



# Regulation of Tissue Growth by the Mammalian Hippo Signaling Pathway

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The integrative control of diverse biological processes such as proliferation, differentiation, apoptosis and metabolism is essential to maintain cellular and tissue homeostasis. Disruption of these underlie the development of many disease states including cancer and diabetes, as well as many of the complications that arise as a consequence of aging. These biological outputs are governed by many cellular signaling networks that function independently, and in concert, to convert changes in hormonal, mechanical and metabolic stimuli into alterations in gene expression. First identified in *Drosophila melanogaster* as a powerful mediator of cell division and apoptosis, the Hippo signaling pathway is a highly conserved regulator of mammalian organ size and functional capacity in both healthy and diseased tissues. Recent studies have implicated the pathway as an effector of diverse physiological cues demonstrating an essential role for the Hippo pathway as an integrative component of cellular homeostasis. In this review, we will: (a) outline the critical signaling elements that constitute the mammalian Hippo pathway, and how they function to regulate Hippo pathway-dependent gene expression and tissue growth, (b) discuss evidence that shows this pathway functions as an effector of diverse physiological stimuli and (c) highlight key questions in this developing field.

**Keywords:** hippo signaling pathway, YAP, TAZ, integrative physiology, cell signaling

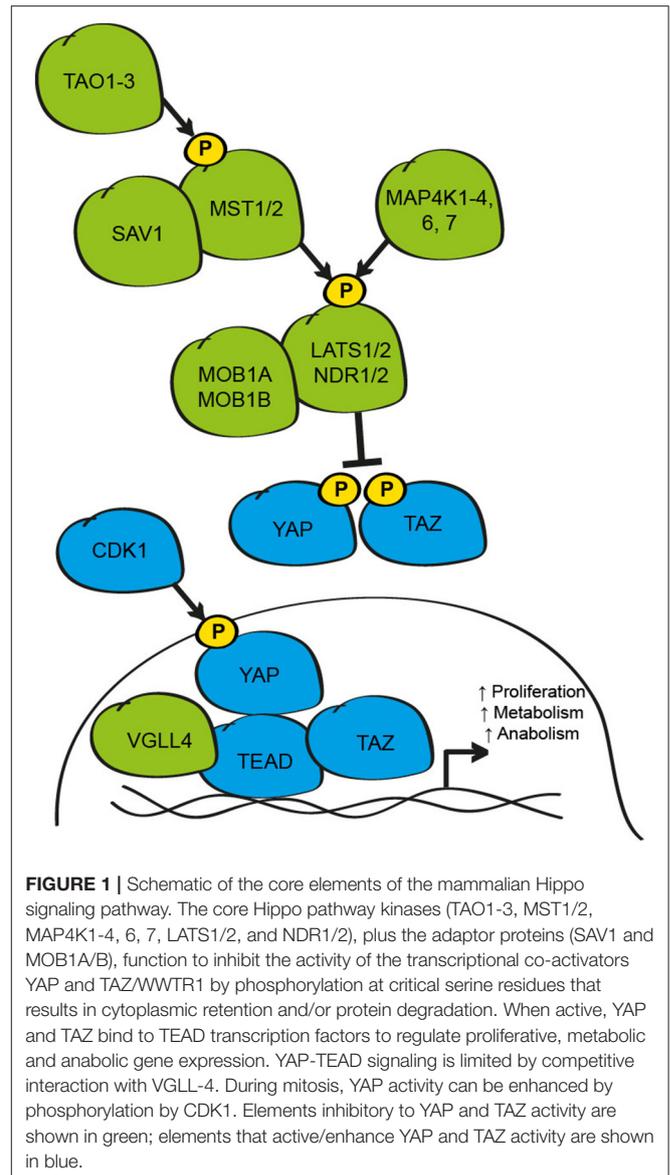
## INTRODUCTION

The fine control of biological processes such as cell division, terminal differentiation, cell death (apoptosis) and metabolism in response to changes in the external environment is essential for biological organisms to maintain homeostasis and function appropriately (Purvis and Lahav, 2013). These processes are mediated by intracellular signaling networks including the Transforming-Growth Factor beta (TGF- $\beta$ ), Notch, WNT and Insulin-PI3K-mTOR signaling pathways that act in isolation to control the expression of sub-sets of genes, and as an orchestrated network that collectively influences biological phenotypes (Bedinger and Adams, 2015; Bray, 2016; Hata and Chen, 2016; Masuda and Ishitani, 2017). Recent evidence also implicates the relatively less-well-characterized Hippo pathway as a major signaling pathway governing the cellular response to diverse physiological stimuli (Harvey et al., 2013; Meng et al., 2016). The role of the Hippo pathway in *Drosophila* (Richardson and Portela, 2017), during early mammalian developmental stages (Sasaki, 2017), or in specific tissues such as the heart (He et al., 2017; Zhang and Del Re, 2017),

intestine (Gregorieff and Wrana, 2017), and liver (Patel et al., 2017) have recently been described. In this review, we aim to provide the reader with an outline of the critical elements that form the core Hippo signaling pathway in mammals, and to describe the experimental evidence supporting a vital role for this pathway as a major regulator of tissue growth and differentiation in response to three main forms of external regulation: hormonal, mechanical and metabolic stimuli. We will use mammalian nomenclature in general, unless discussing specific results in other organisms.

## THE HIPPO SIGNALING PATHWAY NEGATIVELY REGULATES THE ACTIVITY OF YAP AND TAZ

First identified from genetic loss-of-function screens in *Drosophila Melanogaster*, the Hippo signaling pathway has emerged as a powerful regulator of organ size and cell fate across species (Harvey et al., 2013). To date, over 40 proteins have been implicated as members of this diverse pathway; however, the capacity for many of these elements to control Hippo signaling activity is highly context-dependent (Plouffe et al., 2016). Despite this, most stimuli that influence the Hippo pathway converge at a common level to activate, or inhibit, the core Hippo pathway kinases, Mammalian Ste-20 like kinase 1 and 2 (MST1/2) and/or mitogen-activated protein kinase kinase kinases 1-4, 6, and 7 (MAP4K) (Tapon et al., 2002; Harvey et al., 2003; Pantalacci et al., 2003; Udan et al., 2003; Wu et al., 2003; Li et al., 2015; Meng et al., 2015; Zheng et al., 2015; **Figure 1**). The biochemical regulation of these proteins has been studied mainly with MST1/2, where activation of the kinase is dependent on phosphorylation by the TAO family kinases (TAO1-3) in an activation loop at Thr180/183, respectively (Praskova et al., 2004; Boggiano et al., 2011; Poon et al., 2011). This phosphorylation event is critical for increased catalytic activity and, in the case of MST1/2, the formation of a complex with the adaptor protein WW-domain containing 1 (SAV1) (Pantalacci et al., 2003; Wu et al., 2003; Callus et al., 2006). This interaction appears exclusive to MST1/2 since MAP4K do not interact with SAV1 *in vitro* (Meng et al., 2015; Zheng et al., 2015). Upon activation, MST1/2 or MAP4K can phosphorylate the C-terminal hydrophobic motif of the NDR family kinases Large Tumour Suppressor kinase 1 and 2 (LATS1/2<sup>Thr1079</sup>) and/or the related Nuclear dbf-2 related (NDR) kinases 1/2 (Chan et al., 2005; Hergovich et al., 2009; Li et al., 2015; Meng et al., 2015; Tang et al., 2015; Zheng et al., 2015). Phosphorylated LATS1/2 and/or NDR1/2 then undergo auto-phosphorylation in an activation loop (Chan et al., 2005). MST1/2 also binds the adaptor proteins MOB1A/1B (MOB) leading to phosphorylation on two N-terminal residues; Thr12 and Thr35 (Lai et al., 2005; Praskova et al., 2008). MST1/2 phosphorylation results in activation of MOB and a conformational change that favors binding to LATS1/2 or NDR1/2 kinases (Praskova et al., 2008). When active, the LATS/MOB or NDR/MOB complexes suppress the activity of the transcriptional co-activators Yes-associated protein



(YAP1) and transcriptional co-activator with PDZ-binding motif (WWTR1/TAZ) (Huang et al., 2005; Zhao et al., 2007; Lei et al., 2008; Zhang et al., 2015).

YAP and TAZ are the primary effectors of the Hippo pathway in mammals, and are the homologs of the *Drosophila* gene *Yorkie* (Yki) (Huang et al., 2005). While the activity of these proteins can be influenced transcriptionally, YAP and TAZ are mainly regulated by post-translational modifications, in particular by phosphorylation on critical serine residues in a consensus motif (HXRXXS), by LATS1/2 and/or NDR1/2 (Zhao et al., 2007; Lei et al., 2008; Zhang et al., 2015). The importance of this mechanism was highlighted by studies where single and multiple point mutations of critical serine residues (Ser61, 109, 127, 164, and 381; mutated to alanine to create phosphorylation-resistant mutations) were introduced into the human YAP protein (Zhao et al., 2007). Using these mutant YAP proteins,

the authors demonstrated that these serine residues are directly phosphorylated by activated LATS1/2 to limit the activity of YAP (Zhao et al., 2007). Similar findings have been reported for TAZ, where LATS phosphorylates Ser66, 89, 117, and 311 (Lei et al., 2008). Of these residues, the best studied are YAP<sup>Ser127</sup>/TAZ<sup>Ser89</sup> which influence sub-cellular localization and interaction with 14-3-3 binding proteins, and YAP<sup>Ser381</sup>/TAZ<sup>Ser311</sup> which function as priming sites for a second phosphorylation event at Ser384 by casein kinase 1 $\gamma$ / $\delta$  and the subsequent ubiquitination and degradation of YAP or TAZ by the E3 ligase, SCF <sup>$\beta$ -TRCP</sup> (Zhao et al., 2007, 2010; Liu et al., 2010). While the precise function of the other Serine residues remains unclear, these likely also influence YAP and TAZ activity since mutation of all 5 serine residues results in greater activation of the proteins than mutation of individual residues, at least in cultured cells (Zhao et al., 2009).

Counter to inhibitory phosphorylation by LATS1/2, in mitotically active cells during the G2-M phase of the cell cycle, YAP and TAZ activity is enhanced by phosphorylation by cyclin-dependent kinase 1 (CDK1) at multiple threonine and serine residues; findings that may explain the efficacy of CDK inhibitors under certain circumstances (Yang et al., 2013; Zhao et al., 2014; Pegoraro et al., 2015). Independent of direct inhibition by LATS1/2, the activity of YAP and TAZ can also be influenced by physical retention of the proteins in the cytosol by the Angiomotin family proteins (AMOT, AMOT1L, and AMOT2L) in a LATS1/2 dependent- or independent-manner (Chan et al., 2011; Paramasivam et al., 2011; Wang et al., 2011; Zhao et al., 2011), by disruption of protein-protein interactions necessary for transcriptional activity due to phosphorylation by kinases such as AMP-activated protein kinase (AMPK1) (DeRan et al., 2014; Mo et al., 2015; Wang et al., 2015), interaction with tyrosine kinases including YES and Src (Vassilev et al., 2001), the STRIPAK PP2A phosphatase complex (Ribeiro et al., 2010), methylation by the methyltransferase SET-7 at lysine 494 (Oudhoff et al., 2013), sumoylation by the promyelocytic leukemia protein (PML) (Lapi et al., 2008) and acetylation by the nuclear acetyltransferases CREB binding protein (CBP) and p300 (Hata et al., 2012). Collectively, the co-ordinated influence of these post-translational modifications functions to limit the activity of YAP and/or TAZ.

When Hippo pathway activity is low, YAP and TAZ accumulate predominantly in the nucleus of the cell where they can interact with transcription factors to regulate gene expression including p73, Tbx-5, Smad proteins, FoxO, and Runx (Strano et al., 2001; Ferrigno et al., 2002; Zaidi et al., 2004; Murakami et al., 2005; Varelas et al., 2010b; Rosenbluh et al., 2012; Shao et al., 2014). At this level, Hippo signaling may intersect with a number of other signaling pathways to control subsets of genes during specific cellular contexts (Alarcon et al., 2009; Azzolin et al., 2014). However, the most significant interacting partners of YAP and TAZ are the TEA domain family member transcription factors, (TEAD 1-4; *Scalloped* (Sd) in *Drosophila*) that are essential under most conditions for YAP and TAZ to promote growth (Vassilev et al., 2001; Wu et al., 2008; Zhang et al., 2008; Zhao et al., 2008). The

interaction between YAP and TEAD, and TAZ and TEAD is mediated via a C-terminal binding domain in YAP/TAZ and an N-terminal binding domain in TEAD (Vassilev et al., 2001; Zhao et al., 2008). Solving the crystal structure of the YAP-TEAD and TAZ-TEAD complexes has identified the critical regions and residues necessary for this interaction (Chen et al., 2010; Li et al., 2010; Kaan et al., 2017). These studies support previous genetic and bio-chemical studies *in vitro* and *in vivo*, as well as genomic studies of individuals carrying mutations in TEAD1 at Tyr421 who develop Sveinsson's Chorioretinal atrophy, a rare autosomal-dominant disease that leads to degeneration of the photoreceptor cells in the eye (Fossdal et al., 2004).

While the over-expression of YAP or TAZ results in TEAD-dependent gene expression, the over-expression of TEAD or Sd alone leads to the depression of many of these target genes (Koontz et al., 2013). This fascinating observation lead to the demonstration that YAP binding to TEAD results in the de-repression of many of these genes, which under basal conditions are suppressed by TEAD in complex with the Vestigial-like 4 protein (VGLL-4; *Tgi* in *Drosophila*) (Koontz et al., 2013). In these elegant studies, it was demonstrated that under Hippo pathway active conditions, where YAP activity is suppressed, a TEAD/VGLL-4 complex represses the expression of target genes. When the Hippo pathway is inhibited, YAP physically competes with VGLL-4 for TEAD binding, resulting in de-repression of target genes (Koontz et al., 2013). In addition to the activation of YAP and TAZ, CDK1 also phosphorylates VGLL-4 during mitosis to limit binding to TEAD and repression of target genes (Zeng et al., 2017). While Yki/Sd binding occurs mainly in the promoter region of target genes (Oh et al., 2013), active YAP-TEAD and TAZ-TEAD complexes bind mainly to distal enhancer regions where they interact with elements of the transcriptional machinery such as the Mediator complex to influence gene expression (Galli et al., 2015; Kim et al., 2015; Zanconato et al., 2015).

## CONTROL OF ORGAN SIZE BY YAP AND TAZ

The first identified, and best studied, role of the Hippo pathway is the regulation of organ size. This was initially demonstrated during the development of *Drosophila melanogaster* imaginal discs, where loss of upstream elements, or activation of Yki results in a profound over-growth phenotype of epithelial tissues, caused by ectopic cell proliferation, increased progression through the cell cycle and impaired apoptosis (Tapon et al., 2002; Harvey et al., 2003; Pantalacci et al., 2003; Udan et al., 2003; Wu et al., 2003; Huang et al., 2005; Li et al., 2015; Meng et al., 2015; Zheng et al., 2015). Subsequent studies have shown that YAP and TAZ function in a similar manner during the early stages of mammalian embryonic development, and in the specialized development of a number of mammalian tissues, demonstrating the conserved nature of this function for the Hippo pathway (Morin-Kensicki et al., 2006; Camargo et al., 2007; Dong et al., 2007). While the functional output and requirement for TEAD is

conserved across species (Hilman and Gat, 2011), the magnitude and complexity of the genes controlled by YAP-TEAD and TAZ-TEAD complexes in mammals differs in tissue- and temporal-specific manners (Meng et al., 2016). Thus, it is likely that YAP and TAZ influence mammalian cell proliferation and apoptosis by controlling the expression of tissue-specific gene signatures, rather than a common subset of target genes. However, recent reports demonstrate in *Drosophila* and a number of mammalian cell types, that Yki/YAP activation is associated with the upregulation of genes encoding Hippo pathway upstream kinases and adaptor proteins, including Neurofibromin 2 (NF2) and LATS2 (Dai et al., 2015; Moroishi et al., 2015; Park G. S. et al., 2016). The induction of these genes forms a negative feedback loop that acts to limit the transcriptional activity of YAP and TAZ, and is likely a critical mechanism to ensure proper development of mammalian tissues indicating that some subsets of target genes are likely common between mammalian tissues (Park G. S. et al., 2016).

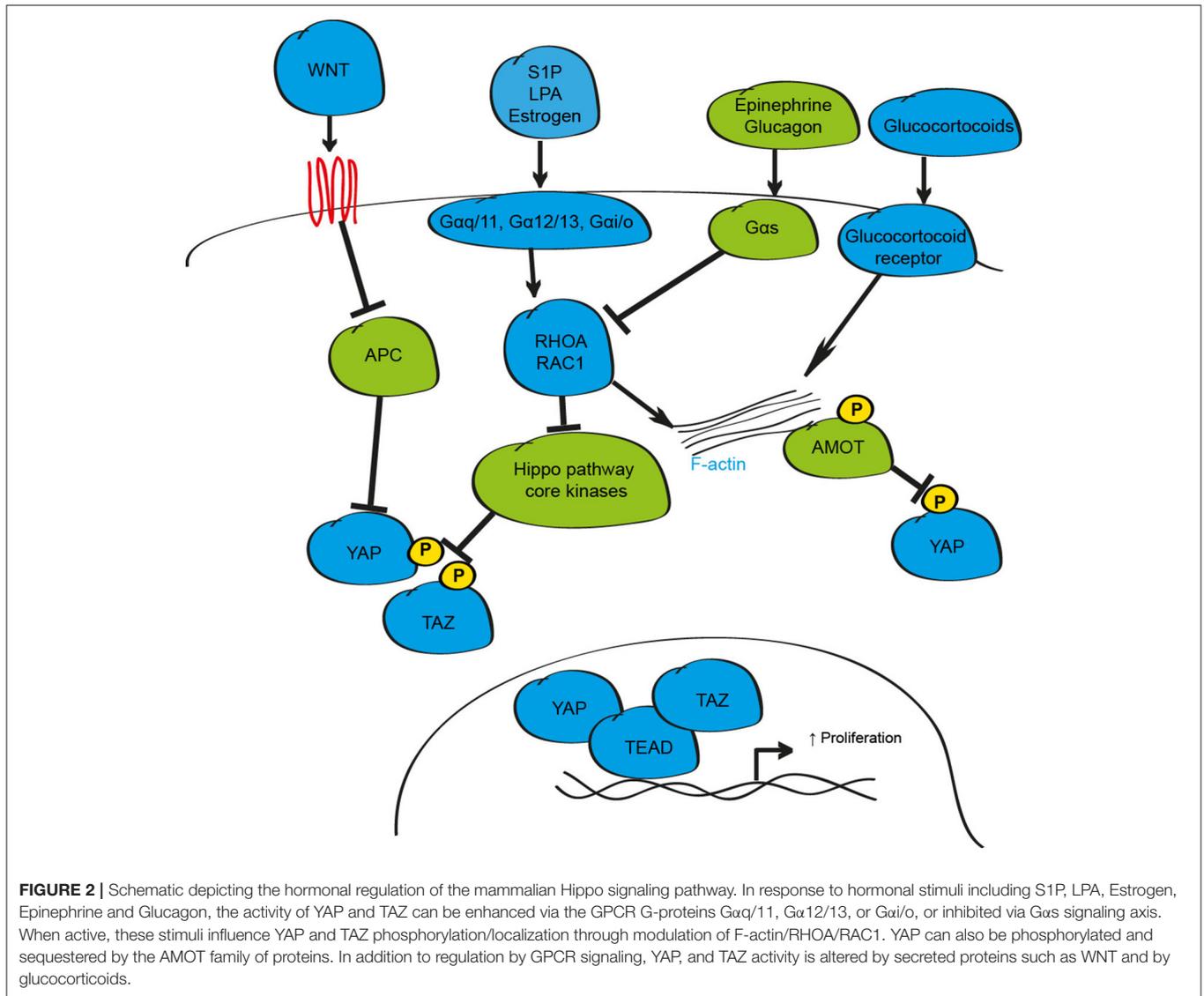
In addition to the well-described developmental role for YAP and TAZ, a number of studies now implicate these genes as critical gate-keepers of stem cell expansion and differentiation in adult tissues. The first example of this in mammals was in the mouse intestine where activation of YAP leads to the rapid proliferation of the undifferentiated stem/progenitor cell population (Camargo et al., 2007). Subsequent studies have demonstrated similar findings in the progenitor cells of the skin, intestine, brain and skeletal muscle (Cao et al., 2008; Gee et al., 2011; Schlegelmilch et al., 2011; Beverdam et al., 2013; Tremblay et al., 2014; Sun et al., 2017). Concurrently, appropriate regulation of tissue homeostasis and regeneration requires the subsequent down-regulation of YAP for terminal differentiation to proceed, as demonstrated in genetic mouse models expressing active YAP mutants, or lacking upstream signaling elements (Cao et al., 2008; Lian et al., 2010; Judson et al., 2012; Tremblay et al., 2014; Sun et al., 2017). While YAP and TAZ function in a redundant manner in many settings, this appears more complex during the differentiation of skeletal muscle cells where YAP inhibits, while TAZ promotes terminal differentiation and regeneration (Jeong et al., 2010; Watt et al., 2010; Park G. H. et al., 2014; Mohamed et al., 2016; Sun et al., 2017). These findings have broad implications for regenerative medicine and suggest that appropriate modulation of YAP and/or TAZ activity may be an approach that can be utilized to treat degenerative conditions. However, the efficacy of such an approach is likely to be tissue- and context-dependent, as demonstrated in the mammalian heart where YAP activation can enhance the regenerative capacity of the heart, but only at early stages of post-natal life (Xin et al., 2013). Caution is also warranted with strategies aimed at modulating YAP activity in tissues such as the skin which display profound phenotypes upon activation and inhibition of YAP-TEAD activity in the adult (Schlegelmilch et al., 2011). However, since not all tissue types display phenotypes in response to loss of YAP or TAZ under basal conditions e.g., the intestine or mammary gland (Cai et al., 2010; Chen et al., 2014), targeting this pathway in a tissue-specific manner may still offer great promise for the treatment of a number of conditions.

In addition to the role of the pathway as a regulator of cell division and differentiation, growing evidence supports a role for the Hippo pathway as a mediator of cell size in post-mitotic tissues such as skeletal muscle and the heart, where activation of YAP directly, or by inhibition of LATS2, causes hypertrophy by influencing the rates of protein synthesis, without altering cell number (Matsui et al., 2008; Goodman et al., 2015; Watt et al., 2015). As in epithelial cells, the ability for YAP to regulate basal tissue size in striated muscle appears mostly dependent on TEAD (Watt et al., 2015) providing further evidence for the critical role for the YAP-TEAD and TAZ-TEAD complexes as the primary effectors of Hippo signaling in mammals.

## INTEGRATION OF HORMONAL SIGNALING BY THE HIPPO PATHWAY

One common approach that cells utilize to modulate intra-cellular responses to changes in the external environment is the synthesis and release of soluble factors such as hormones, growth factors and diffusible molecules including insulin and glucose (Bedinger and Adams, 2015). While genetic studies were instrumental for elucidating the critical intracellular signaling proteins that regulate YAP and TAZ activity, defining how the Hippo pathway is activated by external stimuli to respond to changes in the environment has proved more elusive. Studies exploring this area demonstrated that soluble factors including lysophosphatidic acid (LPA), Sphingosine-1-phosphate (S1P), epinephrine, estrogen, and glucagon can activate, or inhibit, YAP and TAZ via the Hippo pathway by their cognate G-protein coupled receptors (Miller et al., 2012; Yu et al., 2012; Zhou et al., 2015; **Figure 2**). When activated by such soluble factors, these receptors recruit and couple with their associated G-protein sub-units to engage the small GTPases RHOA and RAC1 leading to alterations in LATS1/2 activity (Yu et al., 2012; Plouffe et al., 2016). In most cases, stimulation of  $G_{\alpha_q/11}$ ,  $G_{\alpha_{12/13}}$ , and  $G_{\alpha_{i/o}}$  subunits is reported to activate YAP and TAZ, while  $G_{\alpha_s}$  subunits inhibit; however, this is likely dependent on many factors including receptor recycling rate, G-subunit protein levels, and expression of downstream signaling effector proteins meaning that individual sub-units could both activate, or inhibit, YAP and TAZ depending on the cellular context (Yu et al., 2012; Plouffe et al., 2016). Of note, activating mutations in G protein sub-units are observed in a number of cancer sub-types that display increased YAP protein (Yu et al., 2012; Feng et al., 2014; Zhou et al., 2015).

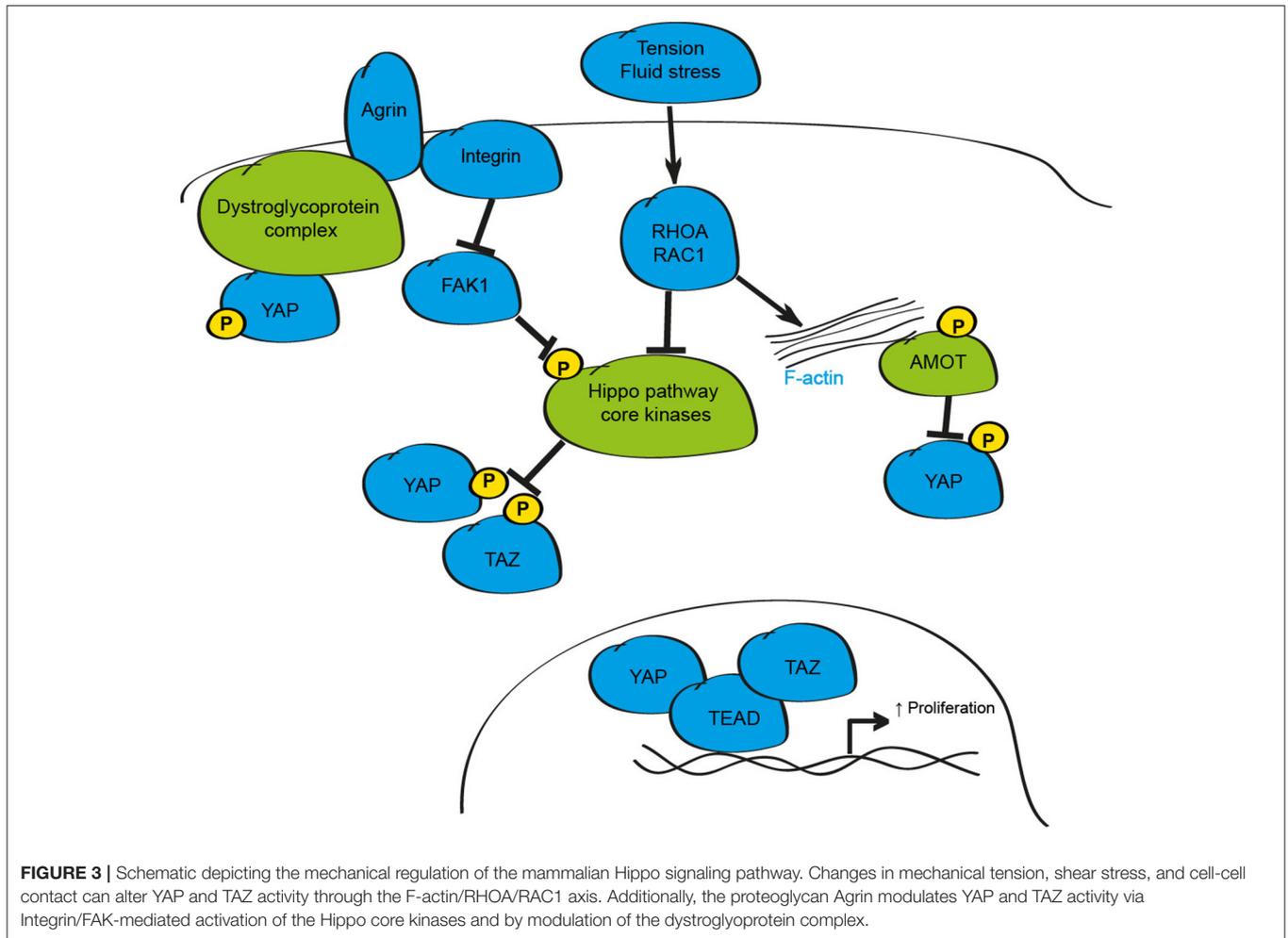
A number of soluble signaling proteins that act independently of the G-protein coupled receptor signaling pathways have also been proposed to influence cell proliferation, differentiation and inflammation through YAP and TAZ including Glucocorticoids, Epidermal Growth Factor Receptor (EGFR), Insulin-like growth factor-1, WNT, TGF- $\beta$ , Bone Morphogenic Proteins (BMPs) and the cytokines leukemia inhibitory factor (LIF) and Interleukin-6 (IL6) (Alarcon et al., 2009; Tamm et al., 2011; Strassburger et al., 2012; Reddy and Irvine, 2013; Azzolin et al., 2014; Haskins et al., 2014; Park H. W. et al., 2015; Taniguchi



et al., 2015; Sorrentino et al., 2017). The importance of these interactions with Hippo signaling in many cell and tissue types, especially during non-pathological conditions, has yet to be demonstrated. However, a growing body of evidence in multiple tissues supports the suggestion that interactions at multiple levels with the WNT signaling pathway may influence YAP and TAZ activity to alter tissue growth in multiple settings. The interaction between these pathways is complex and likely context-dependent, but can include transcriptional regulation of YAP expression, effects on YAP and TAZ protein stability and localization, and modulation of Hippo pathway target gene expression (Varelas et al., 2010a; Heallen et al., 2011; Azzolin et al., 2012, 2014; Rosenbluh et al., 2012). In addition to WNT-mediated control of Hippo signaling, YAP-TEAD, and TAZ-TEAD may also influence WNT activity through transcriptional regulation of WNT signaling pathway elements (Heallen et al., 2011).

## HIPPO SIGNALING AND MECHANO-TRANSDUCTION

In addition to soluble molecules, regulation of physiological function in the local microenvironment is highly dependent on changes in mechanical properties derived from alterations in cell shape, fluid shear-stress or cell-cell contact (Finch-Edmondson and Sudol, 2016). Recent experimental evidence highlights a role for YAP and TAZ as critical effectors of mechanical signals (Figure 3). The first findings linking changes in physical dynamics to Hippo signaling came from studies showing that as cells divide and make contact with neighboring cells, YAP phosphorylation increased and was re-localized to the cytosol of the cell (Zhao et al., 2007). Growing evidence supports the conclusion that in addition, and in isolation of cell-cell contact, changes in mechanical properties of the ECM, cell geometry and polymerisation of the F-actin cytoskeleton are essential inputs



that influence the activity of YAP and TAZ (Dupont et al., 2011; Wada et al., 2011; Aragona et al., 2013; Bertrand et al., 2014).

When grown in isolation on stiff substrates, or under conditions where cells can spread, YAP and TAZ are active and localize to the nucleus (Dupont et al., 2011; Wada et al., 2011; Aragona et al., 2013). However, in soft matrices, or when cultured in small surface areas so that they are compressed, YAP and TAZ are inhibited and re-localize to the cytosol (Dupont et al., 2011; Aragona et al., 2013). These effects were proposed to be mediated by Hippo pathway dependent- and independent-mechanisms; however, as in the case of soluble factors, redundancy with kinases such as NDR1/2 was not tested, and so the precise mechanism of action remains unclear. Despite this, studies assessing the mechanisms downstream of mechanical cues collectively demonstrate that mechanical stimuli influence YAP and TAZ activity through alterations in F-actin polymerisation, and by changes in the activity of the small GTPases RHOA and RAC1 (Dupont et al., 2011; Fernandez et al., 2011; Sansores-Garcia et al., 2011; Aragona et al., 2013; Plouffe et al., 2016). Disruption of the F-actin-RHOA/RAC1-YAP/TAZ pathway has been implicated in the specification of cell identity during development, in the activation and differentiation

of various cells and in the maintenance of vertebrate three-dimensional tissue structure and tension, as well as in response to fluid flow stresses to influence the stability of blood vessels during development and the formation atherosclerotic plaques in  $APOE^{-/-}$  mice, demonstrating the significance of this mode of regulation to a number of cellular processes and disease-relevant settings (Sansores-Garcia et al., 2011; Calvo et al., 2013; Liu et al., 2015; Porazinski et al., 2015; Wang K. C. et al., 2016; Wang L. et al., 2016; Nakajima et al., 2017; Totaro et al., 2017).

The critical pathways that are required to relay external mechanical forces in the extracellular matrix to influence Hippo signaling in mammalian tissues have only recently been identified. Studies in liver and heart cells suggest that Agrin, a proteoglycan that regulates formation and maintenance of the neuromuscular junction, and the dystroglycoprotein-complex (DGC), a multiprotein complex that links the extra-cellular matrix and actin cytoskeleton, may both influence Hippo signaling in mammalian tissues (Bassat et al., 2017; Chakraborty et al., 2017; Morikawa et al., 2017). While Agrin, via Integrin/PAK1 signaling, regulates YAP activity through the core Hippo kinases (Chakraborty et al., 2017), the DGC

appears to limit YAP activity by physical interaction of phosphorylated YAP through the DGC component Dag1 (Morikawa et al., 2017). Recent evidence in cardiomyocytes suggests that Agrin-dependent activation of YAP is also mediated by disruption of the DGC complex in settings of cardiomyocyte regeneration providing further evidence for this axis as a regulator of YAP activity (Bassat et al., 2017). Given the critical role of Agrin-Integrin and DGC protein complexes during development, and in neurodegenerative and neuromuscular diseases, further study of these mechanistic links may offer exciting strategies that can be exploited to modulate YAP and TAZ activity in a range of disease states.

## CELLULAR METABOLISM AND THE HIPPO PATHWAY

Integration of tissue-specific, and whole-body, metabolic signaling responses is essential to ensure homeostasis under basal conditions. Furthermore, the dysregulation of metabolic pathways in many tissues from lipid metabolism toward anaerobic glycolysis (the Warburg effect) is an established event in the development and progression of many cancers, and in the activation of stem cell populations (Agathocleous and Harris, 2013; Zhou et al., 2017). Recent studies highlight a number of essential metabolic pathways that appear to function via modulation of YAP and TAZ (Figure 4).

The first link between the Hippo pathway and cellular metabolism was the demonstration that the inhibition of the mevalonate/HMG-CoA reductase pathway, a critical mediator of cholesterol and isoprenoids production, was sufficient to promote cytoplasmic retention, and to impair the transcriptional activity of YAP and TAZ in breast cancer cells (Sorrentino et al., 2014; Wang et al., 2014). The mevalonate pathway acts to enhance YAP and TAZ activity via geranylgeranyl pyrophosphate (GGPP) and RHOA suggesting that the small GTPases RHOA and RAC1 may form common intercellular mediators of YAP/TAZ function in response to metabolic, hormonal and mechanical stimuli (Sorrentino et al., 2014; Wang et al., 2014). The significance of these findings in non-cancerous cell types is less clear; yet inhibition of HMG-CoA reductase by statin exposure in developing mouse embryos prevents blastocyst formation and impairs YAP activity highlighting a role for this axis during early mammalian development (Alarcon and Marikawa, 2016).

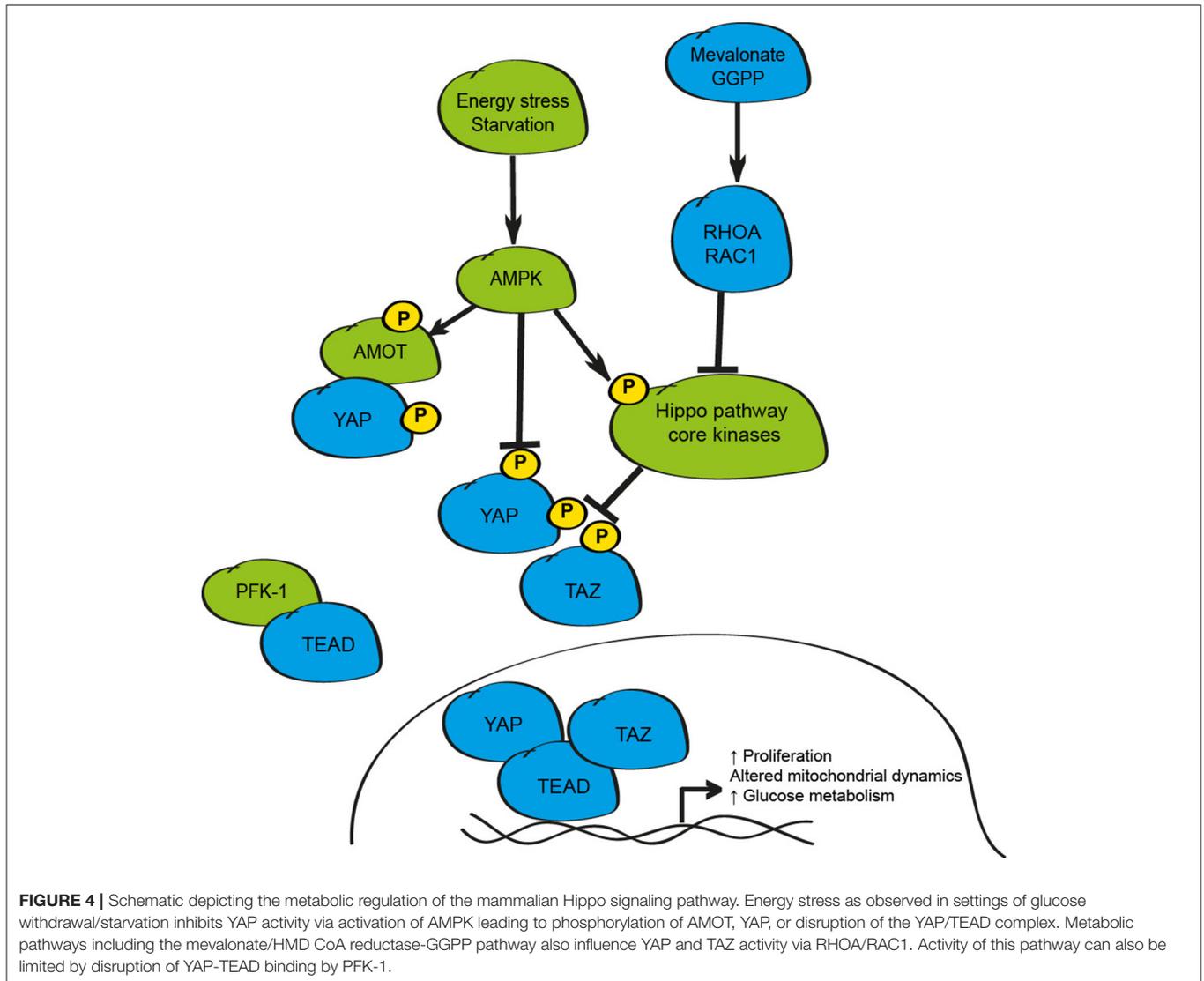
The activity of YAP and TAZ can also be impacted by the cellular concentrations of glucose and glucose-responsive pathways (Adler et al., 2013; DeRan et al., 2014; Enzo et al., 2015; Mo et al., 2015; Wang et al., 2015). Energy stress, as induced by culturing cells in glucose-free conditions, results in inhibition of YAP activity in mouse hepatocytes *in vivo* as demonstrated by starvation/re-feeding experiments (Wang et al., 2015). While these studies collectively demonstrate that glucose withdrawal inhibits YAP activity, the underlying mechanisms reported differ between studies and include AMPK1-mediated phosphorylation

of AMOTL1, direct phosphorylation of YAP on multiple serine residues by AMPK1, disruption of the YAP-TEAD complex by AMPK1 phosphorylation at Ser94, and physical interaction between TEADs and phosphofructokinase-1 (PFK-1), a rate-limiting enzyme in the glycolysis pathway (Adler et al., 2013; DeRan et al., 2014; Enzo et al., 2015; Mo et al., 2015; Wang et al., 2015).

In addition to being responsive to changes in cellular metabolism, the Hippo pathway appears to control key metabolic components to influence cell proliferation under certain conditions including transcriptional control of glucose transporters, gluconeogenic gene expression, amino acid transporters, and elements of the glutamine metabolism pathways (Hansen et al., 2015; Wang et al., 2015; Cox et al., 2016; Park Y. Y. et al., 2016; Hu et al., 2017). Further to the effect of these metabolism-induced changes on cell division, the manipulation of YAP and TAZ can also influence mitochondrial dynamics, through enhancing the rates of mitochondrial fusion and fission, by transcriptional up-regulation of genes such as *Opa-1* and *Mfn2*, critical elements controlling these vital cellular processes (Nagaraj et al., 2012; von Eyss et al., 2015). These findings highlight the interplay between Hippo signaling and multiple metabolic processes and demonstrate further mechanisms of growth control by this pathway that could be exploited in settings such as cancer, metabolic disease or regenerative medicine.

## CONCLUDING REMARKS

Here, we summarize evidence supporting an essential role for the Hippo signaling pathway as a critical element integrating hormonal, mechanical and metabolic stimuli during the growth and differentiation of mammalian tissues during development, in the post-natal environment, and in the progression of specific disease states. Together, these findings suggest that targeting the Hippo pathway may be beneficial in particular clinical settings, with inhibition of the pro-proliferative/anti-apoptotic function of YAP and TAZ during the growth of cancer cells of particular interest. Potential approaches that could be used to achieve this goal include inhibitors of the mevalonate pathway (Statins, Bisphosphonates and Geranylgeranyl-transferase inhibitors), RHO GTPases (ROCK inhibitors), or small molecules that disrupt the interaction between YAP and TEAD, such as Verteporfin; many of which are used in clinical practice for other conditions (Dupont et al., 2011; Liu-Chittenden et al., 2012; Sorrentino et al., 2014; Wang et al., 2014). However, studies using these agents have typically limited their analyses to a single cell/tissue type and so the consequences on whole-body physiology are not clear. A greater understanding of this will be critical for the successful development of therapeutics targeting YAP and TAZ; particularly in light of the detrimental effects of inhibiting basal levels of YAP activity in tissues such as skeletal muscle and skin (Schlegelmilch et al., 2011; Watt et al., 2015). Targeting elements of the Hippo pathway using lower effective doses of agents, but as part of a combinatorial therapeutic approach, may therefore be an alternative means to



inhibit the Hippo pathway while limiting potential detrimental consequences on other tissues. Such approaches appear to be effective in a number of cell types (Lin et al., 2015; Li et al., 2016; Zhao et al., 2017).

A major limitation of studies investigating the function of the Hippo pathway is the use of genetic manipulation whereby pathway members are exogenously over-expressed or completely deleted from a target tissue; yet complete deletion of pathway members in healthy or diseased tissues is not commonly observed (the exception being the *NF2* gene in select cancers; Harvey et al., 2013). Consequently, assessing the function of Hippo pathway members in specific tissues at physiological and appropriate patho-physiological levels using more elegant approaches such as genome editing with CRISPR/CAS9, where the introduction of point-mutations, protein domain deletions, and activation of genes at the endogenous locus is possible may reveal more relevant information about the role of this pathway in the progression of disease pathologies.

While the significance of the Hippo pathway in many aspects of mammalian biology is becoming increasingly clear, evidence of a role for the Hippo pathway in cellular processes such as the response to hypoxia, autophagy and the unfolded protein response is limited to various tumor cell types, tissue culture models, or specific tissues (Liang et al., 2014; Yan et al., 2014; Wu et al., 2015). Future work will be required to explore how significant alterations in the activity of the Hippo pathway are to these critical cellular functions in non-cancerous tissues if we are to understand the significance of the Hippo pathway in these processes.

In summary, the published literature to date implicates the Hippo signaling pathway as a mediator of tissue growth and function in response to diverse physiological cues. While our understanding of the requirement for the Hippo pathway in mammals has expanded in recent years, the consequence of altered Hippo signaling in specific tissues on whole-body physiology, and the effect of such changes upon disease

progression remains unexplored. Future studies aimed at understanding the integrative nature of the Hippo pathway on human physiology will be required to reveal the extent that this pathway influences biological function and the implications of targeting this pathway for clinical benefit.

## AUTHOR CONTRIBUTIONS

KW, KH, and PG wrote and edited the manuscript.

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**Conflict of Interest Statement:** The handling Editor declared a shared affiliation, though no other collaboration, with the authors KW and PG. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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