu Y, Shu X, Zhang Z, Li N, Chai N, Zhang S, Wu K, Nie Y & Lu N., 2018). First, YAP1 was reported to be able to repress PTEN expression through the downstream target miR-29 in a Hippo pathway-dependent manner (Guo L, Chen Y, Luo J, Zheng J & Shao G., 2019) (PTEN is a classic mTOR signaling inhibitor), then regulate the activity of mTOR pathway. Secondly, Mst1/2 can also directly interact with Akt and inhibit the activity of Akt, thereby affecting the activity of the downstream mTOR pathway. In addition, YAP1 can also participate in the regulation of PI3K-Akt signaling through Pik3cd. Recent research results have shown that, in addition to the above two pathways, LATS1 can also phosphorylate Raptor at Ser606, which is an important mTOR pathway element, and the phosphorylation inhibition of Raptor by LATS1 weakens its interaction with Rheb. Thereby reducing the activation of mTORC1, thereby regulating the activity of mTOR pathway (Gan W, Dai X, Dai X, Xie J, Yin S, Zhu J, Wang C, Liu Y, Guo J, Wang M, Liu J, Hu J, Quinton RJ, Ganem NJ, Liu P, Asara JM, Pandolfi PP, Yang Y, He Z, Gao G & Wei W., 2020), in addition, YAP/TAZ has also been reported to regulate amino acid transport signaling through the downstream key amino acid transporter component factor SLC7A5, increase amino acid uptake and induce mTORC1 activation (Hansen CG, Ng YL, Lam WL, Plouffe SW & Guan KL., 2015; Kim SG, Buel GR & Blenis J., 2013), and promote cell growth. However, this view cannot explain the reason why the activation of mTOR pathway is earlier than the inhibition of Hippo pathway in time.

In addition, there are some relatively novel viewpoints. For example, Akihiro Kaneshige et al. found in related research that, accompanied by mechanical load overload or resistance training, Hippo signaling can act as a bridge between mesenchymal progenitor cells and muscle stem cells. Relays signals to enable skeletal muscle cells to hypertrophy in response to mechanical overload induced by coordinated ablation procedures (Kaneshige A, Kaji T, Zhang L, Saito H, Nakamura A, Kurosawa T, Ikemoto-Uezumi M, Tsujikawa K, Seno S, Hori M, Saito Y, Matozaki T, Maehara K, Ohkawa Y, Potente M, Watanabe S, Braun T, Uezumi A & Fukada SI., 2022). This suggests that mesenchymal progenitors play an important role in regulating MuSC expansion during muscle hypertrophy, and that Hippo-YAP/TAZ can signal mesenchymal progenitors to cause MuSC expansion during mechanical overload.

6.4 Alternative Splicing Forms of Yap1 May Play Different Roles in Skeletal Muscle Hypertrophy

Alternative splicing of genes is a post-transcriptional modification phenomenon that widely exists in organisms. After alternative splicing, a DNA gene can transcribe two or more mRNAs, and these mRNAs can be translated into corresponding variable mRNAs. Spliceosome protein isoforms. In mammals, YAP1 has more than four mRNA splicing variants, and in humans, there are as many as 14, and at least 8 proteins are produced, and these YAP1 proteins are widely present in various tissues of organisms (Guo Q, Quan M, Dong J, Bai J, Wang J, Han R, Wang W, Cai Y, Lv YQ, Chen Q, Xu H, Lyu HD, Deng L, Zhou D, Xiao X, De Langhe S, Billadeau DD, Lou Z & Zhang JS., 2020; Sudol M., 2013; Salah Z, Alian A & Aqeilan RI., 2012). They have certain differences in transcriptional activity, and some longer splice variants may also play other different functions in physiological roles (Iglesias-Bexiga M, Castillo F, Cobos ES, Oka T, Sudol M & Luque I., 2015). It has been reported that the YAP1 protein with two WW domains is more likely to be phosphorylated and inhibited by LATS1/2, but it can play unique physiological roles, such as binding to transcription factors such as MEF2C and USF1, and has only one WW domain. Ability to bind to P73 that YAP1 protein does not possess (Oka T, Mazack V & Sudol M., 2008), this is especially important during cell apoptosis

(Guo Q, Quan M, Dong J, Bai J, Wang J, Han R, Wang W, Cai Y, Lv YQ, Chen Q, Xu H, Lyu HD, Deng L, Zhou D, Xiao X, De Langhe S, Billadeau DD, Lou Z & Zhang JS., 2020). However, there is still a lack of relevant research on which alternative splicing isoform plays a more important role in the hypertrophy of skeletal muscle. One possible mechanism is that energy stress and changes in upstream mechanical signaling during exercise affect the subcellular localization of the YAP1 alternative spliceosome, enabling the more pro-proliferative isoform of skeletal muscle cells to enter the nucleus, whereas normally These isoforms may be more susceptible to upstream repression. Considering that different subtypes of YAP1 genes can play different roles in some biological processes such as the proliferation and migration of cancer cells, we also need to consider whether different subtypes of YAP1 genes may also play different roles in the process of skeletal muscle hypertrophy. It is known that during the hypertrophy of skeletal muscle induced by the proliferation of satellite cells, activated satellite cells need to migrate out of their ecological niche and migrate along the basal layer of muscle fibers, which involves changes in the polarity of basal-apical cells, Different types of YAP1 have been reported to have different regulatory functions in this process, so the specific role of different subtypes of YAP1 in this process deserves further exploration.

7. Summary and Prospects

With the gradual maturity of gene editing technology and the deepening of research, the biological functions of YAP1 in various physiological environments have been gradually elucidated. Previous research has mainly focused on the development and migration of cancer, the tissue regeneration process of the heart and nervous system. However, the Hippo-YAP signaling network transduction in skeletal muscle is rarely studied. Skeletal muscle is a tissue with high plasticity, which can bear the pressure of mechanical load and continuously produce hypertrophy effect. It has been proved that Hippo-Yap signal can play a certain physiological effect in the process of hypertrophy of skeletal muscle, but its specific mechanism and Regulation remains to be explored in depth. There is a certain degree of synergy between the Hippo-YAP/TAZ pathway and other signaling pathways that promote skeletal muscle hypertrophy, and there are complex regulatory mechanisms involved in cell proliferation and differentiation, and satellite cell migration and fusion. The role of YAP1 in biological processes still needs to be further explored. Similarly, the reduction of skeletal muscle protein degradation is also one of the factors leading to skeletal muscle hypertrophy. Whether the Hippo signal related to protein degradation is related to the reduction of skeletal muscle cell degradation is also a very interesting question. Whether different YAP1 alternative splices that may have different functions also play different physiological roles in the process of skeletal muscle hypertrophy, and whether they can reduce skeletal muscle atrophy through which pathways still need to be further explored to reveal the Hippo-YAP/. The important physiological role of TAZ signal transduction system in skeletal muscle hypertrophy.

Fund Project

National Natural Science Foundation of China Youth Science Foundation Project: Study on Ameliorating Effect of CaMKII-POPDC3 signal-mediated regular exercise on cardiac aging based on Zebrafish POPDC3 Premature Aging Model (Project Approval Number: 81801392).

Research Project of Teaching Reform in Colleges and Universities of Hunan Province: Reform of the Training Mode of Physical Education Undergraduates in Chinese-Foreign Cooperative Schools Based on the Concept of CARE (Project Approval Number: HNJG-2020-0179).

NOX4 Role and mechanism of exercise-induced cardiac physiological adaptation changes (Project Approval Number: 202210542037).

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