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Synthesis Review

The Hippo signal transduction network for exercise physiologists

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Gabriel BM, Hamilton DL, Tremblay AM, Wackerhage H. The Hippo signal transduction network for exercise physiologists. *J Appl Physiol* 120: 1105–1117, 2016. First published March 3, 2016; doi:10.1152/japplphysiol.01076.2015.—The ubiquitous transcriptional coactivators Yap (gene symbol *Yap1*) and Taz (gene symbol *Wwtr1*) regulate gene expression mainly by coactivating the Tead transcription factors. Being at the center of the Hippo signaling network, Yap and Taz are regulated by the Hippo kinase cassette and additionally by a plethora of exercise-associated signals and signaling 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 IL-6. Consequently, exercise should alter Hippo signaling in several organs to mediate at least some aspects of the organ-specific adaptations to exercise. Indeed, Tead1 overexpression in muscle fibers has been shown to promote a fast-to-slow fiber type switch, whereas Yap in muscle fibers 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.

exercise; Hippo; hypertrophy; skeletal muscle; Yap

KEY DISCOVERIES ESPECIALLY DURING the last decade have led to the characterization 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 signaling molecules affect Hippo signaling. Additionally, Hippo effectors regulate several exercise-related genes and adaptations. Starting with Booth in the mid-1990s (19), exercise physiologists have sporadically studied Hippo pathway members in an exercise context. However, to date only a 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 signaling modules cross-talk to the key Hippo effectors YAP and TAZ. Next, we will review studies that implicate Hippo signaling 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.

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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 knockout 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 skin of a Hippopotamus. Consequently, this kinase was named *hippo* by Georg Halder group of researchers (134). Subsequently "Hippo" was adopted as the name for the pathway in both the fly and mammals. The Hippo pathway is highly evolutionarily conserved (60). In mammals (see Fig. 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 and Lats2 (82, 97, 165). Phosphorylated Lats1 and Lats2 then inhibit the transcriptional cofactors Yap and Taz by phosphorylating multiple serine residues (86, 162).

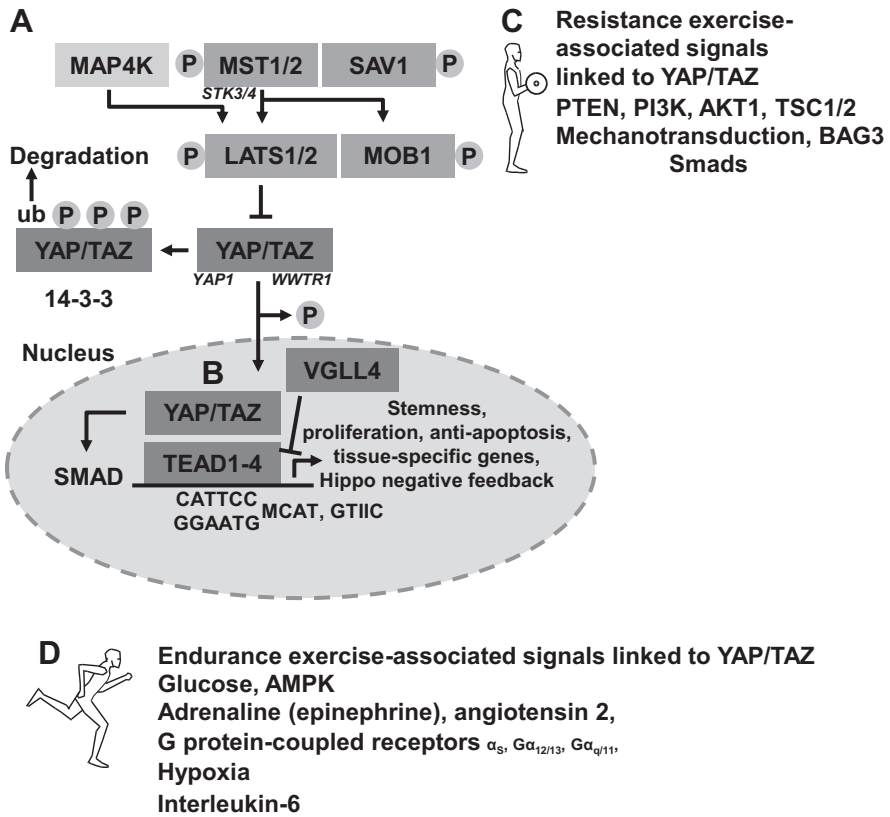

Fig. 1. Schematic representation of the Hippo signal transduction network and its links to exercise-associated signals and signalling modules. *A*: MST1, MST2, LATS1, and LATS2 form the core kinase cassette of the Hippo pathway. SAV1 and MOB1 act as scaffolding proteins. The MAP4K 4, 6, and 7 kinase 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" within HXRXXS indicates the phosphorylated serine) (162). Phosphorylation of YAP on serine127 generates a binding site for 14-3-3 proteins, which sequester YAP and TAZ in the cytoplasm. Phosphorylation of serine381 results in the ubiquitination 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 coactivate 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 [see (39) and the text for more information]. *C*: resistance (strength) exercise and muscle growth-associated signals that are linked to YAP/TAZ (see text for more information). *D*: endurance exercise-associated signals that are linked to YAP/TAZ (see text for more information).

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 corepressor, Vgll4 (66, 76). Teads become activated only when they are bound by the transcriptional cofactor Yap (Yes1-associated protein; gene symbol *Yap1*), which was discovered by Sudol et al. (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 merged when the Pan group of researchers (63) demonstrated that the Hippo kinase cascade inhibited Yorkie, the fly homologue of Yap and Taz. Hippo research then developed exponentially especially after studies by the Pan group (29) and Camargo from the Jaenisch group (18) both found that expression of a constitutively active *YAP1 S127A* in mouse livers resulted in a fourfold increase in liver size. These landmark findings confirmed that Yap also functions as a highly potent organ size regulator in mammals.

However, the Hippo kinase cascade (i.e., the Mst1/2-Lats1/2) is only one of many signaling modules that regulate the activity of Yap and Taz. For this reason, it seems most appropriate to refer to the wider signaling 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.

Cross-Talk Between Exercise-Related Signaling 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 signaling molecules that regulate gene expression in response to the mechanical signal triggered by substrate stiffness, the Piccolo group of researchers (31) cultured mammary epithelial cells 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. 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). Although 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 fibers or satellite cells.

In skeletal muscle, the Höhfeld group (135) 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. Importantly, Bag3 contains a WW domain, a rare protein domain frequently found in Hippo members [WW indicates two tryptophan residues; reviewed in (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 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 Ser289 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 behavior (34).

Cross-Talk with Akt-Tsc-mTOR Signaling

The mechanistic target of rapamycin (mTOR) pathway was first linked to overload-induced muscle growth by Baar and Esser (11). They demonstrated that the phosphorylation of the mTOR-related kinase p70 S6k correlated with increased muscle mass in a rat electrical muscle stimulation model. Since then, many studies have confirmed the key role of mTOR signaling 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 that cross-talk exists between the mTOR and Hippo signaling 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 others 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 because 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 signaling (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 models that are not related to exercise. Therefore, molecular exercise physiologists now need to test whether these mechanisms also function in an exercise context.

Cross-Talk with Myostatin-Smad Signaling

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 that promote 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 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 with muscle mass but also with 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 coregulate not only Teads, but also several other transcription factors, including Smads (143). In line with this, overexpression of Yap in mouse tibialis anterior muscle reduces the activity of a Smad-binding element (SBE) reporter by ~85% (46). In contrast, overexpression of Yap in myoblasts, which are activated satellite cells, potently increases 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 localization (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 Signaling

In the sections above, we discussed the mechanisms connecting the Hippo network to resistance exercise and organ growth signals and signaling modules. Below, we will discuss

the cross-talk between Hippo signaling 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 signaling processes that regulate 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 signaling.

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 research led to 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 (36) showed that the glycolytic enzyme phosphofructokinase (*PFK1*) directly binds to and regulates YAP and TAZ. Finally, two studies (101, 108) have identified the AMPK-kinase LKB1 (gene symbol *STK11*) as an AMPK-independent YAP regulator. 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 signaling responds to glucose and regulates the expression of glucose transporters (145), it should be studied whether Hippo signaling mediates the augmented adaptations in response to endurance training under low carbohydrate supply (12), or mediates some of the antidiabetic effects of exercise.

Cross-Talk with Hypoxia Signaling

The rise in atmospheric oxygen more than 2 billion years ago 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 expression levels of the Hif1α isoform by blocking its degradation. The hypoxia-induced increase in Hif1α then induces multiple adaptations through gene expression (126). During exercise, hypoxia-induced signaling 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 erythropoeitin (EPO)-mediated hematopoiesis that increases the athlete's oxygen transport capacity (118).

Hypoxia and Hippo signaling 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, thereby increasing the activity of Yap in the nucleus (88). Additionally, Yap directly interacts with and stabilizes Hif1α (88). Hif1α also promotes expression of Taz, and Taz transactivates Hif1α, highlighting a mechanism by which Taz and Hif1α are acting as reciprocal coactivators (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 Receptor Ligands by Hippo

Catecholamines such as adrenaline (i.e., epinephrine in the United States) and noradrenaline (norepinephrine in the US), 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 an 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 left ventricular mass changes occurring in response to endurance training (103).

Multiple studies have linked GPCRs to Hippo signaling. 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 signaling is involved in mediating such adaptations.

Interleukin-6 and Hippo

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

Hippo and Exercise-Related Phenomena

In the text above we have shown that many resistance and endurance exercise-associated signals can cross-talk to the

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

Key Protein, Experiment	Effects of Intervention vs. Control	Reference
MST1: *STK4* (protein MST1) knockout vs. wild-type 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 vs. control into mouse tibialis anterior in vivo	Hypertrophy: skeletal muscle mass per body weight ↑; fiber cross-sectional area ↑; protein synthesis ↑ (no evidence for mTOR involvement).	(148)
YAP: electroporation of *YAP1* vs. control constructs into mouse tibialis anterior in vivo	Hypertrophy: fiber cross-sectional area ↑ (mTORC1 independent); MyoD reporter ↑; c-Myc reporter ↑, MurRF1 reporter ↓; Smad reporter ↓.	(46)
YAP: overexpression of *YAP1 S127A*, wild-type *YAP* or empty vector in satellite cells or cultured muscle fibers in vivo	Satellite cell proliferation ↑; differentiation ↓.	(67)
TAZ: injection of TAZ activator IBS008738 (specificity unclear) vs. 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 fibers and heart in vivo	Fast-to-slow muscle phenotype shift but cardiomyopathy: extensor digitorum longus shortening velocity ↓; peak power ↓ by approximately 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 fetal and postnatal cardiomyocytes in vivo	Cardiac proliferation: cardiomyocyte proliferation ↑; relative heart weight ↑; regulation of cell cycle-related genes.	(139)
Salvador: inducible, Myh6-driven knock-out of *Wwtr1* (Salvador), *Lats 1* and *Lats2* in adult cardiomyocytes in mice in vivo; apex resection or myocardial infarction	Cardiac proliferation, regeneration: cardiomyocyte proliferation ↑, regeneration of injured hearts.	(58)
YAP: α myosin heavy chain-driven expression of *Yap1 S112A* in the mouse heart in vivo (homolog 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 signal transduction network (see Fig. 1). However, much of this evidence was obtained in the context of cancer or nonexercise contexts. In the following section, we will review a small number of studies that provide evidence of a role for Hippo signaling in the adaptation to exercise. In relation to this, some key findings are summarized in Table 1. Additionally, we review emerging evidence that body height is associated with single nucleotide polymorphisms (SNPs) in the vicinity of Hippo genes.

Hippo and Adaptive Changes in Skeletal Muscle Fiber Phenotypes

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

In the early 2000s, the Tsika group of researchers (71, 131, 140) investigated the role of MCAT elements and Tead1 transcription factors in the regulation of muscle fiber type-specific gene expression. The functional relevance of their work was demonstrated in vivo using a creatine kinase muscle (CKM) promoter to overexpress Tead1 in mouse skeletal muscle fibers, which caused an increased in slow-muscle-specific gene expression in vivo [Table 1, (132)]. Functionally, CKM-driven Tead1 overexpression reduced the shortening velocity (V_{max}) and increased the contraction and relaxation times of extensor digitalis longus muscles (132). This suggests that Hippo signaling affects muscle fiber type-specific gene expression and fiber 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 signaling, as shown for example, by the inhibitory effect of rapamycin on the increase in 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 signaling [reviewed in (50, 87)], including the Z-disc-located Bag3 mechanosensor in skeletal muscle (135, 136).

Several studies support a link between Hippo signaling and resistance exercise and muscle fiber size. In the first study on Hippo signaling in relation to exercise, the Booth group of

researchers (19) 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 researchers found that the mRNA of Hippo marker genes such as 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 twofold 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 expression of Hippo marker genes. However, it is unclear whether increases in CYR61 and CTGF expression are a direct consequence of altered Hippo signaling.

Two recent studies have linked Yap activity directly to muscle fiber hypertrophy. Watt and colleagues (148) used an adeno-associated viral vector (rAAV6)-mediated shRNA knockdown strategy to reduce Yap levels in mouse limb muscles. They found a decreased muscle fiber size and reduced protein synthesis. Additionally, they used the same rAAV6 system to overexpress 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 signaling discussed in the first part of this review, their YAP interventions did not seem to affect mTOR activity. In another study, the Hornberger group of researchers (46) reported that YAP expression increases up to approximately 4.5-fold in the hypertrophying plantaris muscle days synergist ablation, a model commonly used to induce skeletal muscle hypertrophy. They then used electroporation to overexpress YAP in the tibialis anterior muscles and analyzed the muscles 7 days later. The fibers that overexpressed YAP were larger than control fibers, demonstrating that elevated YAP activity could cause hypertrophy (Table 1). Additionally, they found that YAP induced MyoD and Myc reporters, while 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 knockout similarly induces muscle hypertrophy (95). In summary, Hippo members can affect fiber 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 (92) using electron microscopy and are now well recognized as the resident stem cells of skeletal muscle (115). The key tool that allowed Mauro to characterize their function in vivo was the Pax7-DTA knockout mouse line, which is used specifically to deplete the satellite cell pool in mouse muscles. Studies with the 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 its initial hypertrophy after more than 8 wk (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 they increase when satellite cells become activated and develop into MyoD-expressing myoblasts. Again, high Yap activity resulting from 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 ~40% (67). Overexpression of *YAP1 S127A* in satellite cell-derived myoblasts also increases the expression of proliferation-associated genes and known satellite cell regulators such as BMP4 (109) and CD34 (4), while reducing the expression of differentiation markers and the myogenic differentiation regulator Mrf4 (67). Collectively, these results indicate that Yap promotes myoblast and satellite cell proliferation but inhibits differentiation into myotubes and muscle fibers. This suggests that Yap might be an important regulator of muscle development (myogenesis) and satellite cell-derived myoblast proliferation after injury and in response to hypertrophy. The requirement of Yap and other Hippo members such as Taz during the response to exercise by satellite cells remains to be formally demonstrated.

Hippo and the Athlete's Heart

Maximal oxygen uptake ($\dot{V}O_{2\,max}$) is the key determinant of an individual's endurance capacity (27) and is also associated with longevity (15). Early physiological studies in humans demonstrated that one of the key predictors of an individual's $\dot{V}O_{2\,max}$ is the blood flow generated by the heart, termed cardiac output (99), which determines the efficiency of oxygen transport to the exercising musculature. The $\dot{V}O_{2\,max}$ and cardiac output parameters respond to exercise training and detraining, as demonstrated by Saltin and colleagues (113). They showed that 20 days of bed rest reduces resting heart volume by ~10% and exercise cardiac output by 15%, resulting in a significantly reduced $\dot{V}O_{2\,max}$ (113). Conversely, 55 days of endurance exercise training following the bed rest increased cardiac output above prebed rest levels. This partially explains the restoration of $\dot{V}O_{2\,max}$ (142).

The increase in cardiac output can be attributed to the development of an athlete's heart in response to endurance training. Indeed, electrocardiographic studies show that athletes have enlarged hearts (9), which was later confirmed by comparative echocardiography on endurance athletes (91). Generally, the main cellular mechanism underlying the athlete's heart is cardiomyocyte hypertrophy. For example, endurance running training for 8 wk increases cardiomyocyte size by 17–32% in mice (73). Until several years ago, researchers thought that adult cardiomyocytes were unable to proliferate

and regenerate the heart. However, this view is now changing (33). By determining the levels of ^{14}C DNA integration from nuclear bomb tests, Bergmann et al. (14) estimated that between 0.45 and 1% of human cardiomyocytes renew per annum. Furthermore, they showed that by the age of 50, 40% of cardiomyocytes had emerged after birth (14). Moreover, swim endurance training for 2 wk results in increased expression of proliferation markers in mouse cardiomyocytes (16), suggesting that exercise promotes cardiomyocyte proliferation, at least in mice. There is emerging evidence supporting the existence of a cardiac stem cell population that may engage in some limited regeneration (32) in addition to a low renewal rate of preexisting cardiomyocytes (119). Two recent studies found that both cardiac stem cells and cardiomyocytes proliferate in response to endurance exercise in rodents (80, 146). Collectively, these data demonstrate that endurance exercise increases left ventricular volume, thickness, and pumping performance and suggest that these effects occur mainly through cardiomyocyte hypertrophy with a limited contribution of cardiac stem cells and cardiomyocyte proliferation. Consequently, this results in the development of the athlete's heart, which in turn increases the individual's $\dot{V}O_{2\,max}$ and aerobic exercise capacity.

The heart can respond to increased loads in two different ways, depending on the nature of the load (94): *1*) physiological hypertrophy (i.e., athlete's heart) can occur as a response to endurance exercise or pregnancy (volumetric hypertrophy) or resistance exercise (nonvolumetric hypertrophy); or *2*) pathological hypertrophy can occur after cardiac injury or in individuals with high blood pressure or defective valves.

Physiological hypertrophy, which is associated with exercise or pregnancy, differs from pathological hypertrophy by the nature of the stimuli, the structural response, the absence of fibrosis, and the molecular drivers leading to the adaptation (94). Generally, physiological hypertrophy does not progress into cardiac dysfunction. In contrast, pathological hypertrophy 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 signaling 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 in (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 signaling 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 Table 1). First, *Yap1* overexpression in cultured neonatal rat cardiomyocytes promotes hypertrophy and survival compared with 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 signaling contributes to cardiomyocyte hypertrophy in response to exercise (73).

Another response of the heart to endurance exercise in rodents is the limited proliferation of cardiomyocytes and cardiac stem cells (16, 80, 146). Although it has not been tested whether Hippo members promote cardiomyocyte or cardiac stem cell proliferation in response to endurance exercise, evidence supporting that notion that Hippo members regulate the proliferation of adult cardiomyocytes and can enhance regeneration after cardiac injury has been reported (Table 1). Knocking out the Hippo members *Sav1* or *Lats1/2* in adult mouse cardiomyocytes increases proliferation, promotes regeneration after myocardial infarction, and reduces scar tissue formation (58). Similarly, *Yap1 S112A* overexpression in cardiomyocytes improves cardiac regeneration after myocardial infarction, both in neonatal and adult mice, with evidence for increased cardiomyocyte proliferation compared with controls (154). Finally, in a mouse model of myocardial infarction, forcing human YAP expression in the heart using adeno-associated virus delivery results in increased cardiomyocyte proliferation and improved cardiac function and survival (85).

In summary, the normal function of Yap and Hippo signaling is essential for normal cardiac development. Currently, it is unknown whether Hippo members and Yap in cardiomyocytes and cardiac stem cells respond to exercise and contribute to the development of an athlete's heart. Available studies suggest that Yap can promote cardiomyocyte hypertrophy in some contexts, while in other contexts, Yap appears to promote cardiomyocyte proliferation and enhance cardiac regeneration after injury.

Hippo and Body Height

Body height is a key factor in sports, which is most striking in NBA basketball players. Body height is approximately 70–90% inherited (121) and depends on hundreds, if not thousands, of common DNA sequence variations with a small effect size each (152). In rare cases, body height can be affected by single, rare mutations with a large effect size. Examples for the latter are dwarfism caused by *FGFR3* mutations (37), and acromegaly resulting from *AIP* gene mutations (20).

Given that a core function of Hippo signaling is to control cell numbers, one would expect links between Hippo gene DNA sequence variations and body height. Interestingly, genome-wide association studies (GWAS) involving 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. (78) 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 *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 significantly associated with the trait only in women. So far, no sex-related differences have been reported for the Hippo pathway functions, but this association could suggest that such differences might actually exist in some contexts. Finally, an SNP in *VGLL4* (rs6772112) was associated with height in 36,227 subjects with East Asian ancestry (57). Another interesting association of the study by Cousminer et al. (23) is the identification of a female-specific SNP in *LIN28B* associated with late pubertal growth. 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 because 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 signaling 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 body cell numbers. The task for molecular exercise physiologists is now to directly show that these mechanisms mediate adaptation to exercise in exercise models and that Hippo gene variants are associated with sport and exercise-related traits. We end with three questions:

Because resistance and endurance exercise trigger different adaptations in skeletal muscle, how can it be explained that the activity of Hippo members is both affected by both resistance and endurance exercise-associated signals?

Given that Hippo signaling affects amino acid (52) and glucose transporter expression (145), can this be used to develop strategies to alter the responsiveness to nutrients? For example, can we target through Hippo modulation the leucine transporter LAT1 (52) to make muscles and other organs more sensitive to protein intake? Could such a strategy be beneficial for strength athletes or in cases of muscle weakness and wasting, for example, in elderly individuals or patients with cancer and sarcopenia?

Given that the Hippo pathway is involved in regulating the fate of many stem cells (129), can this be exploited to develop interventions aimed at improving the repair of muscle, tendons, and cartilage after sports injury or in degenerative muscle diseases?

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AUTHOR CONTRIBUTIONS

B.M.G., D.L.H., A.M.T., and H.W. prepared figures; B.M.G., D.L.H., A.M.T., and H.W. drafted manuscript; B.M.G., D.L.H., A.M.T., and H.W. edited and revised manuscript; B.M.G., D.L.H., A.M.T., and H.W. approved final version of manuscript.

REFERENCES

1. **Abel ED, Doenst T.** Mitochondrial adaptations to physiological vs. pathological cardiac hypertrophy. *Cardiovasc Res* 90: 234–242, 2011.
2. **Abou-Khalil R, Yang F, Lieu S, Julien A, Perry J, Pereira C, Relaix F, Miclau T, Marcucio R, Colnot C.** Role of muscle stem cells during skeletal regeneration. *Stem Cells* 33: 1501–1511, 2015.
3. **Alarcon C, Zaromytidou AI, Xi Q, Gao S, Yu J, Fujisawa S, Barlas A, Miller AN, Manova-Todorova K, Macias MJ, Sapkota G, Pan D, Massague J.** Nuclear CDKs drive Smad transcriptional activation and turnover in BMP and TGF-beta pathways. *Cell* 139: 757–769, 2009.
4. **Alfaro LA, Dick SA, Siegel AL, Anonuevo AS, McNagny KM, Megeney LA, Cornelison DD, Rossi FM.** CD34 promotes satellite cell motility and entry into proliferation to facilitate efficient skeletal muscle regeneration. *Stem Cells* 29: 2030–2041, 2011.
5. **Ameln H, Gustafsson T, Sundberg CJ, Okamoto K, Jansson E, Poellinger L, Makino Y.** Physiological activation of hypoxia inducible factor-1 in human skeletal muscle. *FASEB J* 19: 1009–1011, 2005.
6. **Anbanandam A, Albarado DC, Nguyen CT, Halder G, Gao X, Veeraraghavan S.** Insights into transcription enhancer factor 1 (TEF-1) activity from the solution structure of the TEA domain. *Proc Natl Acad Sci USA* 103: 17225–17230, 2006.
7. **Aragon E, Goerner N, Xi Q, Gomes T, Gao S, Massague J, Macias MJ.** Structural basis for the versatile interactions of Smad7 with regulator WW domains in TGF-beta pathways. *Structure* 20: 1726–1736, 2012.
8. **Aragona M, Panciera T, Manfrin A, Giulitti S, Michielin F, Elvassore N, Dupont S, Piccolo S.** A Mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by actin-processing factors. *Cell* 154: 1047–1059, 2013.
9. **Arstila M, Koivikko A.** Electrocardiographic and vectorcardiographic signs of left and right ventricular hypertrophy in endurance athletes. *J Sports Med Phys Fitness* 6: 166–175, 1966.
10. **Atherton PJ, Smith K, Etheridge T, Rankin D, Rennie MJ.** Distinct anabolic signalling responses to amino acids in C2C12 skeletal muscle cells. *Amino Acids* 38: 1533–1539, 2010.
11. **Baar K, Esser K.** Phosphorylation of p70(S6k) correlates with increased skeletal muscle mass following resistance exercise. *Am J Physiol Cell Physiol* 276: C120–C127, 1999.
12. **Bartlett JD, Hawley JA, Morton JP.** Carbohydrate availability and exercise training adaptation: too much of a good thing? *Eur J Sport Sci* 15: 3–12, 2015.
13. **Basu S, Totty NF, Irwin MS, Sudol M, Downward J.** Akt phosphorylates the Yes-associated protein, YAP, to induce interaction with 14-3-3 and attenuation of p73-mediated apoptosis. *Mol Cell* 11: 11–23, 2003.
14. **Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabe-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S, Frisen J.** Evidence for cardiomyocyte renewal in humans. *Science* 324: 98–102, 2009.
15. **Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW.** Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 276: 205–210, 1996.
16. **Bostrom P, Mann N, Wu J, Quintero PA, Plovie ER, Panakova D, Gupta RK, Xiao C, MacRae CA, Rosenzweig A, Spiegelman BM.** C/EBPbeta controls exercise-induced cardiac growth and protects against pathological cardiac remodeling. *Cell* 143: 1072–1083, 2010.
17. **Bouchard C.** Exercise genomics-a paradigm shift is needed: a commentary. *Br J Sports Med* 49: 1492–1496, 2015.

18. **Camargo FD, Gokhale S, Johnnidis JB, Fu D, Bell GW, Jaenisch R, Brummelkamp TR.** YAP1 increases organ size and expands undifferentiated progenitor cells. *Curr Biol* 17: 2054–2060, 2007.
19. **Carson JA, Schwartz RJ, Booth FW.** SRF and TEF-1 control of chicken skeletal alpha-actin gene during slow-muscle hypertrophy. *Am J Physiol Cell Physiol* 270: C1624–C1633, 1996.
20. **Chahal HS, Stals K, Unterlander M, Balding DJ, Thomas MG, Kumar AV, Besser GM, Atkinson AB, Morrison PJ, Howlett TA, Levy MJ, Orme SM, Akker SA, Abel RL, Grossman AB, Burger J, Ellard S, Korbonits M.** AIP mutation in pituitary adenomas in the 18th century and today. *N Engl J Med* 364: 43–50, 2011.
21. **Chaulk SG, Lattanzi VJ, Hiemer SE, Fahlman RP, Varelas X.** The Hippo pathway effectors TAZ/YAP regulate dicer expression and microRNA biogenesis through Let-7. *J Biol Chem* 289: 1886–1891, 2014.
22. **Cinar B, Fang PK, Lutchman M, Di Vizio D, Adam RM, Pavlova N, Rubin MA, Yelick PC, Freeman MR.** The pro-apoptotic kinase Mst1 and its caspase cleavage products are direct inhibitors of Akt1. *EMBO J* 26: 4523–4534, 2007.
23. **Cousminer DL, Berry DJ, Timpson NJ, Ang W, Thiering E, Byrne EM, Taal HR, Huikari V, Bradfield JP, Kerkhof M, Groen-Blokhuis MM, Kreiner-Møller E, Marinelli M, Holst C, Leinonen JT, Perry JR, Surakka I, Pietiläinen O, Kettunen J, Anttila V, Kaakinen M, Sovio U, Pouta A, Das S, Lagou V, Power C, Prokopenko I, Evans DM, Kemp JP, St Pourcain B, Ring S, Palotie A, Kajantie E, Osmond C, Lehtimäki T, Viikari JS, Kähönen M, Warrington NM, Lye SJ, Palmer LJ, Tiesler CM, Flexeder C, Montgomery GW, Medland SE, Hofman A, Hakonarson H, Guxens M, Bartels M, Salomaa V, ReproGen Consortium, Murabito JM, Kaprio J, Sørensen TI, Ballester F, Bisgaard H, Boomsma DI, Koppelman GH, Grant SF, Jaddoe VW, Martin NG, Heinrich J, Pennell CE, Raitakari OT, Eriksson JG, Smith GD, Hyppönen E, Järvelin MR, McCarthy MI, Ripatti S, Widén E, Early Growth Genetics (EGG) Consortium.** Genome-wide association and longitudinal analyses reveal genetic loci linking pubertal height growth, pubertal timing and childhood adiposity. *Hum Mol Genet* 22: 2735–2747, 2013.
24. **Davidson I, Xiao JH, Rosales R, Staub A, Chambon P.** The HeLa cell protein TEF-1 binds specifically and cooperatively to two SV40 enhancer motifs of unrelated sequence. *Cell* 54: 931–942, 1988.
25. **Del Re DP, Yang Y, Nakano N, Cho J, Zhai P, Yamamoto T, Zhang N, Yabuta N, Nojima H, Pan D, Sadoshima J.** Yes-associated protein isoform 1 (Yap1) promotes cardiomyocyte survival and growth to protect against myocardial ischemic injury. *J Biol Chem* 288: 3977–3988, 2013.
26. **DeRan M, Yang J, Shen CH, Peters EC, Fitamant J, Chan P, Hsieh M, Zhu S, Asara JM, Zheng B, Bardeesy N, Liu J, Wu X.** Energy stress regulates Hippo-YAP signaling involving AMPK-mediated regulation of angiomotin-like 1 protein. *Cell Rep* 9: 495–503, 2014.
27. **di Prampero PE.** Factors limiting maximal performance in humans. *Eur J Appl Physiol* 90: 420–429, 2003.
28. **Dickinson JM, Fry CS, Drummond MJ, Gundermann DM, Walker DK, Glynn EL, Timmerman KL, Dhanani S, Volpi E, Rasmussen BB.** Mammalian target of rapamycin complex 1 activation is required for the stimulation of human skeletal muscle protein synthesis by essential amino acids. *J Nutr* 141: 856–862, 2011.
29. **Dong J, Feldmann G, Huang J, Wu S, Zhang N, Comerford SA, Gayyed MF, Anders RA, Maitra A, Pan D.** Elucidation of a universal size-control mechanism in *Drosophila* and mammals. *Cell* 130: 1120–1133, 2007.
30. **Drummond MJ, Fry CS, Glynn EL, Dreyer HC, Dhanani S, Timmerman KL, Volpi E, Rasmussen BB.** Rapamycin administration in humans blocks the contraction-induced increase in skeletal muscle protein synthesis. *J Physiol* 587: 1535–1546, 2009.
31. **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.** Role of YAP/TAZ in mechanotransduction. *Nature* 474: 179–183, 2011.
32. **Ellison GM, Vicinanza C, Smith AJ, Aquila I, Leone A, Waring CD, Henning BJ, Stirparo GG, Papait R, Scarfo M, Agosti V, Viglietto G, Condorelli G, Indolfi C, Ottolenghi S, Torella D, Nadal-Ginard B.** Adult c-kit(pos) cardiac stem cells are necessary and sufficient for functional cardiac regeneration and repair. *Cell* 154: 827–842, 2013.
33. **Ellison GM, Waring CD, Vicinanza C, Torella D.** Physiological cardiac remodelling in response to endurance exercise training: cellular and molecular mechanisms. *Heart* 98: 5–10, 2012.
34. **Engler AJ, Griffin MA, Sen S, Bonnemann CG, Sweeney HL, Discher DE.** Myotubes differentiate optimally on substrates with tissue-like stiffness: pathological implications for soft or stiff microenvironments. *J Cell Biol* 166: 877–887, 2004.
35. **Engler AJ, Sen S, Sweeney HL, Discher DE.** Matrix elasticity directs stem cell lineage specification. *Cell* 126: 677–689, 2006.
36. **Enzo E, Santinon G, Pocaterra A, Aragona M, Bresolin S, Forcato M, Grifoni D, Pession A, Zanconato F, Guzzo G, Bicciato S, Dupont S.** Aerobic glycolysis tunes YAP/TAZ transcriptional activity. *EMBO J* 34: 1349–1370, 2015.
37. **Foldynova-Trantirkova S, Wilcox WR, Krejci P.** Sixteen years and counting: the current understanding of fibroblast growth factor receptor 3 (FGFR3) signaling in skeletal dysplasias. *Hum Mutat* 33: 29–41, 2012.
38. **Fry CS, Lee JD, Jackson JR, Kirby TJ, Stasko SA, Liu H, Dupont-Versteegden EE, McCarthy JJ, Peterson CA.** Regulation of the muscle fiber microenvironment by activated satellite cells during hypertrophy. *FASEB J* 28: 1654–1665, 2014.
39. **Galli GG, Carrara M, Yuan WC, Valdes-Quezada C, Gurung B, Pepe-Mooney B, Zhang T, Geeven G, Gray NS, de Laat W, Calogero RA, Camargo FD.** YAP drives growth by controlling transcriptional pause release from dynamic enhancers. *Mol Cell* 60: 328–337, 2015.
40. **Gateff E.** Malignant neoplasms of genetic origin in *Drosophila melanogaster*. *Science* 200: 1448–1459, 1978.
41. **Gilbert PM, Havenstrite KL, Magnusson KE, Sacco A, Leonardi NA, Kraft P, Nguyen NK, Thrun S, Lutolf MP, Blau HM.** Substrate elasticity regulates skeletal muscle stem cell self-renewal in culture. *Science* 329: 1078–1081, 2010.
42. **Goldberg AL, Etlinger JD, Goldspink DF, Jablecki C.** Mechanism of work-induced hypertrophy of skeletal muscle. *Med Sci Sports* 7: 185–198, 1975.
43. **Gollnick PD, Armstrong RB, Saltin B, Saubert CW, Sembrowich WL, Shepherd RE.** Effect of training on enzyme activity and fiber composition of human skeletal muscle. *J Appl Physiol* 34: 107–111, 1973.
44. **Gollnick PD, Armstrong RB, Saubert CW, Piehl K, Saltin B.** Enzyme activity and fiber composition in skeletal muscle of untrained and trained men. *J Appl Physiol* 33: 312–319, 1972.
45. **Gollnick PD, Piehl K, Saltin B.** Selective glycogen depletion pattern in human muscle fibres after exercise of varying intensity and at varying pedalling rates. *J Physiol* 241: 45–57, 1974.
46. **Goodman CA, Dietz JM, Jacobs BL, McNally RM, You JS, Hornberger TA.** Yes-associated protein is up-regulated by mechanical overload and is sufficient to induce skeletal muscle hypertrophy. *FEBS Lett* 589: 1491–1497, 2015.
47. **Gordon SE, Davis BS, Carlson CJ, Booth FW.** ANG II is required for optimal overload-induced skeletal muscle hypertrophy. *Am J Physiol Endocrinol Metab* 280: E150–E159, 2001.
48. **Grobet L, Martin LJ, Poncelet D, Pirottin D, Brouwers B, Riquet J, Schoeberlein A, Dunner S, Menissier F, Massabanda J, Fries R, Hanset R, Georges M.** A deletion in the bovine myostatin gene causes the double-muscled phenotype in cattle. *Nat Genet* 17: 71–74, 1997.
49. **Guo J, Kleeff J, Zhao Y, Li J, Giese T, Esposito I, Buchler MW, Korc M, Friess H.** Yes-associated protein (YAP65) in relation to Smad7 expression in human pancreatic ductal adenocarcinoma. *Int J Mol Med* 17: 761–767, 2006.
50. **Halder G, Dupont S, Piccolo S.** Transduction of mechanical and cytoskeletal cues by YAP and TAZ. *Nat Rev Mol Cell Biol* 13: 591–600, 2012.
51. **Hansen CG, Moroishi T, Guan KL.** YAP and TAZ: a nexus for Hippo signaling and beyond. *Trends Cell Biol* 25: 499–513, 2015.
52. **Hansen CG, Ng YL, Lam WL, Plouffe SW, Guan KL.** The Hippo pathway effectors YAP and TAZ promote cell growth by modulating amino acid signaling to mTORC1. *Cell Res* 25: 1299–1313, 2015.
53. **Hardie DG.** AMPK: positive and negative regulation, and its role in whole-body energy homeostasis. *Curr Opin Cell Biol* 33: 1–7, 2015.
54. **Hardie DG.** Energy sensing by the AMP-activated protein kinase and its effects on muscle metabolism. *Proc Nutr Soc* 70: 92–99, 2011.
55. **Hardie DG, Ashford ML.** AMPK: regulating energy balance at the cellular and whole body levels. *Physiology* 29: 99–107, 2014.
56. **Harvey K, Tapon N.** The Salvador-Warts-Hippo pathway - an emerging tumour-suppressor network. *Nat Rev Cancer* 7: 182–191, 2007.
57. **He M, Xu M, Zhang B, Liang J, Chen P, Lee JY, Johnson TA, Li H, Yang X, Dai J, Liang L, Gui L, Qi Q, Huang J, Li Y, Adair LS, Aung T, Cai Q, Cheng CY, Cho MC, Cho YS, Chu M, Cui B, Gao YT, Go**

MJ, Gu D, Gu W, Guo H, Hao Y, Hong J, Hu Z, Hu Y, Huang J, Hwang JY, Ikram MK, Jin G, Kang DH, Khor CC, Kim BJ, Kim HT, Kubo M, Lee J, Lee J, Lee NR, Li R, Li J, Liu J, Longe J, Lu W, Lu X, Miao X, Okada Y, Ong RT, Qiu G, Seielstad M, Sim X, Song H, Takeuchi F, Tanaka T, Taylor PR, Wang L, Wang W, Wang Y, Wu C, Wu Y, Xiang YB, Yamamoto K, Yang H, Liao M, Yokota M, Young T, Zhang X, Kato N, Wang QK, Zheng W, Hu FB, Lin D, Shen H, Teo YY, Mo Z, Wong TY, Lin X, Mohlke KL, Ning G, Tsunoda T, Han BG, Shu XO, Tai ES, Wu T, Qi L. Meta-analysis of genome-wide association studies of adult height in East Asians identifies 17 novel loci. *Hum Mol Genet* 24: 1791–1800, 2015.

58. **Heallen T, Morikawa Y, Leach J, Tao G, Willerson JT, Johnson RL, Martin JF.** Hippo signaling impedes adult heart regeneration. *Development* 140: 4683–4690, 2013.
59. **Hikida RS, Staron RS, Hagerman FC, Sherman WM, Costill DL.** Muscle fiber necrosis associated with human marathon runners. *J Neurol Sci* 59: 185–203, 1983.
60. **Hilman D, Gat U.** The evolutionary history of YAP and the hippo/YAP pathway. *Mol Biol Evol* 28: 2403–2417, 2011.
61. **Hoffman NJ, Parker BL, Chaudhuri R, Fisher-Wellman KH, Kleinert M, Humphrey SJ, Yang P, Holliday M, Trefely S, Fazakerley DJ, Stockli J, Burchfield JG, Jensen TE, Jothi R, Kiens B, Wojtaszewski JF, Richter EA, James DE.** Global phosphoproteomic analysis of human skeletal muscle reveals a network of exercise-regulated kinases and AMPK substrates. *Cell Metab* 22: 922–935, 2015.
62. **Homma S, Iwasaki M, Shelton GD, Engvall E, Reed JC, Takayama S.** BAG3 deficiency results in fulminant myopathy and early lethality. *Am J Pathol* 169: 761–773, 2006.
63. **Huang J, Wu S, Barrera J, Matthews K, Pan D.** The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the *Drosophila* homolog of YAP. *Cell* 122: 421–434, 2005.
64. **Hubal MJ, Gordish-Dressman H, Thompson PD, Price TB, Hoffman EP, Angelopoulos TJ, Gordon PM, Moyna NM, Pescatello LS, Visich PS, Zoeller RF, Seip RL, Clarkson PM.** Variability in muscle size and strength gain after unilateral resistance training. *Med Sci Sports Exerc* 37: 964–972, 2005.
65. **Jang SW, Yang SJ, Srinivasan S, Ye K.** Akt phosphorylates MstI and prevents its proteolytic activation, blocking FOXO3 phosphorylation and nuclear translocation. *J Biol Chem* 282: 30836–30844, 2007.
66. **Jiao S, Wang H, Shi Z, Dong A, Zhang W, Song X, He F, Wang Y, Zhang Z, Wang W, Wang X, Guo T, Li P, Zhao Y, Ji H, Zhang L, Zhou Z.** A peptide mimicking VGLL4 function acts as a YAP antagonist therapy against gastric cancer. *Cancer Cell* 25: 166–180, 2014.
67. **Judson RN, Tremblay AM, Knopp P, White RB, Urcia R, De Bari C, Zammit PS, Camargo FD, Wackerhage H.** The Hippo pathway member Yap plays a key role in influencing fate decisions in muscle satellite cells. *J Cell Sci* 125: 6009–6019, 2012.
68. **Justice RW, Zilian O, Woods DF, Noll M, Bryant PJ.** The *Drosophila* tumor suppressor gene warts encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation. *Genes Dev* 9: 534–546, 1995.
69. **Kambadur R, Sharma M, Smith TP, Bass JJ.** Mutations in myostatin (GDF8) in double-muscled Belgian Blue and Piedmontese cattle. *Genome Res* 7: 910–916, 1997.
70. **Kanai F, Marignani PA, Sarbassova D, Yagi R, Hall RA, Donowitz M, Hisaminato A, Fujiwara T, Ito Y, Cantley LC, Yaffe MB.** TAZ: a novel transcriptional co-activator regulated by interactions with 14-3-3 and PDZ domain proteins. *EMBO J* 19: 6778–6791, 2000.
71. **Karasseva N, Tsika G, Ji J, Zhang A, Mao X, Tsika R.** Transcription enhancer factor 1 binds multiple muscle MEF2 and A/T-rich elements during fast-to-slow skeletal muscle fiber type transitions. *Mol Cell Biol* 23: 5143–5164, 2003.
72. **Katz AM, Rolett EL.** Heart failure: when form fails to follow function. *Eur Heart J* 37: 449–454, 2015.
73. **Kemi OJ, Loennechen JP, Wisloff U, Ellingsen O.** Intensity-controlled treadmill running in mice: cardiac and skeletal muscle hypertrophy. *J Appl Physiol* 93: 1301–1309, 2002.
74. **Kim M, Kim M, Lee S, Kuninaka S, Saya H, Lee H, Lee S, Lim DS.** cAMP/PKA signalling reinforces the LATS-YAP pathway to fully suppress YAP in response to actin cytoskeletal changes. *EMBO J* 32: 1543–1555, 2013.
75. **Kivela R, Kyrolainen H, Selanne H, Komi PV, Kainulainen H, Vihko V.** A single bout of exercise with high mechanical loading induces the expression of Cyr61/CCN1 and CTGF/CCN2 in human skeletal muscle. *J Appl Physiol* 103: 1395–1401, 2007.
76. **Koontz LM, Liu-Chittenden Y, Yin F, Zheng Y, Yu J, Huang B, Chen Q, Wu S, Pan D.** The Hippo effector Yorkie controls normal tissue growth by antagonizing scalloped-mediated default repression. *Dev Cell* 25: 388–401, 2013.
77. **Lai D, Ho KC, Hao Y, Yang X.** Taxol resistance in breast cancer cells is mediated by the hippo pathway component TAZ and its downstream transcriptional targets Cyr61 and CTGF. *Cancer Res* 71: 2728–2738, 2011.
78. **Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, Willer CJ, Jackson AU, Vedantam S, Raychaudhuri S, Ferreira T, Wood AR, Weyant RJ, Segrè AV, Speliotes EK, Wheeler E, Soranzo N, Park JH, Yang J, Gudbjartsson D, Heard-Costa NL, Randall JC, Qi L, Vernon Smith A, Mägi R, Pastinen T, Liang L, Heid IM, Luan J, Thorleifsson G, Winkler TW, Goddard ME, Sin Lo K, Palmer C, Workalemahu T, Aulchenko YS, Johansson A, Zillikens MC, Feitosa MF, Esko T, Johnson T, Ketkar S, Kraft P, Mangino M, Prokopenko I, Absher D, Albrecht E, Ernst F, Glazer NL, Hayward C, Hottenga JJ, Jacobs KB, Knowles JW, Kutalik Z, Monda KL, Polasek O, Preuss M, Rayner NW, Robertson NR, Steinthorsdottir V, Tyrer JP, Voight BF, Wiklund F, Xu J, Zhao JH, Nyholt DR, Pellikka N, Perola M, Perry JR, Surakka I, Tammesoo ML, Altmaier EL, Amin N, Aspelund T, Bhangale T, Boucher G, Chasman DI, Chen C, Coin L, Cooper MN, Dixon AL, Gibson Q, Grundberg E, Hao K, Juhani Junttila M, Kaplan LM, Kettunen J, König IR, Kwan T, Lawrence RW, Levinson DF, Lorentzon M, McKnight B, Morris AP, Muller M, Suh Ngwa J, Purcell S, Rafelt S, Salem RM, Salvi E, Sanna S, Shi J, Sovio U, Thompson JR, Turchin MC, Vandenput L, Verlaan DJ, Vitart V, White CC, Ziegler A, Almgren P, Balmforth AJ, Campbell H, Citterio L, De Grandi A, Dominiczak A, Duan J, Elliott P, Elosua R, Eriksson JG, Freimer NB, Geus EJ, Glorioso N, Haiqing S, Hartikainen AL, Havulinna AS, Hicks AA, Hui J, Igl W, Illig T, Jula A, Kajantie E, Kilpeläinen TO, Koiranen M, Kolcic I, Koskinen S, Kovacs P, Laitinen J, Liu J, Lokki ML, Marusic A, Maschio A, Meitinger T, Mulas A, Paré G, Parker AN, Peden JF, Petersmann A, Pichler I, Pietilainen KH, Pouta A, Ridderstråle M, Rotter JI, Sambrook JG, Sanders AR, Schmidt CO, Sinisalo J, Smit JH, Stringham HM, Bragi Walters G, Widen E, Wild SH, Willemsen G, Zagato L, Zgaga L, Zitting P, Alavere H, Farrall M, McArdle WL, Nelis M, Peters MJ, Ripatti S, van Meurs JB, Aben KK, Ardlie KG, Beckmann JS, Beilby JP, Bergman RN, Bergmann S, Collins FS, Cusi D, den Heijer M, Eiriksdottir G, Gejman PV, Hall AS, Hamsten A, Huikuri HV, Iribarren C, Kähönen M, Kaprio J, Kathiresan S, Kiemeney L, Kocher T, Launer LJ, Lehtimäki T, Melander O, Mosley TH Jr, Musk AW, Nieminen MS, O'Donnell CJ, Ohlsson C, Oostra B, Palmer LJ, Raitakari O, Ridker PM, Rioux JD, Rissanen A, Rivolta C, Schunkert H, Shuldiner AR, Siscovick DS, Stumvoll M, Tönjes A, Tuomilehto J, van Ommen GJ, Viikari J, Heath AC, Martin NG, Montgomery GW, Province MA, Kayser M, Arnold AM, Atwood LD, Boerwinkle E, Chanock SJ, Deloukas P, Gieger C, Grönberg H, Hall P, Hattersley AT, Hengstenberg C, Hoffman W, Lathrop GM, Salomaa V, Schreiber S, Uda M, Waterworth D, Wright AF, Assimes TL, Barroso I, Hofman A, Mohlke KL, Boomsma DI, Caulfield MJ, Cupples LA, Erdmann J, Fox CS, Gudnason V, Gyllensten U, Harris TB, Hayes RB, Jarvelin MR, Mooser V, Munroe PB, Ouwehand WH, Penninx BW, Pramstaller PP, Quertermous T, Rudan I, Samani NJ, Spector TD, Völzke H, Watkins H, Wilson JF, Groop LC, Haritunians T, Hu FB, Kaplan RC, Metspalu A, North KE, Schlessinger D, Wareham NJ, Hunter DJ, O'Connell JR, Strachan DP, Wichmann HE, Borecki IB, van Duijn CM, Schadt EE, Thorsteinsdottir U, Peltonen L, Uitterlinden AG, Visscher PM, Chatterjee N, Loos RJ, Boehnke M, McCarthy MI, Ingelsson E, Lindgren CM, Abecasis GR, Stefansson K, Frayling TM, Hirschhorn JN.** Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 467: 832–838, 2010.
79. **Lee SJ.** Quadrupling muscle mass in mice by targeting TGF-beta signaling pathways. *PLoS One* 2: e789, 2007.
80. **Leite CF, Lopes CS, Alves AC, Fuzaro CS, Silva MV, Oliveira LF, Garcia LP, Farnesi TS, Cuba MB, Rocha LB, Rodrigues V Jr, Oliveira CJ, Dias da Silva VJ.** Endogenous resident c-Kit cardiac stem cells increase in mice with an exercise-induced, physiologically hypertrophied heart. *Stem Cell Res* 15: 151–164, 2015.

81. **Lepper C, Partridge TA, Fan CM.** An absolute requirement for Pax7-positive satellite cells in acute injury-induced skeletal muscle regeneration. *Development* 138: 3639–3646, 2011.
82. **Li Q, Li S, Mana-Capelli S, Roth Flach RJ, Danai LV, Amcheslavsky A, Nie Y, Kaneko S, Yao X, Chen X, Cotton JL, Mao J, McCollum D, Jiang J, Czech MP, Xu L, Ip YT.** The conserved misshapen-warts-Yorkie pathway acts in enteroblasts to regulate intestinal stem cells in *Drosophila*. *Dev Cell* 31: 291–304, 2014.
83. **Liang N, Zhang C, Dill P, Panasyuk G, Pion D, Koka V, Gallazzini M, Olson EN, Lam H, Henske EP, Dong Z, Apte U, Pallet N, Johnson RL, Terzi F, Kwiatkowski DJ, Scoazec JY, Martignoni G, Pende M.** Regulation of YAP by mTOR and autophagy reveals a therapeutic target of tuberous sclerosis complex. *J Exp Med* 211: 2249–2263, 2014.
84. **Lin Z, Pu WT.** Harnessing Hippo in the heart: Hippo/Yap signaling and applications to heart regeneration and rejuvenation. *Stem Cell Res* 13: 571–581, 2014.
85. **Lin Z, von Gise A, Zhou P, Gu F, Ma Q, Jiang J, Yau AL, Buck JN, Gouin KA, van Gorp PR, Zhou B, Chen J, Seidman JG, Wang DZ, Pu WT.** Cardiac-specific YAP activation improves cardiac function and survival in an experimental murine MI model. *Circ Res* 115: 354–363, 2014.
86. **Liu CY, Zha ZY, Zhou X, Zhang H, Huang W, Zhao D, Li T, Chan SW, Lim CJ, Hong W, Zhao S, Xiong Y, Lei QY, Guan KL.** The hippo tumor pathway promotes TAZ degradation by phosphorylating a phosphodegron and recruiting the SCFβ-TrCP E3 ligase. *J Biol Chem* 285: 37159–37169, 2010.
87. **Low BC, Pan CQ, Shivashankar G, Bershadsky A, Sudol M, Sheetz M.** YAP/TAZ as mechanosensors and mechanotransducers in regulating organ size and tumor growth. *FEBS Lett* 588: 2663–2670, 2014.
88. **Ma B, Chen Y, Chen L, Cheng H, Mu C, Li J, Gao R, Zhou C, Cao L, Liu J, Zhu Y, Chen Q, Wu S.** Hypoxia regulates Hippo signalling through the SIAH2 ubiquitin E3 ligase. *Nat Cell Biol* 17: 95–103, 2015.
89. **MacLennan PA, Edwards RH.** Effects of clenbuterol and propranolol on muscle mass. Evidence that clenbuterol stimulates muscle beta-adrenoceptors to induce hypertrophy. *Biochem J* 264: 573–579, 1989.
90. **Mar JH, Ordahl CP.** A conserved CATTCCT motif is required for skeletal muscle-specific activity of the cardiac troponin T gene promoter. *Proc Natl Acad Sci USA* 85: 6404–6408, 1988.
91. **Maron BJ.** Structural features of the athlete heart as defined by echocardiography. *J Am Coll Cardiol* 7: 190–203, 1986.
92. **Mauro A.** Satellite cell of skeletal muscle fibers. *J Biophys Biochem Cytol* 9: 493–495, 1961.
93. **McCarthy JJ, Mula J, Miyazaki M, Erfani R, Garrison K, Farooqui AB, Srikuea R, Lawson BA, Grimes B, Keller C, Van ZG, Campbell KS, Esser KA, Dupont-Versteegden EE, Peterson CA.** Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. *Development* 138: 3657–3666, 2011.
94. **McMullen JR, Jennings GL.** Differences between pathological and physiological cardiac hypertrophy: novel therapeutic strategies to treat heart failure. *Clin Exp Pharmacol Physiol* 34: 255–262, 2007.
95. **McPherron AC, Lawler AM, Lee SJ.** Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. *Nature* 387: 83–90, 1997.
96. **McPherron AC, Lee SJ.** Double muscling in cattle due to mutations in the myostatin gene. *Proc Natl Acad Sci USA* 94: 12457–12461, 1997.
97. **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.** MAP4K family kinases act in parallel to MST1/2 to activate LATS1/2 in the Hippo pathway. *Nat Commun* 6: 8357, 2015.
98. **Meyer RA, Foley JM.** Cellular processes integrating the metabolic response to exercise. In: *Handbook of Physiology. Section 12 Exercise: Regulation and Integration of Multiple Systems*, edited by Rowell LB, and Shepherd JT. Oxford, UK: Oxford University Press, 1996, p. 841–869.
99. **Mitchell JH, Sproule BJ, Chapman CB.** The physiological meaning of the maximal oxygen intake test. *J Clin Invest* 37: 538–547, 1958.
100. **Mo JS, Meng Z, Kim YC, Park HW, Hansen CG, Kim S, Lim DS, Guan KL.** Cellular energy stress induces AMPK-mediated regulation of YAP and the Hippo pathway. *Nat Cell Biol* 17: 500–510, 2015.
101. **Mohseni M, Sun J, Lau A, Curtis S, Goldsmith J, Fox VL, Wei C, Frazier M, Samson O, Wong KK, Kim C, Camargo FD.** A genetic screen identifies an LKB1-MARK signalling axis controlling the Hippo-YAP pathway. *Nat Cell Biol* 16: 108–117, 2014.
102. **Moleirinho S, Guerrant W, Kissil JL.** The angiomotins - from discovery to function. *FEBS Lett* 588: 2693–2703, 2014.
103. **Montgomery HE, Clarkson P, Dollery CM, Prasad K, Losi MA, Hemingway H, Statters D, Jubb M, Girvain M, Varnava A, World M, Deanfield J, Talmud P, McEwan JR, McKenna WJ, Humphries S.** Association of angiotensin-converting enzyme gene I/D polymorphism with change in left ventricular mass in response to physical training. *Circulation* 96: 741–747, 1997.
104. **Mori M, Triboulet R, Mohseni M, Schlegelmilch K, Shrestha K, Camargo FD, Gregory RI.** Hippo signaling regulates microprocessor and links cell-density-dependent miRNA biogenesis to cancer. *Cell* 156: 893–906, 2014.
105. **Mosher DS, Quignon P, Bustamante CD, Sutter NB, Mellersh CS, Parker HG, Ostrander EA.** A mutation in the myostatin gene increases muscle mass and enhances racing performance in heterozygote dogs. *PLoS Genet* 3: e79, 2007.
106. **Munoz-Canoves P, Scheele C, Pedersen BK, Serrano AL.** Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? *FEBS J* 280: 4131–4148, 2013.
107. **Murphy MM, Lawson JA, Mathew SJ, Hutcheson DA, Kardon G.** Satellite cells, connective tissue fibroblasts and their interactions are crucial for muscle regeneration. *Development* 138: 3625–3637, 2011.
108. **Nguyen HB, Babcock JT, Wells CD, Quilliam LA.** LKB1 tumor suppressor regulates AMP kinase/mTOR-independent cell growth and proliferation via the phosphorylation of Yap. *Oncogene* 32: 4100–4109, 2013.
109. **Ono Y, Calhabeu F, Morgan JE, Katagiri T, Amthor H, Zammit PS.** BMP signalling permits population expansion by preventing premature myogenic differentiation in muscle satellite cells. *Cell Death Differ* 18: 222–234, 2011.
110. **Pedersen BK, Febbraio MA.** Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol Rev* 88: 1379–1406, 2008.
111. **Puthucheary Z, Skipworth JR, Rawal J, Loosemore M, Van Someren K, Montgomery HE.** The ACE gene and human performance: 12 years on. *Sports Med* 41: 433–448, 2011.
112. **Sadoshima J, Xu Y, Slayter HS, Izumo S.** Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. *Cell* 75: 977–984, 1993.
113. **Saltin B, Blomqvist G, Mitchell JH, Johnson RL Jr, Wildenthal K, Chapman CB.** Response to exercise after bed rest and after training. *Circulation* 38: VII1–VII78, 1968.
114. **Sartori R, Gregorevic P, Sandri M.** TGFbeta and BMP signaling in skeletal muscle: potential significance for muscle-related disease. *Trends Endocrinol Metab* 25: 464–471, 2014.
115. **Scharner J, Zammit PS.** The muscle satellite cell at 50: the formative years. *Skelet Muscle* 1: 28, 2011.
116. **Schuelke M, Wagner KR, Stolz LE, Hubner C, Riebel T, Komen W, Braun T, Tobin JF, Lee SJ.** Myostatin mutation associated with gross muscle hypertrophy in a child. *N Engl J Med* 350: 2682–2688, 2004.
117. **Selcen D, Muntoni F, Burton BK, Pegoraro E, Sewry C, Bite AV, Engel AG.** Mutation in BAG3 causes severe dominant childhood muscular dystrophy. *Ann Neurol* 65: 83–89, 2009.
118. **Semenza GL.** Regulation of oxygen homeostasis by hypoxia-inducible factor 1. *Physiology* 24: 97–106, 2009.
119. **Senyo SE, Steinhauser ML, Pizzimenti CL, Yang VK, Cai L, Wang M, Wu TD, Guerquin-Kern JL, Lechene CP, Lee RT.** Mammalian heart renewal by pre-existing cardiomyocytes. *Nature* 493: 433–436, 2013.
120. **Shyh-Chang N, Daley GQ.** Lin28: primal regulator of growth and metabolism in stem cells. *Cell Stem Cell* 12: 395–406, 2013.
121. **Silventoinen K, Sammalisto S, Perola M, Boomsma DI, Cornes BK, Davis C, Dunkel L, De Lange M, Harris JR, Hjelmborg JV, Luciano M, Martin NG, Mortensen J, Nistico L, Pedersen NL, Skytthe A, Spector TD, Stazi MA, Willemsen G, Kaprio J.** Heritability of adult body height: a comparative study of twin cohorts in eight countries. *Twin Res* 6: 399–408, 2003.
122. **Sudol M.** Yes-associated protein (YAP65) is a proline-rich phosphoprotein that binds to the SH3 domain of the Yes proto-oncogene product. *Oncogene* 9: 2145–2152, 1994.
123. **Sudol M, Bork P, Einbond A, Kastury K, Druck T, Negrini M, Huebner K, Lehman D.** Characterization of the mammalian YAP (Yes-associated protein) gene and its role in defining a novel protein module, the WW domain. *J Biol Chem* 270: 14733–14741, 1995.

124. **Sudol M, Harvey KF.** Modularity in the Hippo signaling pathway. *Trends Biochem Sci* 35: 627–633, 2010.
125. **Taniguchi K, Wu LW, Grivennikov SI, de Jong PR, Lian I, Yu FX, Wang K, Ho SB, Boland BS, Chang JT, Sandborn WJ, Hardiman G, Raz E, Maehara Y, Yoshimura A, Zucman-Rossi J, Guan KL, Karin M.** A gp130-Src-YAP module links inflammation to epithelial regeneration. *Nature* 519: 57–62, 2015.
126. **Taylor CT, McElwain JC.** Ancient atmospheres and the evolution of oxygen sensing via the hypoxia-inducible factor in metazoans. *Physiology* 25: 272–279, 2010.
127. **Tipton KD, Borsheim E, Wolf SE, Sanford AP, Wolfe RR.** Acute response of net muscle protein balance reflects 24-h balance after exercise and amino acid ingestion. *Am J Physiol Endocrinol Metab* 284: E76–E89, 2003.
128. **Tipton KD, Ferrando AA, Phillips SM, Doyle D Jr, Wolfe RR.** Postexercise net protein synthesis in human muscle from orally administered amino acids. *Am J Physiol Endocrinol Metab* 276: E628–E634, 1999.
129. **Tremblay AM, Camargo FD.** Hippo signaling in mammalian stem cells. *Semin Cell Dev Biol* 23: 818–826, 2012.
130. **Tsika RW, Ma L, Kehat I, Schramm C, Simmer G, Morgan B, Fine DM, Hanft LM, McDonald KS, Molkentin JD, Krenz M, Yang S, Ji J.** TEAD-1 overexpression in the mouse heart promotes an age-dependent heart dysfunction. *J Biol Chem* 285: 13721–13735, 2010.
131. **Tsika RW, McCarthy J, Karasseva N, Ou Y, Tsika GL.** Divergence in species and regulatory role of β-myosin heavy chain proximal promoter muscle-CAT elements. *Am J Physiol Cell Physiol* 283: C1761–C1775, 2002.
132. **Tsika RW, Schramm C, Simmer G, Fitzsimons DP, Moss RL, Ji J.** Overexpression of TEAD-1 in transgenic mouse striated muscles produces a slower skeletal muscle contractile phenotype. *J Biol Chem* 283: 36154–36167, 2008.
133. **Tumaneng K, Schlegelmilch K, Russell RC, Yimlamai D, Basnet H, Mahadevan N, Fitamant J, Bardeesy N, Camargo FD, Guan KL.** YAP mediates crosstalk between the Hippo and PI(3)K-TOR pathways by suppressing PTEN via miR-29. *Nat Cell Biol* 14: 1322–1329, 2012.
134. **Udan RS, Kango-Singh M, Nolo R, Tao C, Halder G.** Hippo promotes proliferation arrest and apoptosis in the Salvador/Warts pathway. *Nat Cell Biol* 5: 914–920, 2003.
135. **Ulbricht A, Eppler FJ, Tapia VE, Van der Ven PF, Hampe N, Hersch N, Vakeel P, Stadel D, Haas A, Saftig P, Behrends C, Fürst DO, Volkmer R, Hoffmann B, Kolanus W, Höhfeld J.** Cellular mechanotransduction relies on tension-induced and chaperone-assisted autophagy. *Curr Biol* 23: 430–435, 2013.
136. **Ulbricht A, Gehlert S, Leciejewski B, Schiffer T, Bloch W, Hohfeld J.** Induction and adaptation of chaperone-assisted selective autophagy CASA in response to resistance exercise in human skeletal muscle. *Autophagy* 11: 538–546, 2015.
137. **Varelas X, Samavarchi-Tehrani P, Narimatsu M, Weiss A, Cockburn K, Larsen BG, Rossant J, Wrana JL.** The Crumbs complex couples cell density sensing to Hippo-dependent control of the TGF-beta-SMAD pathway. *Dev Cell* 19: 831–844, 2010.
138. **Vassilev A, Kaneko KJ, Shu H, Zhao Y, DePamphilis ML.** TEAD/TEF transcription factors utilize the activation domain of YAP65, a Src/Yes-associated protein localized in the cytoplasm. *Genes Dev* 15: 1229–1241, 2001.
139. **Von Gise A, Lin Z, Schlegelmilch K, Honor LB, Pan GM, Buck JN, Ma Q, Ishiwata T, Zhou B, Camargo FD, Pu WT.** YAP1, the nuclear target of Hippo signaling, stimulates heart growth through cardiomyocyte proliferation but not hypertrophy. *Proc Natl Acad Sci USA* 109: 2394–2399, 2012.
140. **Vyas DR, McCarthy JJ, Tsika GL, Tsika RW.** Multiprotein complex formation at the beta myosin heavy chain distal muscle CAT element correlates with slow muscle expression but not mechanical overload responsiveness. *J Biol Chem* 276: 1173–1184, 2001.
141. **Wackerhage H, Del Re DP, Judson RN, Sudol M, Sadoshima J.** The Hippo signal transduction network in skeletal and cardiac muscle. *Sci Signal* 7: re4, 2014.
142. **Wagner PD.** A re-analysis of the 1968 Saltin et al. "Bedrest" paper. *Scand J Med Sci Sports* 25, *Suppl* 4: 83–87, 2015.
143. **Wang K, Degerny C, Xu M, Yang XJ.** YAP, TAZ, and Yorkie: a conserved family of signal-responsive transcriptional coregulators in animal development and human disease. *Biochem Cell Biol* 87: 77–91, 2009.
144. **Wang P, Mao B, Luo W, Wei B, Jiang W, Liu D, Song L, Ji G, Yang Z, Lai YQ, Yuan Z.** The alteration of Hippo/YAP signaling in the development of hypertrophic cardiomyopathy. *Basic Res Cardiol* 109: 435, 2014.
145. **Wang W, Xiao ZD, Li X, Aziz KE, Gan B, Johnson RL, Chen J.** AMPK modulates Hippo pathway activity to regulate energy homeostasis. *Nat Cell Biol* 17: 490–499, 2015.
146. **Waring CD, Vicinanza C, Papalamprou A, Smith AJ, Purushothaman S, Goldspink DF, Nadal-Ginard B, Torella D, Ellison GM.** The adult heart responds to increased workload with physiologic hypertrophy, cardiac stem cell activation, and new myocyte formation. *Eur Heart J* 35: 2722–2731, 2014.
147. **Watt KI, Judson R, Medlow P, Reid K, Kurth TB, Burniston JG, Ratkevicius A, De Bari C, Wackerhage H.** Yap is a novel regulator of C2C12 myogenesis. *Biochem Biophys Res Commun* 393: 619–624, 2010.
148. **Watt KI, Turner BJ, Hagg A, Zhang X, Davey JR, Qian H, Beyer C, Winbanks CE, Harvey KF, Gregorevic P.** The Hippo pathway effector YAP is a critical regulator of skeletal muscle fibre size. *Nat Commun* 6: 6048, 2015.
149. **Wei B, Dui W, Liu D, Xing Y, Yuan Z, Ji G.** MST1, a key player, in enhancing fast skeletal muscle atrophy. *BMC Biol* 11: 12, 2013.
150. **Wennmann DO, Vollenbroker B, Eckart AK, Bonse J, Erdmann F, Wolters DA, Schenk LK, Schulze U, Kremerskothen J, Weide T, Pavenstadt H.** The Hippo pathway is controlled by angiotensin II signaling and its reactivation induces apoptosis in podocytes. *Cell Death Dis* 5: e1519, 2014.
151. **Wilson JM, Loenneke JP, Jo E, Wilson GJ, Zourdos MC, Kim JS.** The effects of endurance, strength, and power training on muscle fiber type shifting. *J Strength Cond Res* 26: 1724–1729, 2012.
152. **Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, Chu AY, Estrada K, Luan J, Kutalik Z, Amin N, Buchkovich ML, Croteau-Chonka DC, Day FR, Duan Y, Fall T, Fehrmann R, Ferreira T, Jackson AU, Karjalainen J, Lo KS, Locke AE, Mägi R, Mihailov E, Porcu E, Randall JC, Scherag A, Vinkhuyzen AA, Westra HJ, Winkler TW, Workalemahu T, Zhao JH, Absher D, Albrecht E, Anderson D, Baron J, Beekman M, Demirkan A, Ehret GB, Feenstra B, Feitosa MF, Fischer K, Fraser RM, Goel A, Gong J, Justice AE, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Lui JC, Mangino M, Mateo Leach I, Medina-Gomez C, Nalls MA, Nyholt DR, Palmer CD, Pasko D, Pechlivanis S, Prokopenko I, Ried JS, Ripke S, Shungin D, Stancáková A, Strawbridge RJ, Sung YJ, Tanaka T, Teumer A, Trompet S, van der Laan SW, van Setten J, Van Vliet-Ostaptchouk JV, Wang Z, Yengo L, Zhang W, Afzal U, Arnlöv J, Arscott GM, Bandinelli S, Barrett A, Bellis C, Bennett AJ, Berne C, Blüher M, Bolton JL, Böttcher Y, Boyd HA, Bruinenberg M, Buckley BM, Buyske S, Caspersen IH, Chines PS, Clarke R, Claudi-Boehm S, Cooper M, Daw EW, De Jong PA, Deelen J, Delgado G, Denny JC, Dhonukshe-Rutten R, Dimitriou M, Doney AS, Dörr M, Eklund N, Eury E, Folkersen L, Garcia ME, Geller F, Giedraitis V, Go AS, Grallert H, Grammer TB, Gräßler J, Grönberg H, de Groot LC, Groves CJ, Haessler J, Hall P, Haller T, Hallmans G, Hannemann A, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q, Hemani G, Henders AK, Hillege HL, Hlatky MA, Hoffmann W, Hoffmann P, Holmen O, Houwing-Duistermaat JJ, Illig T, Isaacs A, James AL, Jeff J, Johansen B, Johansson A, Jolley J, Juliusdottir T, Junttila J, Kho AN, Kinnunen L, Klopp N, Kocher T, Kratzer W, Lichtner P, Lind L, Lindström J, Lobbens S, Lorentzon M, Lu Y, Lyssenko V, Magnusson PK, Mahajan A, Maillard M, McArdle WL, McKenzie CA, McLachlan S, McLaren PJ, Menni C, Merger S, Milani L, Moayyeri A, Monda KL, Morken MA, Muller G, Müller-Nurasyid M, Musk AW, Narisu N, Nauck M, Nolte IM, Nöthen MM, Oozageer L, Pilz S, Rayner NW, Renstrom F, Robertson NR, Rose LM, Roussel R, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Schunkert H, Scott RA, Sehmi J, Seufferlein T, Shi J, Silventoinen K, Smit JH, Smith AV, Smolonska J, Stanton AV, Stirrups K, Stott DJ, Stringham HM, Sundström J, Swertz MA, Syvanen AC, Tayo BO, Thorleifsson G, Tyrer JP, van Dijk S, van Schoor NM, van der Velde N, van Heemst D, van Oort FV, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Waldenberger M, Wennauer R, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A, Wright AF, Zhang Q, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Bergmann S, Biffar R, Blangero J, Boomsma DI, Bornstein SR, Bovet P, Brambilla P, Brown MJ, Campbell H, Caulfield MJ, Chakravarti A, Collins R, Collins FS, Crawford DC,**

Cupples LA, Danesh J, de Faire U, den Ruijter HM, Erbel R, Erdmann J, Eriksson JG, Farrall M, Ferrannini E, Ferrières J, Ford I, Forouhi NG, Forrester T, Gansevoort RT, Gejman PV, Gieger C, Golay A, Gottesman O, Gudnason V, Gyllensten U, Haas DW, Hall AS, Harris TB, Hattersley AT, Heath AC, Hengstenberg C, Hicks AA, Hindorff LA, Hingorani AD, Hofman A, Hovingh GK, Humphries SE, Hunt SC, Hypponen E, Jacobs KB, Jarvelin MR, Jousilahti P, Jula AM, Kaprio J, Kastelein JJ, Kayser M, Kee F, Keinanen-Kiukaanniemi SM, Kiemeney LA, Kooner JS, Kooperberg C, Koskinen S, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimaki T, Lupoli S, Madden PA, Mãnnistö S, Manunta P, Marette A, Matise TC, McKnight B, Meitinger T, Moll FL, Montgomery GW, Morris AD, Morris AP, Murray JC, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Ouwehand WH, Pasterkamp G, Peters A, Pramstaller PP, Price JF, Qi L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ritchie M, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schwarz PE, Sebert S, Sever P, Shuldiner AR, Sinisalo J, Steinthorsdottir V, Stolk RP, Tardif JC, Tönjes A, Tremblay A, Tremoli E, Virtamo J, Vohl MC; Electronic Medical Records and Genomics (eMEMERGEGE) Consortium; MIGen Consortium; PAGEGE Consortium; LifeLines Cohort Study, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bottinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker PI, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hayes MG, Hui J, Hunter DJ, Hveem K, Jukema JW, Kaplan RC, Kivimaki M, Kuh D, Laakso M, Liu Y, Martin NG, März W, Melbye M, Moebus S, Munroe PB, Njølstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Pérusse L, Peters U, Powell JE, Power C, Quertermous T, Rauramaa R, Reinmaa E, Ridker PM, Rivadeneira F, Rotter JI, Saaristo TE, Saleheen D, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Strauch K, Stumvoll M, Tuomilehto J, Uusitupa M, van der Harst P, Völzke H, Walker M, Wareham NJ, Watkins H, Wichmann HE, Wilson JF, Zanen P, Deloukas P, Heid IM, Lindgren CM, Mohlke KL, Speliotes EK, Thorsteinsdottir U, Barroso I, Fox CS, North KE, Strachan DP, Beckmann JS, Berndt SI, Boehnke M, Borecki IB, McCarthy MI, Metspalu A, Stefansson K, Uitterlinden AG, van Duijn CM, Franke L, Willer CJ, Price AL, Lettre G, Loos RJ, Weedon MN, Ingelsson E, O'Connell JR, Abecasis GR, Chasman DI, Goddard ME, Visscher PM, Hirschhorn JN, Frayling TM. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet* 46: 1173–1186, 2014.

153. **Xiang L, Gilkes DM, Hu H, Luo W, Bullen JW, Liang H, Semenza GL.** HIF-1alpha and TAZ serve as reciprocal co-activators in human breast cancer cells. *Oncotarget* 6: 11768–11778, 2015.
154. **Xin M, Kim Y, Sutherland LB, Murakami M, Qi X, McAnally J, Porrello ER, Mahmoud AI, Tan W, Shelton JM, Richardson JA, Sadek HA, Bassel-Duby R, Olson EN.** Hippo pathway effector Yap promotes cardiac regeneration. *Proc Natl Acad Sci USA* 110: 13839–13844, 2013.
155. **Xin M, Olson EN, Bassel-Duby R.** Mending broken hearts: cardiac development as a basis for adult heart regeneration and repair. *Nat Rev Mol Cell Biol* 14: 529–541, 2013.
156. **Xu T, Wang W, Zhang S, Stewart RA, Yu W.** Identifying tumor suppressors in genetic mosaics: the *Drosophila* lats gene encodes a putative protein kinase. *Development* 121: 1053–1063, 1995.
157. **Yang Z, Nakagawa K, Sarkar A, Maruyama J, Iwasa H, Bao Y, Ishigami-Yuasa M, Ito S, Kagechika H, Hata S, Nishina H, Abe S, Kitagawa M, Hata Y.** Screening with a novel cell-based assay for TAZ activators identifies a compound that enhances myogenesis in C2C12 cells and facilitates muscle repair in a muscle injury model. *Mol Cell Biol* 34: 1607–1621, 2014.
158. **Yu FX, Zhang Y, Park HW, Jewell JL, Chen Q, Deng Y, Pan D, Taylor SS, Lai ZC, Guan KL.** Protein kinase A activates the Hippo pathway to modulate cell proliferation and differentiation. *Genes Dev* 27: 1223–1232, 2013.
159. **Yu FX, Zhao B, Guan KL.** Hippo pathway in organ size control, tissue homeostasis, and cancer. *Cell* 163: 811–828, 2015.
160. **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.** Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. *Cell* 150: 780–791, 2012.
161. **Yuan Z, Kim D, Shu S, Wu J, Guo J, Xiao L, Kaneko S, Coppola D, Cheng JQ.** Phosphoinositide 3-kinase/Akt inhibits MST1-mediated pro-apoptotic signaling through phosphorylation of threonine 120. *J Biol Chem* 285: 3815–3824, 2010.
162. **Zhao B, Li L, Tumaneng K, Wang CY, Guan KL.** A coordinated phosphorylation by Lats and CK1 regulates YAP stability through SCF(beta-TRCP). *Genes Dev* 24: 72–85, 2010.
163. **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.** Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes Dev* 21: 2747–2761, 2007.
164. **Zhao B, Ye X, Yu J, Li L, Li W, Li S, Yu J, Lin JD, Wang CY, Chinnaiyan AM, Lai ZC, Guan KL.** TEAD mediates YAP-dependent gene induction and growth control. *Genes Dev* 22: 1962–1971, 2008.
165. **Zheng Y, Wang W, Liu B, Deng H, Uster E, Pan D.** Identification of Happyhour/MAP4K as alternative Hpo/Mst-like kinases in the Hippo kinase cascade. *Dev Cell* 34: 642–655, 2015.
166. **Zhu X, Topouzis S, Liang LF, Stotish RL.** Myostatin signaling through Smad2, Smad3 and Smad4 is regulated by the inhibitory Smad7 by a negative feedback mechanism. *Cytokine* 26: 262–272, 2004.