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The Hippo signal transduction network for exercise physiologists

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Running head: The Hippo pathway for exercise physiologists

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Abstract

The ubiquitous transcriptional co-activators Yap (gene symbol *Yap1*) and Taz (gene symbol *Wwtr1*) regulate gene expression mainly by co-activating the Tead transcription factors. Being at the centre of the Hippo signalling network, Yap and Taz are regulated by the Hippo kinase cassette and additionally by a plethora of often exercise-associated signals and signalling modules. These include mechanotransduction, the AKT-mTORC1 network, the SMAD transcription factors, hypoxia, glucose homeostasis, AMPK, adrenaline/epinephrine and angiotensin II through G protein-coupled receptors, and interleukin 6 (Il-6). Consequently, exercise should alter Hippo signalling in several organs to mediate at least some aspects of the organ-specific adaptations to exercise. Indeed, Tead1 overexpression in muscle fibres has been shown to promote a fast-to-slow fibre type switch, whereas Yap in muscle fibres and cardiomyocytes promotes skeletal muscle hypertrophy and cardiomyocyte adaptations, respectively. Finally, genome wide-association studies in humans have linked the Hippo pathway members *LATS2, TEAD1, YAP1, VGLL2, VGLL3* and *VGLL4* to body height, which is a key factor in sports.

Keywords

Exercise, Hippo, Hypertrophy, Skeletal Muscle, Yap

Introduction

Especially during the last decade, key discoveries have led to the characterisation of the mammalian Hippo signal transduction pathway or network (51, 141, 159). The Hippo signal transduction network is relevant for exercise physiologists because many exercise-associated signals and signalling molecules affect Hippo signalling. Additionally, Hippo effectors regulate several exercise-related genes and adaptations. Starting with Booth in the mid-1990s (19), exercise physiologists have sporadically studied the Hippo pathway members in an exercise context. However, to date only few studies on Hippo in an exercise context have been published. In this review, we will first introduce the Hippo pathway to exercise physiologists. We will then discuss evidence showing that exercise-associated signals and signalling modules cross-talk to the key Hippo effectors YAP and TAZ. Next, we will review studies that implicate Hippo signalling in the regulation of exercise adaptations. Finally, we will discuss the emerging genetic link between Hippo and body height, a key variable linked to performance in several sports.

Hippo signal transduction pathway and network

The discovery of the Hippo pathway is based on two strands of research. First, since the early 20th century, researchers have used the fruit fly (*Drosophila melanogaster*) to identify genes whose knock out results in cancer-like overgrowth (40). Since 1995, this line of research has led to the discovery of the several growth-inhibiting genes (68, 156) that together form the core Hippo pathway (56). In the fly, the mutation of one kinase resulted in an overgrown head that reminded the researchers of the Hippopotamus' skin. Consequently, this kinase was named *hippo* by the Halder group. (134). Subsequently "Hippo" was adopted as the name for the pathway in both the fly and mammals. The Hippo pathway is highly conserved evolutionarily (60). In mammals (see Figure 1 for a schematic of the mammalian Hippo pathway), two homologues of the fly *hippo* gene exist, namely the upstream kinases Mst1 (*Stk4*) and Mst2 (*Stk3*). With the help of scaffolding proteins, Mst1 and Mst2 activate the downstream kinases Lats1 and Lats2. Recently, Map4k4/6/7 isoforms were identified as

alternative kinases capable of phosphorylating Lats1/2 (82, 97, 165). Phosphorylated Lats1 and Lats2 then inhibit the transcriptional co-factors Yap and Taz by phosphorylating multiple serine residues (86, 162).

The second strand of research started with the identification of CATTCC DNA motifs, termed muscle CAT (MCAT) (90) or GTIIC (24) motifs. Such CATTCC DNA motifs and their reverse strand GGAATG complement form a DNA binding site for the Tead (TEA domain) transcription factors (named Transcription enhancer factors or Tefs in earlier papers) (6, 24). Teads repress their target genes, especially when bound by their co-repressor Vgll4 (66, 76). Teads only become activated when bound by the transcriptional co-factor Yap (Yes1-associated protein; gene symbol *Yap1*), which was discovered by Sudol (122, 123, 138). In contrast to the fly, mammals possess a Yap paralogue termed Taz (Transcriptional coactivator with PDZ-binding motif (70)).

The two origins of Hippo research were only merged when the Pan group demonstrated that the Hippo kinase cascade inhibited Yorkie, the fly homologue of Yap and Taz (63). Hippo research then developed exponentially especially after the Pan group (29) and Camargo from the Jaenisch group (18) both found that the expression of a constitutively active *YAP1 S127A* in mouse livers resulted in a 4-fold liver size increase. These landmark findings confirmed that Yap also functions as a highly potent organ size regulator in mammals.

However, the Hippo kinase (i.e. the Mst1/2-Lats1/2 kinase cascade) is only one of many signalling modules that regulate the activity of Yap and Taz. For this reason, it seems most appropriate to refer to the wider signalling system as the Hippo signal transduction network. Importantly, numerous exercise-related signals also cross-talk to Yap and Taz, as illustrated in **Figure 1** and discussed in the next section.

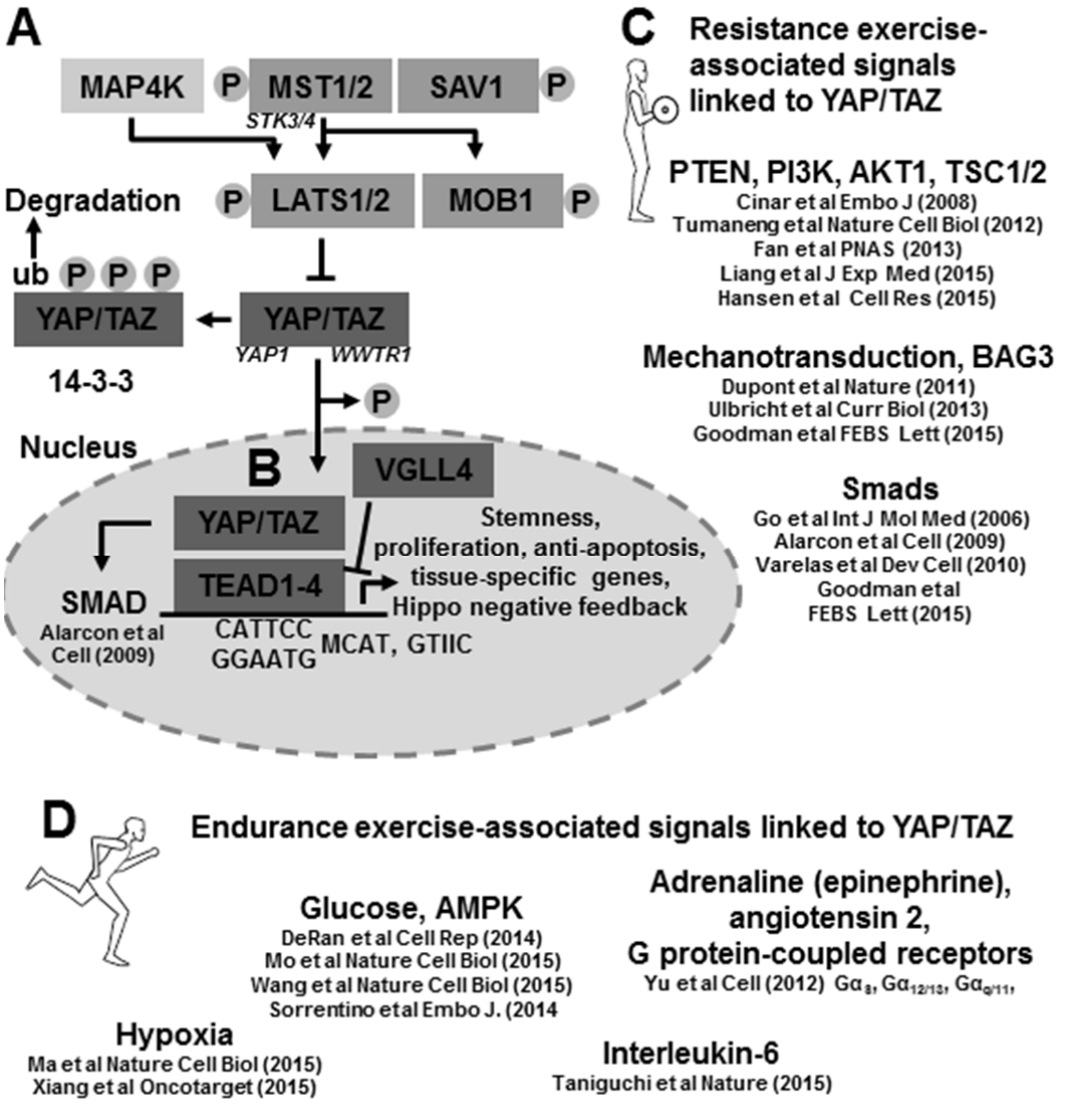

Figure 1. Schematic representation of the Hippo signal transduction network and its links to exercise-associated signals and signalling modules. **A**, MST1, MST2, LATS1 and LATS2 form the core kinase cassette of the Hippo pathway. SAV1 and MOB1 act as scaffolding proteins. The MAP4K 4, 6 and 7 kinase isoforms can independently regulate LATS1/2 (82, 97, 165). Active LATS1 and LATS2 inhibits YAP and TAZ through the phosphorylation of multiple HXRXXS motifs (where "S" indicates the phosphorylated serine) (162). Phosphorylation of YAP on serine 127 generates a binding site for 14-3-3 proteins, which sequester YAP and TAZ in the cytoplasm. Phosphorylation of serine 381 results in the ubiquitation and degradation of YAP (162). Similar regulatory events also affect TAZ. **B**, The

classical model stipulates that active unphosphorylated YAP and TAZ are nuclear and co-activate the TEAD transcription factors, whereas VGLL4 acts as a repressor. YAP/TAZ-TEAD complexes bind the CATTCC/GGAATG (MCAT or GTIIC) motifs found especially in enhancers that loop to the promoters of genes even though they are located several base pairs away from the promoter itself (39). **C,** Resistance (strength) exercise and muscle growth-associated signals that are linked to YAP/TAZ (see text for more detail). **D,** Endurance exercise-associated signals that are linked to YAP/TAZ (see text for more detail).

Cross-talk between exercise-related signalling molecules and Hippo

Mechanotransduction

Mechanical loading, in the form of resistance exercise or synergist ablation, stimulates skeletal muscle growth (42). However, the molecular mechanosensor that triggers growth processes in response to mechanical loading has long remained elusive. Additionally, the stiffness of the cellular environment or niche is an additional mechanical signal that influences for example the differentiation of mesenchymal stem cells into muscle and other cell types (34, 35). Moreover, mechanical cues also influence the fate of resident stem cells in skeletal muscle, named satellite cells (41). To identify signalling molecules that regulate gene expression in response to the mechanical signal triggered by substrate stiffness, the Piccolo group cultured mammary epithelial cells (MEC) on soft and stiff substrates. They found that Hippo-related genes showed the most important changes between the two conditions in terms of expression levels (31). Subsequent experiments confirmed that stiffer substrates led to increased Yap/Taz activity in a cytoskeleton-dependent manner (31). Later, it was shown that increased cell-cell contact reduces the mechanical loading of cells, which explained the previously observed (163) deactivation of Yap and Taz in response to cell-cell contact at high cell density (8). Whilst this is intriguing and relevant for processes such as myoblast differentiation, it is unclear whether mechanical changes of the extracellular matrix during exercise regulate transcriptional responses through Yap and Taz in muscle fibres or satellite cells.

In skeletal muscle, the Höhfeld group has identified a specific Hippo and autophagy-regulating mechanosensor complex located at the Z disc. In this complex, the protein Bag3 senses mechanical unfolding of the actin-crosslinking protein filamin (135). Importantly, Bag3 contains a WW domain, a rare protein domain frequently found in Hippo members (WW indicates two tryptophan residues; reviewed by (124)). The location of Bag3 in the Z disc is an ideal position for a mechanosensor. Indeed, unlike proteins that lie in parallel to the force-generating sarcomeres, such as integrins, Z disc proteins directly experience contractile force. One Hippo-independent function of Bag3 is to mediate tension-induced autophagy, which might contribute to the increased protein breakdown observed during resistance exercise (127). Additionally, Bag3 regulates Yap and Taz activity by binding to Yap and Taz binding partners, such as the Hippo kinase Lats1, Amotl1 and Amotl2 (reviewed in (102)). Given that increased Yap activity can promote muscle hypertrophy (46, 148), Bag3-Hippo mechanosensing might be one of the several mechanisms regulating muscle growth in response to mechanical signals. The importance of Bag3 for skeletal muscle is further demonstrated by the finding that a loss-of-function of Bag3 causes severe myopathy symptoms in mice and humans (62, 117). Moreover, the phosphorylation of human BAG3 on Thr285 and Ser 289 decreases in response to endurance exercise (61). Also, BAG3 expression decreases after acute high intensity resistance exercise, but increases together with force-bearing cytoskeleton proteins (136). Therefore, the Hippo-dependent and -independent functions of Bag3 are of potentially great interest to exercise physiologists. Currently, it is unclear whether Bag3 is the major mediator of mechanical loading-induced hypertrophy or whether it mainly senses the changes in the stiffness of a cell's niche, for example satellite cells, and accordingly regulates their behaviour (34).

Cross-talk with Akt-Tsc-mTOR signalling

The mTOR pathway has first been linked to overload-induced muscle growth by Baar and Esser. They demonstrated that the phosphorylation of the mTOR-related kinase p70 S6k

correlated with increased muscle mass in a rat electrical muscle stimulation model (11). Since then, many studies have confirmed the key role of mTOR signalling for resistance exercise-induced muscle hypertrophy. This includes a study in humans showing that the mTORC1 inhibitor rapamycin prevented the increased muscle protein synthesis triggered by resistance exercise (28).

Given that both the Hippo and mTOR networks regulate organ size, it is intuitive to assume a cross-talk between the mTOR and Hippo signalling pathways. This is indeed the case. Akt was initially shown to phosphorylate Yap on Ser127 (13) but this finding was not confirmed by subsequent studies. In another study, the Hippo kinase Mst1 (gene symbol *Stk4*) was shown to bind and inhibit Akt1 (also known as Pkb) (22). Conversely, Akt phosphorylates Mst1 on Thr387 (65) and Thr120 (161), suggesting that Akt1 and Mst1 regulate each other's activity. Additionally, the Hippo effector Yap de-represses mTOR by inhibiting the expression of the phosphatase Pten via the Pten-targeting miRNA miR-29 (133). Cross-talk also exists between Tsc1 and Tsc2 and the Hippo effector Yap as Tsc1/2-deficient cells have higher Yap levels due to less Yap degradation via the autophagosome system (83). YAP/TAZ also increase the expression of genes that encode the leucine transporter LAT1 (52), which is significant because leucine is a potent stimulator of mTORC1 signalling (10). Collectively, these findings demonstrate that Hippo and mTOR-mediated growth signals are closely coupled by multiple mechanisms. However, a caveat of this research from an exercise physiology standpoint is that most of the above studies have been conducted in cancer models. Therefore, molecular exercise physiologists now need to test whether these mechanisms also function in an exercise context.

Cross-talk with myostatin-Smad signalling

TGFβ and BMPs are two classes of small extracellular molecules that bind to activin receptors. Bound activin receptors then either phosphorylate the receptor-regulated Smad2/3 or Smad1/5/8 proteins, respectively. These two classes of receptor-regulated

Smads compete for the common mediator Smad4 to form either transcriptionally active Smad2/3-4 complexes promoting muscle loss or Smad1/3/5-4 complexes that have recently been proposed to promote muscle growth (114). In skeletal muscle, the knockout of myostatin (gene symbol *Gdf8*, a TGFβ-related ligand) or its "natural" loss-of-function mutation resulted in a doubling of the muscle size in mice and cattle, respectively (48, 69, 95, 96). The link between myostatin and muscle mass was confirmed in humans by showing that a toddler with a high muscle mass was homozygous for a knockout mutation in the first intron of the human myostatin-encoding *GDF8* gene (116). Furthermore, dogs with a heterozygous loss of *Gdf8* show increased racing performance (105), linking myostatin not only to muscle mass but also to actual athletic performance. If the loss of myostatin is combined with the overexpression of a follistatin transgene, then muscle mass quadruples, suggesting that myostatin is not the only muscle mass regulator in the TGFβ-Smad system (79).

Several studies have shown that Yap and Taz co-regulate not only Teads but also several other transcription factors, including Smads (143). In line with this, the overexpression of Yap in mouse tibialis anterior muscle reduced the activity of a Smad binding element (SBE) reporter by approximately 85% (46). In contrast, the overexpression of Yap in myoblasts, which are activated satellite cells, potently increases the expression of the Smad regulator Bmp4 (67). This is intriguing because both Yap (67) and Bmp4 (109) stimulate satellite cell proliferation while inhibiting differentiation into myotubes. Several mechanisms have been proposed that can explain how Yap or Taz can interact with Smads. These include the binding of Yap to the inhibitory Smad7 (7, 49), the promotion of Smad1 transcriptional action by Yap binding (3), and an effect of Yap and Taz on Smad2/3 localisation (137). For molecular exercise physiologists, the challenge is to determine whether Hippo-Smad cross-talk regulates exercise phenomena and especially where it is involved in skeletal muscle mass regulation.

Cross-talk with AMPK and glucose signalling

In the above sections, we have discussed the mechanisms connecting the Hippo network to resistance exercise and organ growth signals and signalling modules. Below, we will discuss the cross-talk between Hippo signalling and endurance exercise.

During the transition from rest to exercise ATP turnover can rise potentially more than 200 fold (98). To maintain homeostasis during such a large step change in ATP hydrolysis, systems have evolved to sense energy levels and initiate the signalling processes regulating both short- and long-term adaptations of energy metabolism. In this system, glucose, glycogen, AMP and ADP are sensed principally by the heterotrimeric AMPK complex (53, 55). Indeed, exercise increases the concentrations of AMP and ADP in contracting skeletal and cardiac muscle and exercise depletes glycogen, especially in muscle (45). Therefore, it comes as no surprise that AMPK is a key mediator of the adaptation to endurance exercise, particularly in skeletal muscle (54). Several recent studies have demonstrated that AMPK is a regulator of YAP, linking a key exercise kinase to Hippo signalling.

Both glucose starvation (36, 100, 145) and AMPK activators (26, 100, 145) inhibit Yap in different cell types. This suggests that Yap-dependent growth is inhibited when cellular energy levels are low. Further work led to the identification of the molecular mechanisms mediating this effect. These include the phosphorylation of the Yap regulator Amotl1 on Ser293 by AMPK (26) and the direct phosphorylation of YAP on Ser61/94, which is key for the interaction between Yap and Teads (100, 145). In another study, the Dupont group showed that the glycolytic enzyme phosphofructokinase (*PFK1*) directly binds to and regulates YAP and TAZ (36). Finally, two studies have identified the AMPK-kinase LKB1 (gene symbol *STK11*) as an AMPK-independent YAP regulator (101, 108). Collectively, these studies demonstrate that glucose starvation and energy stress inhibit YAP via both AMPK-dependent and -independent mechanisms in multiple cell types.

The fact that energy stress and the key exercise kinase AMPK regulate Yap suggest that Yap should be affected by exercise and diet. This now needs to be demonstrated in an exercise model. Also, because Hippo signalling responds to glucose and regulates the expression of glucose transporters (145), it should be studied whether Hippo signalling mediates the augmented adaptations in response endurance training under low carbohydrate supply (12), or mediates some of the anti-diabetic effects of exercise.

Cross-talk with hypoxia signalling

During evolution, the rise in atmospheric oxygen was followed by the evolution of oxidative phosphorylation by mitochondria, which use oxygen as their main electron acceptor. The emergence of oxygen-related metabolism drove the evolution of oxygen-sensing systems, as oxygen became critical for survival. Oxygen-sensing systems allow cells and organisms to adapt to low oxygen levels (i.e., hypoxia) especially through the transcription factor hypoxia-inducible factor (Hif1). Hypoxic conditions lead to an increase in the expression levels of the Hif1α isoform by blocking its degradation. The hypoxia-induced increase of Hif1α then induces multiple adaptations through gene expression (126). During exercise, hypoxia-induced signalling is also at work. For example, HIF1α levels increase in response to normoxic endurance exercise (5). Moreover, altitude training is often used to stimulate the molecular adaptations to hypoxia, including the EPO-mediated haematopoiesis that increases the athlete's oxygen transport capacity (118).

Hypoxia and Hippo signalling also interact. For example, hypoxia activates the E3 ligase Siah2, which leads to the degradation of Lats2. This results in a decreased level of Yap phosphorylation, increasing the activity of Yap in the nucleus (88). Additionally, Yap directly interacts with and stabilises Hif1α (88). Hif1α also promotes the expression of Taz and Taz transactivates Hif1α, highlighting a mechanism by which Taz and Hif1α are acting as reciprocal co-activators (153). It is unknown whether hypoxia-Hippo mechanisms function

during normoxic endurance exercise (5) and mediate adaptations to high altitude or low-intensity occlusion training. Direct evidence in an exercise or altitude model is required.

Sensing of catecholamines and other G protein-coupled receptors (GPCRs) ligands by Hippo

Catecholamines, such as adrenaline (US: epinephrine) and noradrenaline (US: norepinephrine), mediate the "fight-or-flight" responses. Catecholamine concentrations generally increase with the intensity and duration of exercise and drive the systemic responses to exercise via the α- and β-adrenergic receptors. These receptors, in turn, signal through G-protein coupled receptors (GPCRs) to trigger exercise adaptations, such as increasing the heart rate and muscle contractility. Moreover, β2 agonists such as clenbuterol promote skeletal muscle hypertrophy, suggesting an involvement of this system in the control of skeletal muscle growth (89). In the renin-angiotensin system (RAS), the angiotensin receptors are also coupled to protein G. The RAS was related to exercise when the ACE I/D polymorphism was associated with exercise-related traits, such as strength and endurance (111). Also, angiogensin II contributes to the adaptation to overload-induced skeletal muscle hypertrophy (47) and stretch-induced cardiac hypertrophy (112). In accordance with this, the ACE I/D polymorphism was associated with the left ventricular mass changes occurring in response to endurance training (103).

Multiple studies have linked GPCRs to Hippo signalling. Adrenaline/epinephrine represses YAP/TAZ through $G\alpha_S$-coupled GPCRs and protein kinase A (PKA) (74, 158). In contrast, angiotensin II and other ligands signal through the $G\alpha_{12/13}$ and $G\alpha_{q/11}$ GPCRs to activate YAP/TAZ (150, 160). Given that Yap has been shown to mediate skeletal muscle hypertrophy (46, 148) and can promote cardiac hypertrophy (reviewed in (141)), it will be key to test whether GPCR-Hippo signalling is involved in mediating such adaptations.

297 **Interleukin-6 and Hippo**

298 Interleukin-6 is a myokine (i.e. a circulating signalling molecule) that is produced by
299 contracting muscle but whose functions are incompletely understood (106, 110). Recently,
300 interleukin-6 has been shown to activate Yap through the gp130 co-receptor in the intestine
301 (125). However, it remains unclear whether this mechanism explains some of the effects of
302 exercise-generated interleukin-6.

303

304 **Hippo & exercise-related phenomena**

305 In the text above we have shown that many resistance and endurance exercise-associated
306 signals can cross-talk to the Hippo signal transduction network (see **Figure 1**). However,
307 much of this evidence was obtained in the context of cancer or non-exercise contexts. In the
308 following section, we will review a small number of studies that provide evidence for a role of
309 Hippo signalling in the adaptation to exercise. In relation to this, some key findings are
310 summarised in **Table 1**. Additionally, we review emerging evidence that body height is
311 associated with single nucleotide polymorphisms (SNPs) in the vicinity of Hippo genes.

312

313 **Table 1** Key experiments where the perturbation of Hippo members affects skeletal and
314 cardiac muscle in a way that is relevant to exercise physiology.

Key protein, experiment	Effects of intervention versus control	Reference
MST1: *STK4* (protein MST1) knockout versus wildtype mice, denervation-induced atrophy *in vivo*	**Attenuation of atrophy:** skeletal muscle atrophy after denervation ↓; expression of atrophy mediators ↓.	(149)
YAP: Injection of rAAV vector to express the main *YAP1* isoform versus control into mouse tibialis anterior *in vivo*	**Hypertrophy:** Skeletal muscle mass per body weight ↑; fibre cross sectional area ↑; protein synthesis ↑ (no evidence for mTOR involvement).	(148)
YAP: Electroporation of *YAP1*	**Hypertrophy:** Fibre cross sectional	(46)

versus control constructs into mouse tibialis anterior *in vivo*	area ↑ (mTORC1 independent); MyoD reporter ↑; c-Myc reporter ↑, MurRF1 reporter ↓; Smad reporter ↓.	
YAP: Overexpression of *YAP1 S127A*, wildtype *YAP* or empty vector in satellite cells or cultured muscle fibres *in vitro*	**Satellite cell proliferation** ↑; differentiation ↓.	(67)
TAZ: Injection of TAZ activator IBS008738 (specificity unclear) versus vehicle into mouse tibialis anterior after cardiotoxin-induced injury or dexamethasone-induced atrophy *in vivo*	**Regeneration, atrophy prevention**: IBS008738 injections accelerated skeletal muscle regeneration after injury and reduced atrophy after dexamethasone-induced atrophy.	(157)
TEAD1: Muscle creatine kinase promoter-driven expression of *TEAD1* in mouse muscle fibres and heart *in vivo*	**Fast-to-slow muscle phenotype shift but cardiomyopathy**: Extensor digitorum longus shortening velocity ↓; peak power ↓ by ~40%; fast-to-slow shift in myosin heavy chains; cardiomyopathy and heart failure.	(130, 132)
YAP: Transduction of neonatal rat cardiomyocytes with Yap1 or control adenovirus *in vitro*	**Cardiomyocyte hypertrophy:** Cardiomyocyte size ↑ (Akt-independent) and survival ↑ (Akt-dependent).	(25)
YAP: Inducible, Tnnt2-promoter driven expression of *YAP1 S127A* in foetal and post-natal cardiomyocytes *in vivo*	**Cardiac proliferation:** Cardiomyocyte proliferation ↑; relative heart weight ↑; regulation of cell cycle-related genes.	(139)
Salvador: Inducible, Myh6-driven	**Cardiac proliferation,**	(58)

knock out of *Wwtr1* (Salvador), *Lats 1* and *Lats2* in adult cardiomyocytes in mice *in vivo*; apex resection or myocardial infarction	**regeneration:** cardiomyocyte proliferation ↑, regeneration of injured hearts.	
YAP: α myosin heavy chain-driven expression of *Yap1 S112A* in the mouse heart *in vivo* (homologue of human S127A mutation); myocardial infarction	**Cardiac proliferation, regeneration:** Cardiomyocyte proliferation ↑; relative heart weight ↑. After myocardial infarction: cardiac function ↑, cardiomyocyte proliferation ↑, fibrosis ↓.	(154)
YAP: inducible expression of α myosin heavy chain-driven expression of *Yap1 S127A* in the adult mouse heart *in vivo*; myocardial infarction	**Cardiac proliferation, regeneration:** Cardiomyocyte proliferation ↑; relative heart weight unchanged. After myocardial infarction: cardiac function ↑, cardiomyocyte proliferation ↑, scar size ↓.	(85)

rAAV, recombinant adeno-associated virus; Nkx2.5 and Tnnt2 are promoters used to drive the specific expression of genes in cardiomyocytes.

Hippo and adaptive changes in skeletal muscle fibre phenotypes

Gollnick and Saltin were the first to demonstrate a higher percentage of slow type 1 muscle fibres and a higher oxidative activity in the muscles of endurance athletes when compared to controls and other athletes (44). They also observed a non-significant increase from 32% to 36% in the frequency of slow type 1 fibres in response to endurance training (43). Subsequent research has shown that chronic exercise training programmes mainly induce type 2X-to-2A interconversions (151).

In the early 2000's, the Tsika group investigated the role of MCAT elements and Tead1 transcription factors in the regulation of muscle fibre type-specific gene expression (71, 131, 140). The functional relevance of this work was demonstrated *in vivo* using a creatine kinase muscle (CKM) promoter to overexpress Tead1 in mouse skeletal muscle fibres, which caused an increased in slow muscle-specific gene expression *in vivo* (Table 1, (132)). Functionally, CKM-driven Tead1 overexpression reduced the shortening velocity (Vmax) and increased the contraction and relaxation times of extensor digitalis longus muscles (132). This suggests that Hippo signalling affects muscle fibre type-specific gene expression and fibre type percentages.

Hippo and skeletal muscle hypertrophy

Muscle hypertrophy is a key response to resistance exercise. After resistance exercise, protein synthesis and protein breakdown both increase. In the fed state, protein synthesis is higher than breakdown, resulting in protein accretion and hypertrophy (128). However, the effect of resistance exercise on muscle hypertrophy and strength differs greatly among the human population (64). A key mediator of muscle protein synthesis is mTOR signalling, as shown for example by the inhibitory effect of rapamycin on the increase of muscle protein synthesis after resistance exercise in human muscles (30). The key effect of resistance exercise on muscles is mechanical loading, which was discussed in the first part of this review along with the extensive links between mechanosensing and Hippo signalling (reviewed in (50, 87)), including the Z-disc located Bag3 mechanosensor in skeletal muscle (135, 136).

Several studies support a link between Hippo signalling, resistance exercise and muscle fibre size. In the first study on Hippo signalling in relation to exercise, the Booth group used chronic stretch overload to induce hypertrophy of the anterior latissimus dorsi muscle and found an increased expression of the skeletal α-actin gene. They showed that stretch overload activated a CATTCC (MCAT) motif-containing luciferase reporter, suggesting that

Tead transcription factor activity was present during mechanical overload of skeletal muscle (19). In a human study, eight men performed 100 unilateral maximal drop jumps followed by submaximal jumping until exhaustion (75). The mRNA of the Hippo pathway marker genes cysteine-rich angiogenic protein 61 (CYR61) and connective tissue growth factor (CTGF) (77, 164) increased 14- and 2.5-fold 30 min after exercise, respectively. Additionally, CYR61 protein levels were approximately 2-fold higher at both 30 min and 48 h after the exercise compared with resting control levels. This suggests that some forms of mechanical loading can induce the expression of Hippo marker genes. However, it is unclear whether the increases of CYR61 and CTGF expression are a direct consequence of altered Hippo signalling.

Two recent studies linked Yap activity directly to muscle fibre hypertrophy. Watt in the Harvey group used an adeno-associated viral vector (rAAV6)-mediated shRNA knock down strategy to reduce Yap levels in mouse limb muscles. They found a decreased muscle fibre size and reduced protein synthesis (148). Additionally, they used the same rAAV6 system to over express the predominant YAP isoform in muscle and found increases in muscle mass, cross sectional area and protein synthesis (Table 1, (148)). Intriguingly, despite the extensive evidence of cross-talk between Hippo and mTOR signalling discussed in the first part of this review, their YAP interventions did not seem to affect mTOR activity. In another study, the Hornberger group reported that YAP expression increases up to approximately 4.5 folds in the hypertrophying plantaris muscle days synergist ablation, a model commonly used to induce skeletal muscle hypertrophy (46). Then, they used electroporation to overexpress YAP in the tibialis anterior muscles and analysed the muscles 7 days later. The fibres overexpressing YAP were larger than control fibres, demonstrating that elevated YAP activity could cause hypertrophy (**Table 1**). Additionally, they found that YAP induced MyoD and Myc reporters, whilst inhibiting a Smad binding element (CAGA)-containing reporter (46). Reductions in myostatin produce a similar effect on a Smad binding element (CAGA) reporter (166), and a myostatin knock out also induces muscle hypertrophy (95). In

summary, Hippo members can affect fibre type proportions and increased levels of Yap can induce skeletal muscle hypertrophy. Additionally, Hippo marker genes increase after resistance exercise in human skeletal muscle.

Hippo and satellite cells

Satellite cells were discovered by Mauro using electron microscopy (92) and are now well-recognized as the resident stem cells of skeletal muscle (115). The key tool allowing to characterise their function *in vivo* was the Pax7-DTA knockout mice line, which is used to specifically deplete the satellite cell pool in mouse muscles. Studies with these mice showed that satellite cells are essential for the regeneration of skeletal muscle after injury (2, 81, 107), suggesting that, in a sports context, satellite cells are needed to regenerate the muscles damaged by eccentric exercises, such as marathon running (59). In contrast, satellite cell-depleted muscles show a normal hypertrophic response to overload in the short term (93). However, satellite cell-depleted muscle cannot maintain the initial hypertrophy after more than 8 weeks (38), suggesting that satellite cells are essential for muscle regeneration after injury and are required to maintain the size of hypertrophied muscles in the long term.

Hippo members are key mediators of proliferation and differentiation in satellite cells and myoblasts (mononuclear muscle cells). Yap is active in proliferating C2C12 myoblasts, and high Yap activity promotes their proliferation but inhibits myogenic differentiation (147). In satellite cells, Yap protein levels are low in the quiescent state, but increase when satellite cells become activated and develop into MyoD-expressing myoblasts. Again, high Yap activity resulting from the expression of the constitutively active *YAP1 S127A* mutant promotes proliferation but inhibits differentiation (67). Conversely, knocking down Yap in satellite cell-derived myoblasts reduces proliferation by approximately 40% (67). The overexpression of *YAP1 S127A* in satellite cell-derived myoblasts also increases the expression of proliferation-associated genes and known satellite cell regulators, such as

410 BMP4 (109) and CD34 (4), while reducing the expression of differentiation markers and the
411 myogenic differentiation regulator Mrf4 (67). Collectively, these results indicate that Yap
412 promotes myoblast and satellite cell proliferation but inhibits differentiation into myotubes
413 and muscle fibres. This suggests that Yap might be an important regulator of muscle
414 development (myogenesis) and satellite cell-derived myoblasts proliferation after injury and
415 in response to hypertrophy. The requirement of Yap and other Hippo members, such as Taz,
416 during the satellite cells response to exercise remains to be formally demonstrated.
417
418 **Hippo and the Athlete's heart**
419 The maximal oxygen uptake (VO_2max) is the key determinant of an individual's endurance
420 capacity (27) and is also associated with longevity (15). Early physiological studies in
421 humans demonstrated that one of the key predictors of an individual's VO_2max is the blood
422 flow generated by the heart, termed cardiac output (99), which determines the efficiency of
423 oxygen transport to the exercising musculature. The VO_2max and cardiac output parameters
424 respond to exercise training and detraining, as demonstrated by Saltin and colleagues (113).
425 They showed that 20 days of bed rest reduces resting heart volume by approximately 10%
426 and exercise cardiac output by 15%, resulting in a significantly reduced VO_2max (113).
427 Conversely, 55 days of endurance exercise training following the bed rest increased cardiac
428 output above pre-bed rest levels. This partially explains the restoration of VO_2max (142).
429
430 The increase in cardiac output can be attributed to the development of an athlete's heart in
431 response to endurance training. Indeed, electrocardiographic studies show that athletes
432 have enlarged hearts (9) which was later confirmed by comparative echocardiography on
433 endurance athletes (91). Generally, the main cellular mechanism underlying the athlete's
434 heart is cardiomyocyte hypertrophy. For example endurance running training for 8 weeks
435 increases cardiomyocyte size by 17-32% in mice (73). Until several years ago, researchers
436 thought that adult cardiomyocytes were unable to proliferate and regenerate the heart.
437 However, this view is now changing (33). By determining the levels of ^{14}C DNA integration

438 from nuclear bomb tests, Bergmann et al. estimated that between 0.45 and 1% of human
439 cardiomyocytes renew per annum. Furthermore, they showed that by the age of 50, 40% of
440 the cardiomyocytes had emerged after birth (14). Moreover, swim endurance training for 2
441 weeks increased the expression of proliferation markers in mouse cardiomyocytes (16),
442 suggesting that exercise promotes cardiomyocytes proliferation, at least in mice. There is
443 emerging evidence supporting the existence of a cardiac stem cell population that may
444 engage in some limited regeneration processes (32) in addition to a low rate renewal of pre-
445 existing cardiomyocytes (119). Two recent studies found that both cardiac stem cells and
446 cardiomyocytes proliferate in response to endurance exercise in rodents (80, 146).
447 Collectively, these data demonstrate that endurance exercise increases left ventricular
448 volume, thickness and pumping performance and suggest that these effects occur mainly
449 through cardiomyocyte hypertrophy with a limited contribution of cardiac stem cells and
450 cardiomyocytes proliferation. Consequently, this results in the development of the athlete's
451 heart, which in turn increases the VO_2max and aerobic exercise capacity of an individual.
452
453 The heart can respond to increased load in two different ways, depending upon the nature of
454 the load (94):
455 1) **Physiological hypertrophy** (i.e., athlete's heart) can occur as a response to endurance
456 exercise or pregnancy (volumetric hypertrophy) or resistance exercise (non-volumetric
457 hypertrophy);
458 2) **Pathological hypertrophy** can occur after cardiac injury or in individuals with high blood
459 pressure or defective valves.
460
461 Physiological hypertrophy, which is associated with exercise or pregnancy, differs from
462 pathological hypertrophy by the nature of the stimuli, the structural response, the absence of
463 fibrosis and the molecular drivers leading to the adaptation (94). Generally, physiological
464 hypertrophy does not progress into cardiac dysfunction. In contrast, pathological hypertrophy
465 often decompensates, reducing cardiac function and resulting in end-stage heart failure (72).

Both types of hypertrophy differ at the molecular level in their response the divergent stimuli (1).

Currently, whether and how Hippo signalling contributes to the different forms of cardiac hypertrophy remains incompletely understood. Several studies show that Yap loss- or gain-of-function in the embryonic heart is frequently lethal (reviewed by (84, 141, 155)). This suggests that normal Yap function is essential for normal cardiac development. Presumably, Yap is active only in certain cell populations during specific periods, which could explain why permanent Yap gain- or loss-of-function has such a detrimental effect. There is some evidence that Hippo signalling is perturbed during pathological cardiac hypertrophy. Yap is expressed at higher levels and dephosphorylated (activated) in samples obtained from pathologically hypertrophied human hearts (144). Furthermore, Yap is activated in hearts stressed by pathological pressure overload (144) and in the area bordering a myocardial infarction in mice (25).

Are Hippo members contributing to the formation of the athlete's heart in response to exercise? Although this question has not been addressed directly, published data suggest possible roles for Hippo members in mediating the athlete's heart (see also **Table 1**). First, *Yap1* overexpression in cultured neonatal rat cardiomyocytes promotes hypertrophy and survival compared to control cardiomyocytes (25). In contrast, two other teams reported no cardiomyocyte hypertrophy upon Yap activation in postnatal mouse hearts *in vivo* (139, 154). The reasons behind these contrasting results are unknown and so it is unclear whether Hippo signalling contributes to cardiomyocyte hypertrophy in response to exercise (73).

Another response of the heart to endurance exercise is the limited proliferation of cardiomyocytes and cardiac stem cells in rodents (16, 80, 146). While it has not been tested whether Hippo members promote cardiomyocyte or cardiac stem cell proliferation in response to endurance exercise, evidence supporting that Hippo members regulate the

494 proliferation of adult cardiomyocytes and can enhance regeneration after cardiac injury has
495 been reported (**Table 1**). Knocking out the Hippo members *Sav1* or *Lats1/2* in adult mouse
496 cardiomyocytes increases proliferation, promotes regeneration after myocardial infarction
497 and reduces scar tissue formation (58). Similarly, *Yap1 S112A* overexpression in
498 cardiomyocytes improves cardiac regeneration after myocardial infarction, both in neonatal
499 and adult mice, with evidence for increased cardiomyocyte proliferation compared to controls
500 (154). Finally, in a mouse model of myocardial infarction, forcing human YAP expression in
501 the heart using adeno-associated virus delivery increases cardiomyocyte proliferation and
502 improves cardiac function as well as survival (85).
503
504 In summary, the normal function of Yap and Hippo signalling is essential for normal cardiac
505 development. Currently, it is unknown whether Hippo members and Yap in cardiomyocytes
506 and cardiac stem cells respond to exercise and contribute to the development of an athlete's
507 heart. Available studies suggest that Yap can promote cardiomyocyte hypertrophy in some
508 contexts, while, in other contexts, Yap appears to promote cardiomyocyte proliferation and
509 enhance cardiac regeneration after injury.
510
511 **Hippo & body height**
512 Body height is a key factor in sports, which is most striking in NBA basketball players. Body
513 height is approximately 70-90% inherited (121) and depends on hundreds, if not thousands,
514 of common DNA sequence variations with a small effect size (152). In rare cases, body
515 height can be affected by single, rare mutations with a large effect size. Examples for the
516 latter are dwarfism caused by *FGFR3* mutations (37), and acromegaly resulting from *AIP*
517 gene mutations (20).
518
519 Given that a core function of Hippo signalling is to control cell numbers, one would expect
520 links between Hippo gene DNA sequence variations and body height. Interestingly, genome-
521 wide association studies (GWAS) involving the analysis of data from up to 250,000

individuals (152) show that single nucleotide polymorphisms (SNPs) in several Hippo genes are associated with body height (23, 78, 152). Indeed, SNPs associated with genes encoding for *LATS2, TEAD1, YAP1, VGLL2, VGLL3, and VGLL4* are associated with body height (23, 57, 78, 152). In the largest meta-analysis study using data obtained from 253,288 individuals of recent European ancestry (152), body height-associated SNPs in *LATS2* (rs1199734), *TEAD1* (rs6485978, rs2099745), *VGLL2* (rs1405212) and *VGLL4* (rs13078528) were identified. In 2010, Lango Allen et al. identified an association between SNPs in *TEAD1* (rs7926971) and *VGLL2* (rs961764) with body height in 133,653 individuals of recent European ancestry. Also, SNPs in *YAP1* (rs11225148) and in *VGLL3* (rs7628864) were individually associated with a shorter stature during pubertal growth in a longitudinal meta-analysis involving 18,737 European individuals (23). Interestingly, the SNP in *VGLL3* was only significantly associated with the trait in females. So far, no sex-related differences were reported for the Hippo pathway functions but this association could suggest that such differences might actually exist in some contexts. Finally, a SNP in *VGLL4* (rs6772112) was associated with height in 36,227 East Asian ancestry subjects (57). Another interesting association of the study by Cousminer et al. is the identification of a female-specific SNP in *LIN28B* associated with late pubertal growth (23). The *LIN28/LET-7* pathway, which has recently emerged as a potent regulator of organismal development and cellular metabolism (120), has been functionally linked with the Hippo pathway (21, 104). In summary, common DNA sequence variants in several Hippo genes influence body height but the effect of each variant on height is small, presumably as *de novo* DNA sequence variants with a large effect size either become fixed or lost relatively quickly (17).

Summary and future research

In this review, we have listed mainly indirect evidence suggesting that Hippo signalling may mediate some of the physiological adaptations to exercise and that SNPs, especially in the Hippo transcriptional regulators, are associated with body height as a measure of whole

549 body cell numbers. The task for molecular exercise physiologists is now to directly show that
550 these mechanisms mediate adaptation to exercise in exercise models and that Hippo gene
551 variants are associated with sport and exercise-related traits. We end with three questions:
552 1) Because resistance and endurance exercise trigger different adaptations in skeletal
553 muscle, how can it be explained that the activity of Hippo members is both affected by
554 both resistance and endurance exercise-associated signals?
555 2) Given that Hippo signalling affects amino acid (52) and glucose transporter expression
556 (145), can this be used to develop strategies to alter the responsiveness to nutrients?
557 For example, can we target through Hippo modulation the leucine transporter LAT1 (52)
558 to make muscles and other organs more sensitive to protein intake ? Could such
559 strategy be beneficial for strength athletes or in cases of muscle weakness and wasting,
560 for example, in elderly individuals or cancer patients with sarcopenia?
561 3) Given that the Hippo pathway is involved in regulating the fate of many stem cells (129),
562 can this be exploited to develop interventions aimed at improving the repair of muscle,
563 tendons and cartilage after sports injury or in degenerative muscle diseases?
564

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We have no conflicts of interest to disclose.

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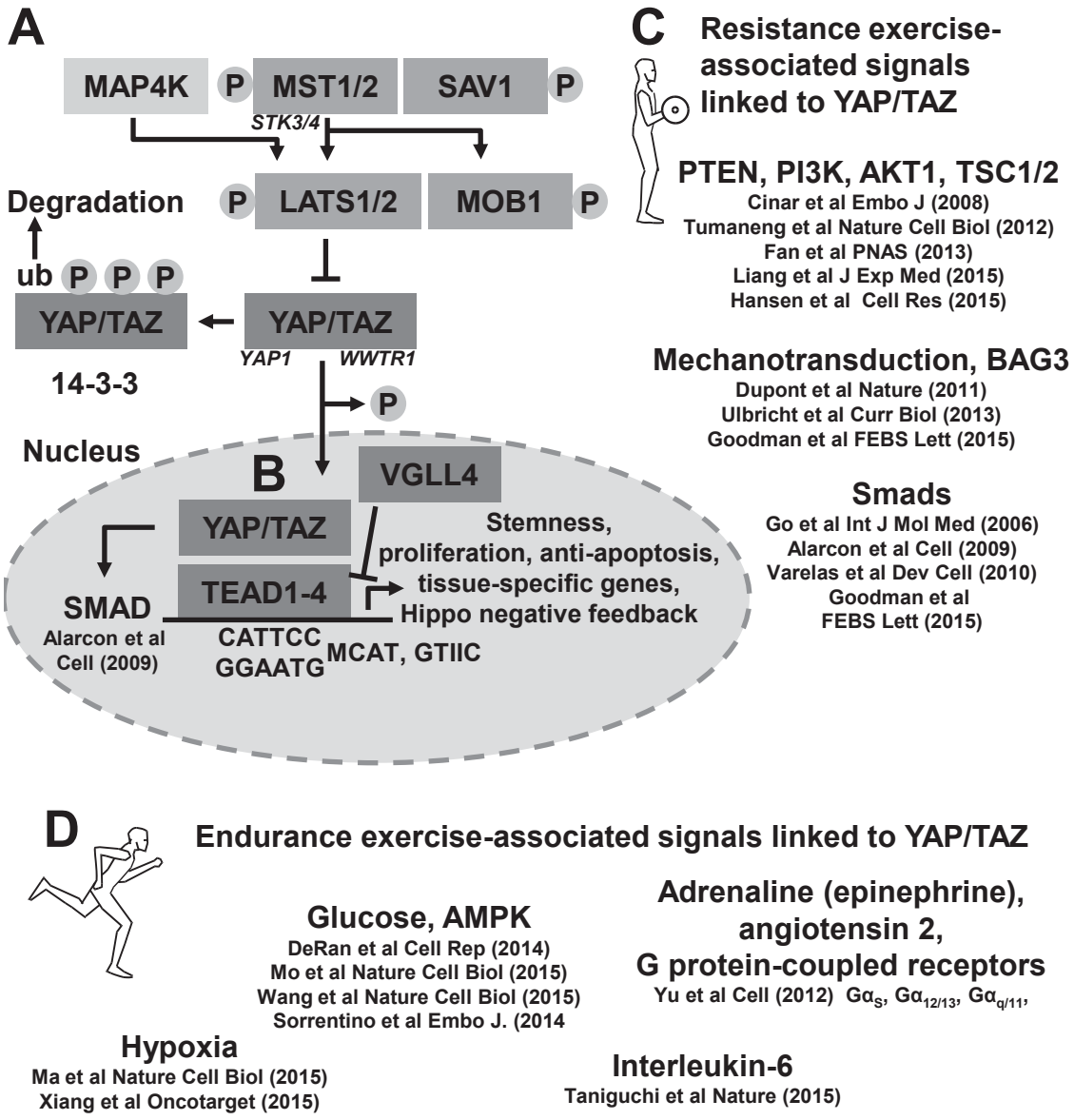
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