

Regulation and mechanism of YAP/TAZ in the mechanical microenvironment of stem cells (Review)

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Abstract. Stem cells receive cues from their physical and mechanical microenvironment via mechanosensing and mechanotransduction. These cues affect proliferation, self-renewal and differentiation into specific cell fates. A growing body of evidence suggests that yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) mechanotransduction is key for driving stem cell behavior and regeneration via the Hippo and other signaling pathways. YAP/TAZ receive a range of physical cues, including extracellular matrix stiffness, cell geometry, flow shear stress and mechanical forces in the cytoskeleton, and translate them into cell-specific transcriptional programs. However, the mechanism by which mechanical signals regulate YAP/TAZ activity in stem cells is not fully understood. The present review summarizes the current knowledge of the mechanisms involved in YAP/TAZ regulation on the physical and mechanical microenvironment, as well as its potential effects on stem cell differentiation.

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1. Introduction

Stem cells are a group of progenitor cells characterized by self-renewal and differentiation ability. Within their niche or local microenvironment, stem cells communicate via physical and mechanical cues to regulate cell fate and behavior (1). Early research has focused on biochemical signals produced by chemical or solution media when discussing the molecular signaling mechanisms underlying stem cell self-renewal, growth and differentiation (2). However, it is hypothesized that cells perceive their microenvironment not only through soluble signals but also via physical and mechanical cues, such as extracellular matrix (ECM) stiffness or confined adhesiveness (3). Similar to intrinsic and extrinsic biochemical factors, mechanical cues resulting from both intracellularly generated and externally applied forces have a broad range of effects on stem cell fate. For example, MSCs have the ability to differentiate into neuroblast, chondrocyte, osteoblast, adipocytes and numerous other cell types within matrices, which mimic the stiffness of their native substrate (4-6). Also, the extracellular matrix structure such as nanotopographic structures or fluid shear stress can affect differentiation of stem cells (7,8). Studies have shown that yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) serves an important role in biomechanical and mechanical signaling that affects self-renewal and differentiation of stem cells (3,9). The present review summarizes the current knowledge of the mechanisms involved in YAP/TAZ regulation on the physical and mechanical microenvironment and its potential effects on stem cell differentiation.

2. Regulation of YAP/TAZ in mechanotransduction in stem cells

Stem cells are a paradigm model system in the mechanotransduction field; it has been shown that differentiation of stem cells into distinct cell fates is dictated by the physical features of the cellular microenvironment (10). Numerous studies have shown that YAP/TAZ is a key regulator of mechanical properties of the stem cell microenvironment (11-14). Various biophysical stimuli from external forces, such as cyclic stretching, shear stress and acoustic tweezing, also modulate stem cell fate via YAP/TAZ (15-18).

Flow shear stress. Flow shear stress can be defined as a function of strain rate, which is the frictional force generated by the flow of fluid on a contact surface (19). More specifically, fluid shear stress is defined as stress (i.e., force per unit area) applied by a fluid to the tangential direction of the contact surface. Fluid shear stress serves an important role in the differentiation of embryonic and mesenchymal stem cells (MSCs) (20).

MSCs are mechanically regulated by shear stress generated in tissues by extravascular liquid flow. To date, the regulation of YAP by shear stress has rarely been characterized in the literature. YAP is regulated by fluid shear stress in osteoblasts and stem cells (8,21). Zhong *et al.* (8) found that increased YAP expression levels, triggered by flow shear stress, increased osteogenesis and decreased adipogenesis of MSCs and initiated dedifferentiation of chondrocytes. Furthermore, culturing MSCs on microfluidic chips that mimic interstitial flow shear stress increases YAP and TAZ activity in an Rho-Rho-associated coiled-coil containing protein kinase (ROCK)-dependent manner, enhancing osteogenic and fibrochondrogenic differentiation (8,22). Dupont *et al.* (3) used rigid vs. highly elastic micropillars to assess the effects of cell-generated mechanical force; on the elastic substrate, cytoplasmic localization of YAP/TAZ was markedly increased. Collectively, it has been indicated that YAP/TAZ responds to cytoskeletal tension (3). Wang *et al.* (23) used a parallel flow chamber to perform *in vitro* shear stress experiments and a partial carotid ligation model in apolipoprotein E-deficient mice to perform *in vivo* flow perturbation experiments. They proved that the activation and expression levels of YAP/TAZ were lower in the laminar flow region of the straight segment of thoracic aorta than in the disturbed flow region of the inner curvature of aortic arch (Fig. 1) (23).

ECM stiffness and shape. Each organ of the human body has a specific ECM stiffness. The role of mechanical cues needs to be understood in the context of the multicellular organization that characterizes natural tissue (24,25). The importance of ECM sensing elasticity has been demonstrated in fibroblasts, mesenchymal and epidermal stem cells and other areas of cells (5,26-28). For example, gelatinous polyacrylamide gel has been used as an artificial cell matrix for *in vitro* adherence culture of cells. The cell matrix was induced to take on a different stiffness by adjusting the proportion of chemical components and human epidermal stem cells were cultured in the matrix. The results showed that different levels of stiffness had different effects on the shape of cell growth (5,29). When cells were cultured on a soft matrix, which is similar to brain tissue, they exhibited characteristics of neurons; when cells were cultured on a middle-stiffness matrix, which is similar to muscle tissue, they showed characteristics of myocytes; and when cells were cultured on a hard matrix, which is similar to collagen, they showed characteristics of osteoblastic differentiation (30). Thus, the varying elastic properties of the different tissue types seem to influence tissue regeneration.

Different basal shapes of cell culture have an important effect on cell proliferation and differentiation. *In vitro* cell culture experiments have demonstrated that cell proliferation is fastest in the outer region of the culture dish (31). In round dishes, this area is the outermost circle, while in square dishes the fastest

proliferation occurs in the four corners. There is also research suggesting that the topological terrain of the substrate serves an important role in regulating the stemness of stem cells. Clones formed in a groove and column are relatively flat, whereas clones formed in a hexagonal pattern are more rounded (25,32). Based on these reports, it is hypothesized that ECM shape induces cell geometry and regulates cell fate and behavior. In similar studies, microprinted ECM islands of different sizes were engineered to control the extent of spreading of a single endothelial cell (28,33,34). It was observed that well-spread cells proliferated, whereas cells confined to small adhesive areas did not proliferate and instead underwent apoptosis. It has been proven that this effect was due to changes in cell shape, rather than due to the extent of cell-ECM contact (13).

It has been proposed that cell fate induced by stiff ECM requires YAP/TAZ function and, conversely, cell fate associated with soft ECM requires its inactivation (Fig. 1) (35-37). The activity of YAP/TAZ in cells grown on stiff hydrogels is comparable to that of cells grown on plastics, whereas growing cells on soft matrices inhibits YAP/TAZ activity to levels comparable with that of short interfering RNA-mediated YAP/TAZ depletion (3).

Internal force of cytoskeleton. The cytoskeleton, within the cytoplasm, is a fundamental structure for mediating force transmission (38,39). It contains filamentous actin, intermediate filaments and microtubules that transmit force over long distances in the cell. Various types of external force applied to the cell can be transformed into internal force via the cytoskeleton. Therefore, force transmission contains both an external component and an internal component and is completed via the cytoskeleton (40). Focal adhesions, a type of multiprotein clustered from integrins, provide a direct physical link between the ECM and cytoskeletal adaptors, consequently connecting the ECM with the actin cytoskeleton (24). The organization of the cytoskeleton sustains cell shape; however, the dynamics of actin microfilaments are the focus of much research on mechanotransduction (41,42).

Experiments using *Drosophila* have revealed that increased actin stress fiber assembly correlates with YAP nuclear localization and overgrowth of the wing disc (43,44). However, it is unclear by which mechanisms cytoskeletal tension regulates YAP/TAZ, although the nucleus may serve a mechanotransductive role in the regulation of YAP (45). The focal adhesions and stress fibers that are generated on stiff substrates transduce mechanical forces to the nucleus, leading to nuclear flattening. This increases YAP nuclear import by decreasing mechanical restriction in nuclear pores (46,47).

Cell geometry. A number of stem cells differentiate into distinct lineages depending on local cues present in their environment. Previous studies have suggested that changes in cell shape regulate the degree of development of lineage-specific markers, or differentiation, in pre-committed preadipocytes or preosteoblasts (10,48). Different basal shapes of cell culture have an important effect on cell proliferation and differentiation. Average focal-adhesion stress per cell increases with micropost rigidity for both human MSCs and umbilical vein endothelial cells but to different magnitudes in each cell type (49,50). These differences in focal adhesion stress

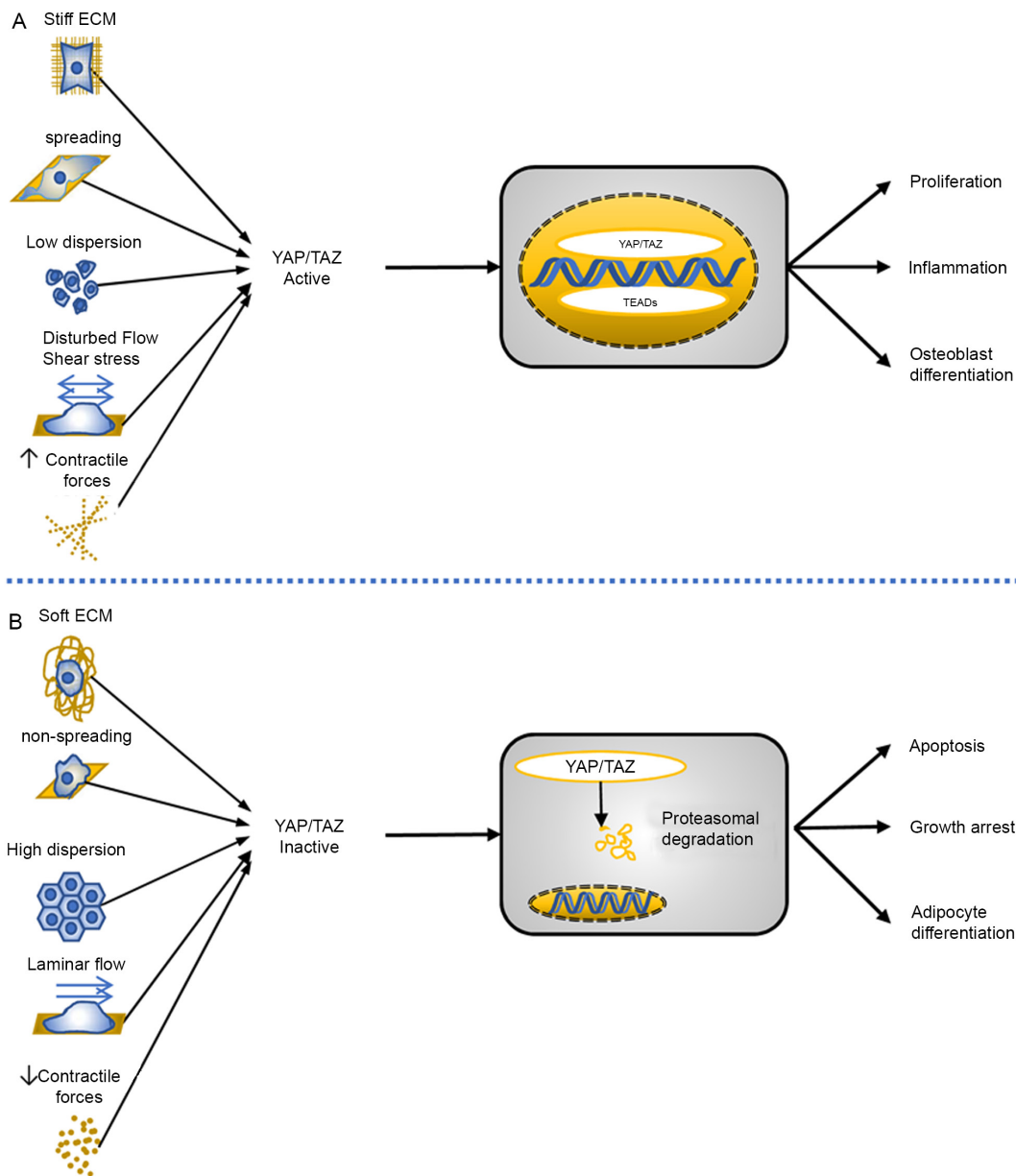


Figure 1. (A) Activation of YAP/TAZ by high levels of mechanical cues; (B) Inactivation of YAP/TAZ by low levels of mechanical cues. Different mechanical inputs regulate YAP activity. When YAP is active, it promotes cell proliferation and osteoblast differentiation and inflammation. When YAP is inactive, it improves proteasomal degradation and contributes to apoptosis and growth arrest and adipocyte differentiation. YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; ECM, extracellular matrix; TEAD, the transcriptional enhanced associate domain.

between cell types suggest that there may be multiple ways for cells to mechanically adapt to their environment (49).

Cells seeded on stiff hydrogels or large islands show increased cell spreading and greater cell-ECM contact. YAP/TAZ was localized in the nucleus when cells were seeded on micropillars, indicating that YAP/TAZ are primarily regulated by cell spreading imposed by the ECM (51,52). Morphometric analysis of cell populations revealed a strong correlation between focal adhesions and cell spreading, regardless of micropost rigidity (49). These findings indicate how ECM is able to mediate its effects on stem cell morphology and stemness, and show the role of mechanotransduction and stiffness on cell fate determination (53,54).

Changes in shape and morphological characteristics occur during and after cell differentiation. Previous studies

have proven that there is an important connection between cell morphology and proliferation, survival and differentiation (55,56). Cell shape may impact the state transition of cell from life to death or between proliferation and quiescence (57).

Fibronectin-coated micropillars have been used to test whether YAP/TAZ is regulated by cell spreading independently of the total amount of ECM (3,49). It has been shown that the actual area available for cell-ECM interaction is only ~10% of their projected area and YAP/TAZ remained nuclear on micropillars, indicating that YAP/TAZ is primarily regulated by cell spreading imposed by the ECM (Fig. 1) (3,51). Similarly, Wada *et al* (58) proposed a model by using a micro-domain culture system in which the cell area of a single cell was defined, while cell-cell contact was prevented to show that cell morphology alone can modulate YAP activity.

The geometrical morphology and area of cell spread are associated with proliferation, differentiation and migration of bone marrow MSCs. When the width of the cells is narrow, the proliferation of bone marrow MSCs is inhibited and cell migration is enhanced when the cell area is limited (59-61).

3. Mechanism of YAP/TAZ regulation

A growing body of research has revealed that YAP/TAZ serves a central role in delivering information of mechanical environments surrounding cells to the nucleus transcriptional machinery via Hippo and non-Hippo mechanisms; this is an underlying principle for YAP/TAZ-mediated regulation of biological functions (9,62,63). YAP also interacts with components of other signaling pathways, which serve a role in mechanotransduction (64-66). However, the focus of most research has been the mechanism by which mechanical signals regulate YAP/TAZ activity.

Classic Hippo signaling pathway and YAP/TAZ regulation. The Hippo pathway serves a key role in the regulation of tissue homeostasis, abnormalities of which are associated with human cancer. Research has provided an overview of the functional importance of numerous Hippo pathway components. It has been demonstrated that neurofibromin 2 and Ras Homolog Family Member A (RhoA) are important regulators of YAP/TAZ, and TAO kinase 1/3 are direct kinases for large tumor suppressor kinase (LATS) 1/2 (67). Phosphorylation activates LATS1/2, resulting in its activity as a kinase of YAP/TAZ (68). Hippo core components, as well as YAP and TAZ activity, are regulated by a variety of mechanisms (Fig. 2) (69-71). There is a requirement for balanced amounts of YAP/TAZ in neural stem and progenitor cells, which are involved in controlling the correct expansion of the progenitor pool and timely differentiation; this may be ensured by a crosstalk system between CDK5 regulatory subunit-associated protein 2 and the Hippo pathway (72). YAP/TAZ transfers into the nucleus and participates in proliferation with the transcriptional enhanced associate domain (TEADs) following dephosphorylation by phosphatases, including protein phosphatase 1A and 2A (73-75).

Mechanical signals act on the Rho protein to promote the effect of filamentous (F-)actin, which resists LATS1/2. LATS1/2 has a YAP/TAZ complex that inhibits phosphorylation of the Snail/Slug-YAP/TAZ complex in the nucleus and cytoplasm, while phosphorylated YAP/TAZ in the cytoplasm promotes the Snail-YAP/TAZ complex formation. Therefore, mechanical signaling controls the function of YAP/TAZ via the classic Hippo pathway (Fig. 2).

Ras-related protein 2 (RAP2) GTPase has been identified as a key intracellular mechanotransducer that relays extracellular mechanical signals for transcriptional regulation via the Hippo pathway (76). ECM stiffness acts via RAP2 and its downstream Hippo kinase cascade to modulate a YAP/TAZ-mediated mechanoresponsive transcriptome. The identification of this signaling axis provides mechanistic insights into how cellular machinery is driven by mechanical stimuli (Fig. 3). In addition, another study validated the role of AT-rich interaction domain (ARID)1A-containing SWI/sucrose non-fermentable (SWI/SNF) complex as a

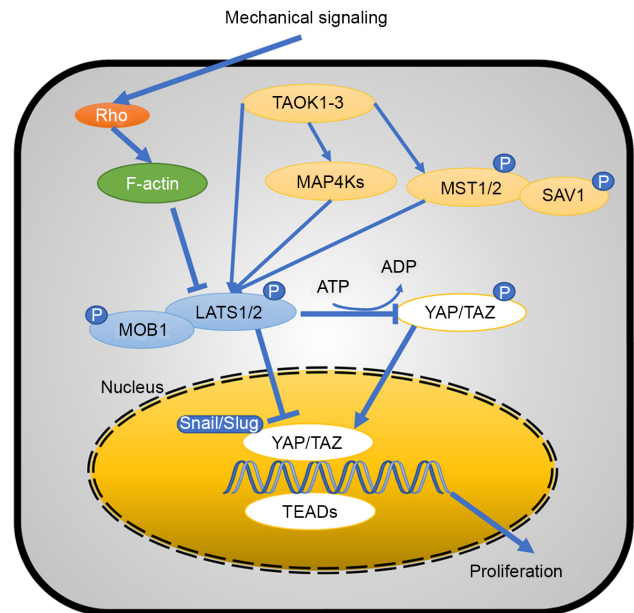


Figure 2. YAP/TAZ in Hippo pathway. The Hippo pathway serves an important role in the regulation of tissue homeostasis. Hippo core components, as well as YAP and TAZ activity, are regulated by a variety of mechanisms. YAP/TAZ transfers into the nucleus and participates in proliferation with TEADs following dephosphorylation. YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif; TEAD, the transcriptional enhanced associate domain; F-actin, filamentous actin; TAOK, TAO kinase; SAV, Salvador family WW-domain-containing protein; LATS, large tumor suppressor kinase; MOB1, MOB kinase activator 1; P, phosphorylated; MST, macrophage stimulating.

mechanoregulated inhibitor of YAP/TAZ *in vivo* (77). In environments with high levels of mechanical stress, nuclear F-actin binds to ARID1A-SWI/SNF, thereby relieving YAP/TAZ from SWI/SNF inhibition in favor of an association between TEAD and YAP/TAZ.

ROCK signaling pathway. Tissue stiffness can be a predictor of tumor development and carries a high risk of pathogenesis of malignant transformation (78,79); to the best of our knowledge, however, the association between tissue rigidity and tumor pathogenesis has not been fully characterized. The situation is similar for stem cell self-renewal and regulation of differentiation (1). Research has shown that tumor rigidity reflects an increase in stromal stiffness and tumor cell tension (26). Rho GTPase-dependent ROCK activation upregulates cytoskeletal tension by triggering the assembly of actomyosin networks (80). RhoA-mediated adipogenesis depends on a circular or expanded shape, whereas in of RhoA-mediated osteogenesis, RhoA effector ROCK constitutive activation induces osteogenesis independent of cell shape (10). This RhoA-ROCK commitment signal requires actin-myosin to produce tension. Studies have shown that the commitment of stem cells to various lineages is modulated by different physical cues embodied by cytoskeletal tension, cell shape and RhoA signaling (Fig. 4) (10,81,82).

It has been demonstrated that membrane type 1 (MT1)-MMP directs skeletal stem cell lineage commitment and differentiation by controlling ECM remodeling, in turn promoting cytoskeletal tension via the integrin-RhoA-ROCK

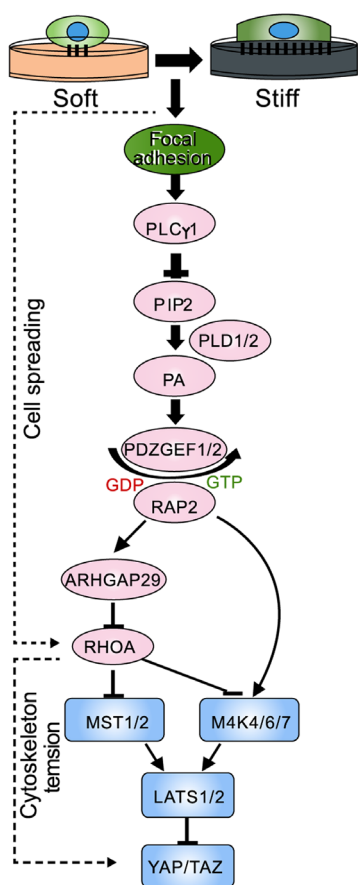


Figure 3. Signaling pathway by which stiffness regulates YAP/TAZ. RAP2 is a key intracellular mechanotransducer that relays extracellular mechanical signals for transcriptional regulation through the Hippo pathway. Extracellular matrix stiffness acts via RAP2 and its downstream Hippo kinase cascade to modulate a YAP/TAZ-mediated mechanoresponsive transcriptome. YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif; RAP2, Ras-related protein 2; PL, phospholipase; ARHGAP29, rho GTPase activating protein 29; LATS, large tumor suppressor kinase, PIP2, Phosphatidylinositol 4,5-bisphosphate; PA, phosphatidic acid; PDZGEF1/2, PDZ-guanine nucleotide exchange factor 1/2; MST1/2, macrophage stimulating 1/2; M4K4/6/7 (MAP4K4, MAP4K6, MAP4K7), Mitogen-activated protein kinase kinase kinase kinase 4/6/7.

pathway, thereby triggering nuclear localization of YAP/TAZ co-transcriptional activators, which activates a program that favors osteogenic differentiation over alternative adipogenic and chondrogenic cell fate (52).

TGF- β signaling pathway. Both TGF- β canonical and non-canonical signaling cascades simultaneously occur via crosstalk of core pathway components and combined utilization of SMAD/non-SMAD transcription factors (83). Tissue mechanics are translated into the activation or inhibition of transcription factors and their co-activating factors (84). Previous research has investigated the impact of morphological alterations on cellular signaling of TGF β -1 (85,86). From the non-canonical TGF- β signaling pathway, Rho and ROCK activate F-actin and RhoA activates ROCK and mammalian diaphanous (mDia); ROCK activates MCC regulator of Wnt signaling pathway (MCC) and LIM domain kinase (LIMK) (87); LIMK activates Cofilin; and mDia, MCC and Cofilin activate F-actin (88). This is a cascade amplification process (Fig. 5). Canonical TGF β /bone morphogenetic

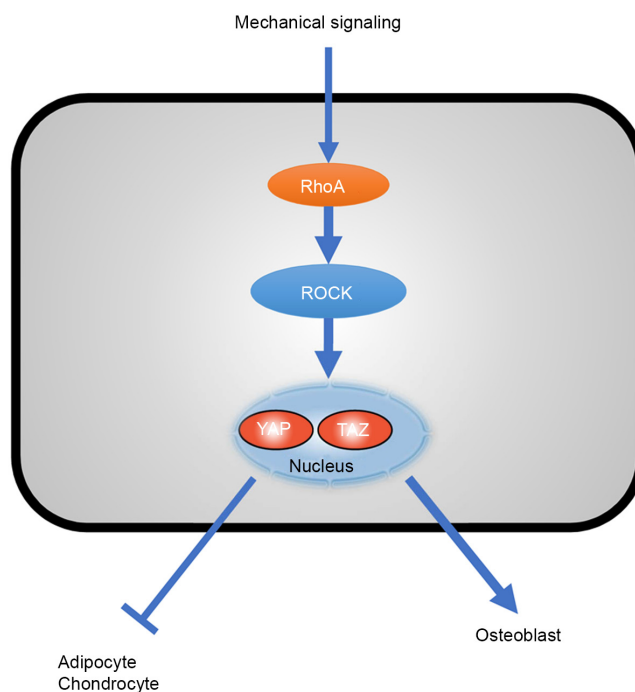


Figure 4. ROCK signaling pathway. Mechanical signaling acts via the integrin-RhoA-ROCK pathway, thereby triggering nuclear localization of the YAP/TAZ co-transcriptional activators, which activates a program that favors osteogenic differentiation over alternative adipogenic and chondrogenic cell fate. YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif; ROCK, Rho-associated coiled-coil containing protein kinase; RhoA, Ras Homolog Family Member A.

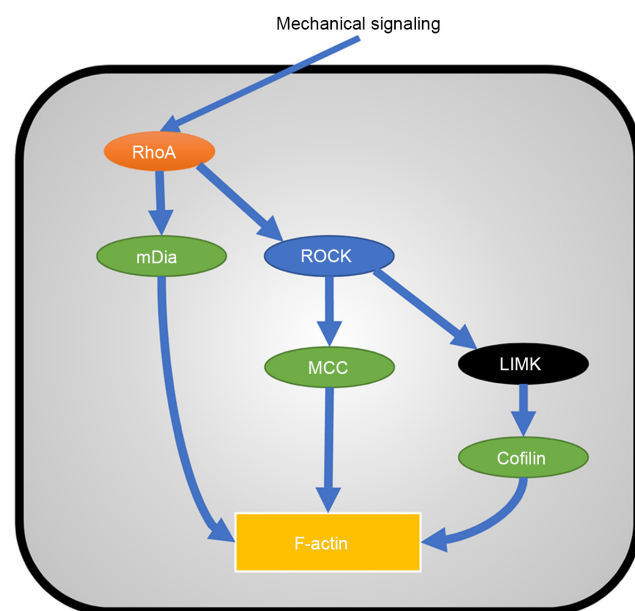


Figure 5. TGF- β signaling pathway. YAP/TAZ are mechanoregulators of TGF- β -SMAD signaling. YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif; ROCK, Rho-associated coiled-coil containing protein kinase; MCC, MCC regulator of Wnt signaling pathway; LIMK, LIM domain kinase; F-actin, filamentous actin; RhoA, Ras Homolog Family Member A; mDia, mammalian diaphanous.

protein (BMP) signaling acts via SMADs and has also been shown to be sensitive to mechanical inputs into the cell (89). It has been confirmed that YAP/TAZ are mechanoregulators

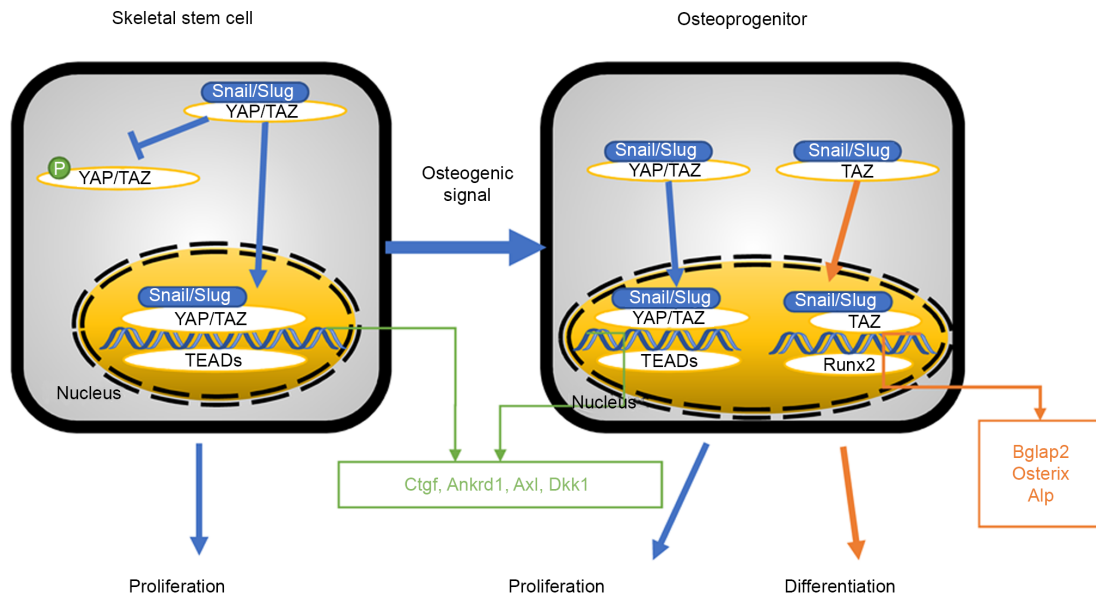


Figure 6. Snail/Slug binding interactions. The Snail/Slug-YAP/TAZ complex promotes YAP/TAZ phosphorylation in the cytoplasm and Snail/Slug-YAP/TAZ-TEAD complex in the nucleus, and induces expression of Ctgf, Ankrd1, Axl, Dkk1, and cell proliferation. YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif; TEAD, the transcriptional enhanced associate domain; Ctgf, connective tissue growth factor; Ankrd1, ankyrin repeat domain 1; Axl, axonin 1; Dkk1, Dickkopf-related protein 1; P, phosphorylated; Bglap2, bone γ -carboxyglutamate protein 2.

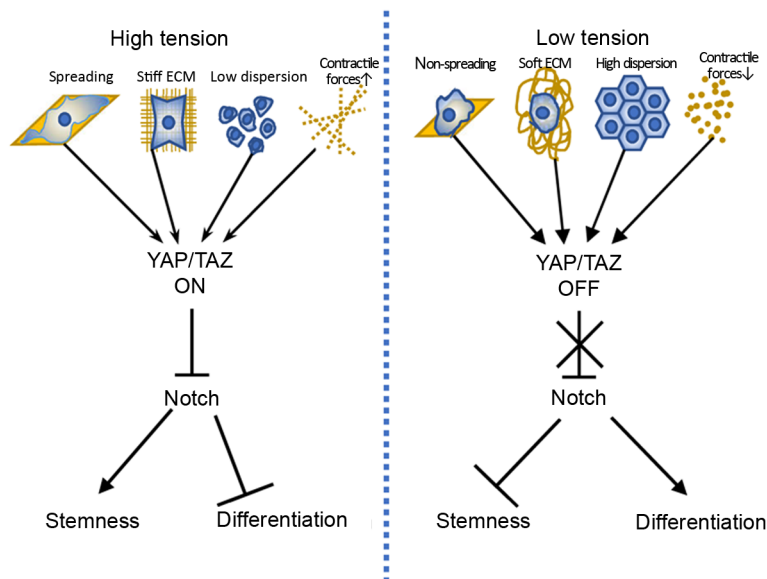


Figure 7. Notch signaling pathway. YAP/TAZ and notch regulation have a synergistic effect with each other to control stem cell preservation vs. differentiation and intercellular communication. YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif.

of TGF- β -SMAD signaling (66). YAP/TAZ interaction with SMAD2/3 serves a key role in SMAD nuclear-cytoplasmic shuttling (90). YAP nuclear exclusion sequesters the SMAD2/3 protein to the cytoplasm and therefore suppresses TGF- β signaling (91,92). YAP binds to activated SMAD1 protein to enhance BMP-induced transcriptional activity (93). In addition, YAP/TAZ functions as an endogenous repressor of SMAD7 expression to modulate TGF- β signaling (94).

Snail/Slug binding interactions. Bone-marrow-derived skeletal stem cell (SSC) self-renewal and function is key to bone development, *in vivo* balance and repair (95). Mechanically,

Snail/segment regulates SSC function by forming a complex with transcription co-activators YAP and TAZ and suppressing Hippo pathway-dependent adjustment of the YAP/TAZ signal cascade. In turn, the Snail/Slug-YAP/TAZ axis activates a series of YAP/TAZ-TEAD/Runx2 downstream targets that control the stability and osteogenesis of SSCs (65). In conclusion, these results indicate that SSCs mobilize the Snail/Slug-YAP/TAZ complex to control stem cell function (65).

The Snail/Slug-YAP/TAZ complex promotes YAP/TAZ phosphorylation in the cytoplasm and Snail/Slug-YAP/TAZ-TEADs complex in the nucleus, thus inducing expression of connective tissue growth factor, ankyrin

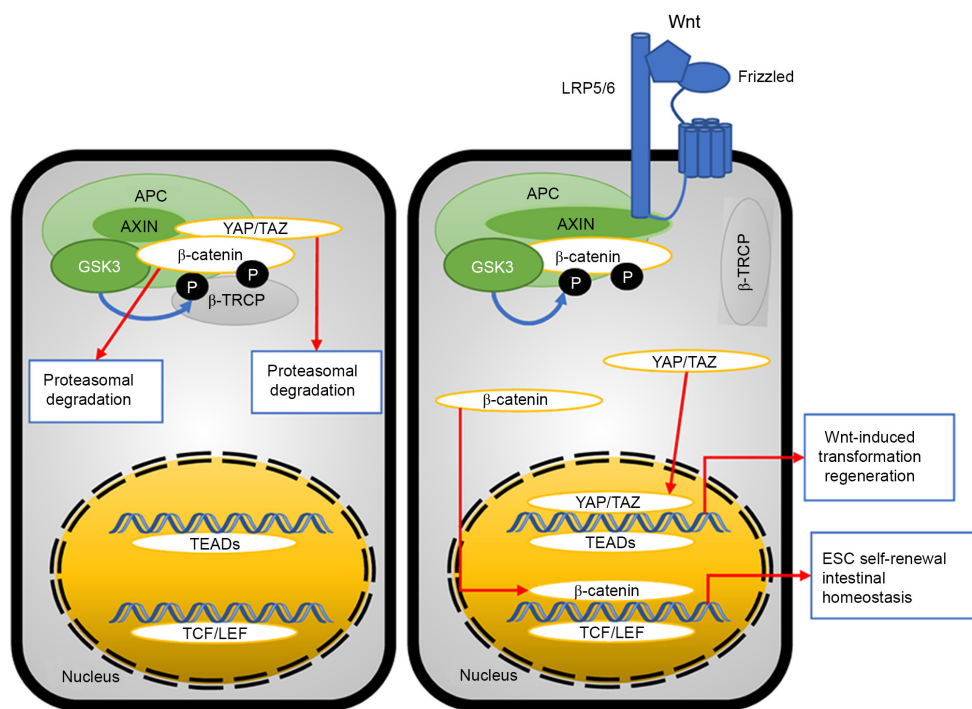


Figure 8. Wnt/ β -catenin pathway. The primary purpose of the YAP/TAZ-associated Wnt/ β pathway is the control action of β -catenin. YAP/TAZ has to be banded with TEADs or β -catenin has to be banded with TCF/LEF in the nucleus to perform their roles. YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif; TEAD, the transcriptional enhanced associate domain; TCF/LEF, transcription factor/lymphoid enhancer binding factor; P, phosphorylated; LRP, LDL receptor-related protein; ESC, embryonic stem cell; β -TRCP, β -transducin repeats-containing proteins; APC, adenomatous polyposis coli.

repeat domain 1, axonin 1 and Dickkopf-related protein 1, as well as cell proliferation (96). This is established in SSCs and osteoprogenitors. In osteoprogenitors, the Snail/Slug-TAZ complex promotes the Snail/Slug-TAZ-Runx2 complex in the nucleus (97), thereby inducing the expression of bone γ -carboxyglutamate protein 2, Osterix and Alp, and inducing differentiation (Fig. 6).

Hedgehog signaling pathway. Functional interactions between Hippo and the Sonic hedgehog (Shh) signaling pathway have been observed in medulloblastoma and neural differentiation (98,99). Shh expression in the regenerating limb bud in *Xenopus* can be decreased under the functional inhibition of YAP (100). Furthermore, the Hedgehog pathway acts upstream of the Hippo pathway in regulating follicle stem cell maintenance in the *Drosophila* ovary, in which the Hedgehog pathway regulates Yorkie activity via a post-translational mechanism (101). It has been observed that in non-alcoholic steatohepatitis-associated liver injury and inflammation, injured hepatocytes release Shh ligands, which promotes the YAP-induced accumulation of reactive-appearing ductular cells (102). However, in healthy liver, the activation of YAP does not result in its growth (103). YAP/TAZ inhibition of smooth muscle cell differentiation is mediated by the Hedgehog pathway, but signal transduction in mouse embryonic pluripotent mesenchymal cells is not (104,105). This suggests a working interaction between YAP and Shh signal transduction.

Notch signaling pathway. It has been reported that following loss of cell attachment to the basement membrane, epidermis

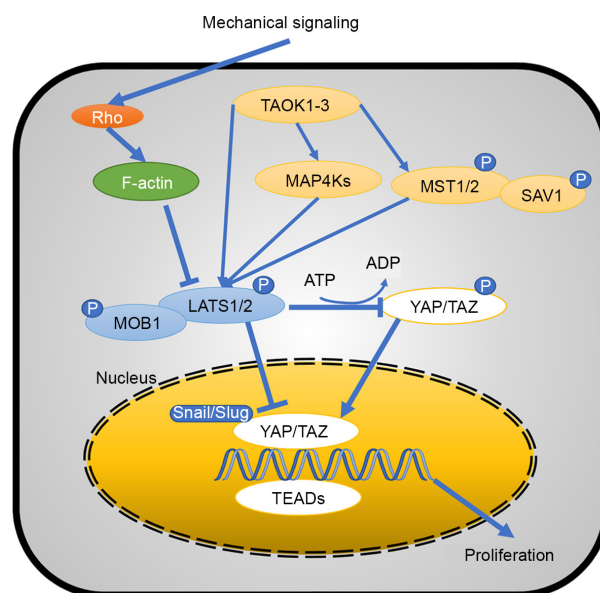


Figure 9. YAP and TAZ mechanotransduction in stem cell biology. A variety of mechanisms of YAP/TAZ regulation via the Hippo pathway and cross-talk with other signaling pathways have been identified. YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif; F-actin, filamentous actin; TAOK, TAO kinase; SAV, Salvador family WW-domain-containing protein; LATS, large tumor suppressor kinase; MOB, MOB kinase activator; TEAD, the transcriptional enhanced associate domain; MAP4K4, Mitogen-activated protein kinase kinase kinase 4; MST1/2, macrophage stimulating 1/2.

cells begin a terminal differentiation program until they fall off from the tissue form surface (106-109). As YAP/TAZ

serves an important role in organ size control during the period of embryonic development (44,110-114) and the notch signaling pathway is core in the paradigm of the epidermis, it is hypothesized that YAP/TAZ and notch regulation have a synergistic effect with each other to control stem cell preservation vs. differentiation and intercellular communication (Fig. 7) (109). This was also confirmed by Totaro *et al.* (109), who demonstrated that notch was downstream of YAP/TAZ and that inhibition of YAP/TAZ preserved the undifferentiated state of human epidermal stem cells, although the specific mechanism remains unclear.

Wnt/ β -catenin pathway. YAP/TAZ participates in the Wnt/ β -catenin pathway, which is involved in cell proliferation, tumorigenesis, regeneration and stem cell expansion (115-117). It has been confirmed that the primary purpose of the YAP/TAZ-associated Wnt/ β pathway is control of β -catenin (118,119). In cells lacking the Wnt signal, YAP and TAZ are sequestered in the β -catenin destruction complex and they play an essential role for phospho- β -catenin degradation by recruiting β -transducin repeats-containing proteins (β -TRCP) (118). As a result, there is no reason that YAP/TAZ has to be banded with TEADs or β -catenin has to be banded with TCF/LEF in the nucleus to perform their respective roles. (Fig. 8). In cells possessing the Wnt signal, β -TRCP is released, as well as β -catenin and YAP/TAZ; YAP/TAZ and β -catenin can transfer into the nucleus to form YAP/TAZ-TEAD and β -catenin-TCF/LEF complexes, resulting in Wnt-induced transformation regeneration and ESC self-renewal (117,120). In addition, YAP/TAZ is the key downstream effector of alternative Wnt signaling to induce cell migration and osteogenic differentiation, as well as negative regulation of canonical Wnt/ β -catenin signaling (119). The functional interactions between Wnt activation and YAP localization have also been demonstrated in maintaining undifferentiated mouse ESCs (64,121). Cytoplasmic YAP/TAZ can sequester β -catenin, resulting in the loss of self-renewal ability and differentiation activation of ESCs (121).

JNK pathway. The JNK pathway, one of the major signaling cassettes of the MAPK signaling pathway, serves an important role in cytoskeletal modulation, apoptosis and cell proliferation (122-124). JNK is a stress-activated kinase, which can be activated by stretch-induced actin stress (123,125). LATS activity can be decreased by cyclic stretch stress due to increased LIM domain-containing 1-LATS1 banding through activation of JNK, consequently, leading to elevated YAP activity (126). In addition, YAP/TAZ activation induced by disturbed flow shear stress can promote inflammation and atherogenesis by enhancing JNK activity (127).

4. Conclusion

A variety of mechanisms controlling YAP/TAZ regulation have been described (Fig. 9). With research on structural and functional regulation of stem cells, the mechanical transduction mechanisms of response to stress have gained recognition, but there are still several unknown details. For example, YAP/TAZ has been identified in the mechanical mechanics micro-environment response (3,62), but the specific details of

the mechanism have yet to be studied. Therefore, further study of YAP/TAZ regulation is required to increase understanding of the role of force in the pathogenesis of certain diseases and the role of trauma repair processes in mediating these mechanisms, which may lead to novel effective treatment strategies (128,129). This also applies to tissue engineering, gene therapy, stem cell regeneration medicine and space and aerospace medicine research.

Future research will investigate the mechanisms by which YAP/TAZ modulates cell mechanics to enable cell function and the role of YAP/TAZ in ECM shape-induced stem cell function and shape/geometry.

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Authors' contributions

YL and WZ contributed to the conception of the review, wrote the manuscript, performed the literature search and prepared the original draft. JW performed the literature search and constructed the figures. All the authors read and approved the final manuscript. Data sharing is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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