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Review Article

Role of YAP/TAZ in bone diseases: A transductor from mechanics to biology

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ABSTRACT

Wolff's Law and the Mechanostat Theory elucidate how bone tissues detect and convert mechanical stimuli into biological signals, crucial for maintaining bone equilibrium. Abnormal mechanics can lead to diseases such as osteoporosis, osteoarthritis, and nonunion fractures. However, the detailed molecular mechanisms by which mechanical cues are transformed into biological responses in bone remain underexplored. Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), key regulators of bone homeostasis, are instrumental in this process. Emerging research highlights bone cells' ability to sense various mechanical stimuli and relay these signals intracellularly. YAP/TAZ are central in receiving these mechanical cues and converting them into signals that influence bone cell behavior. Abnormal YAP/TAZ activity is linked to several bone pathologies, positioning these proteins as promising targets for new treatments. Thus, this review aims to provide an in-depth examination of YAP/TAZ's critical role in the interpretation of mechanical stimuli to biological signals, with a special emphasis on their involvement in bone cell mechanosensing, mechanotransduction, and mechanoresponse.

The translational potential of this article: Clinically, appropriate stress stimulation promotes fracture healing, while bed rest can lead to disuse osteoporosis and excessive stress can cause osteoarthritis or bone spurs. Recent advancements in the understanding of YAP/TAZ-mediated mechanobiological signal transduction in bone diseases have been significant, yet many aspects remain unknown. This systematic review summarizes current research progress, identifies unaddressed areas, and highlights potential future research directions. Advancements in this field facilitate a deeper understanding of the molecular mechanisms underlying bone mechanics regulation and underscore the potential of YAP/TAZ as therapeutic targets for bone diseases such as fractures, osteoporosis, and osteoarthritis.

1. Introduction

In 1892, Julius Wolff, a German surgeon, posited that bone adapts to the mechanical loads under which it is placed, growing denser in areas of high pressure and resorbing in areas of low pressure [1]. This adaptive response of bones to mechanical stress is known as Wolff's Law,which suggests that activities like exercise can strengthen bones, whereas inactivity can lead to bone density loss [2–4]. In 1987, Harold Frost expanded on this by introducing the mechanostat theory, suggesting bones sense mechanical stimuli and convert them into signals for remodeling, the underlying molecular and cellular mechanisms remain mostly unknown [5]. The Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), central to the Hippo signaling pathway [6], have emerged as potential mediators of Wolff's Law and the bone homeostasis theory.

YAP and TAZ share significant homology featuring similar yet distinct structural components [7,8]. These include a central WW domain, a conserved C-terminal sequence, and a 14-3-3 binding motif within the conserved N-terminal sequence. Notably, human YAP and TAZ possess one WW domain, while the mouse YAP variant contains

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two, and TAZ maintains a single domain. Unique to YAP are an SH3-binding motif and a proline-rich region, elements not found in TAZ (9). Despite their structural similarities, the distinct features of YAP and TAZ contribute to their functional diversity. Both proteins interact with transcription factors through their WW domain, influencing the activity of various regulatory proteins such as RUNX2, c-Jun, and P73α, among others [9,10].

Moreover, YAP/TAZ are phosphorylated to be retained in the cytoplasm and to prevent them from entering the nucleus [11,12]. However, phosphorylated YAP/TAZ also engage in multiple signaling pathways including the Hippo [13,14], Wnt [15], and NF-κB pathways [16,17], which are crucial for processes like proliferation [18,19], apoptosis [20,21], stem cell renewal [22,23], differentiation [24], and response to mechanical stress.

YAP/TAZ's unique structures and active roles enable their interaction with multiple signaling pathways. Within the Hippo pathway, activation leads to the phosphorylation of YAP/TAZ by MST1/2 and LATS1/2, resulting in their retention in the cytoplasm. When deactivated, YAP/TAZ migrate into the nucleus and interact with TEAD transcription factors to execute their biological roles [25]. They also participate in canonical [26,27] and alternative [28] Wnt signaling influential in osteogenesis and play roles in NF-κB signaling relevant to osteoporosis [16] and osteoarthritis [17]. Additionally, they engage with MAPK signaling, and are vital in pathways driven by growth factors like TGFβ [29], BMPs [30], and EGFR [31], integrating signals from metabolic regulators, hormones, and various G-protein-coupled receptors (GPCRs) [32–34].

A critical aspect of YAP/TAZ function lies in their capacity to sense and respond to biomechanical signals, integrating these cues into cellular signaling networks. This process, known as mechanotransduction [35,36], involves the translation of external mechanical stimuli into intracellular biological responses. Specific pathways transmit mechanical signals to YAP/TAZ, which then modulate these cues into downstream signaling cascades. This modulation influences cellular activities, including proliferation, differentiation, and apoptosis. Consequently, YAP/TAZ-mediated signaling pathways play a vital role in coordinating cellular behavior with the mechanical context of the environment, impacting both pathological and physiological states in vivo.

In addition, as target cells of Wolff's law and the bone homeostasis theory, bone cells sense various mechanical cues and respond to biological signals depending on YAP/TAZ. Crucially, the dysregulation of YAP/TAZ is implicated in a variety of bone diseases, including developmental abnormalities [37], osteoporosis [16,38], and arthritis [39]. Through their intricate regulation of cellular activity [40] and response to environmental cues [41,42], YAP/TAZ represent key players in the dynamic interplay of cell signaling pathways, offering promising targets for therapeutic interventions in bone-related disorders and beyond.

Therefore, the purpose of this review is to comprehensively summarize the key role of YAP/TAZ as core elements in the transduction of mechanical stimuli into biological signals, with a particular focus on their role in bone cell mechanosensing, mechanotransduction, and mechanoresponse.

2. YAP/TAZ in Hippo and other signaling

2.1. YAP/TAZ in Hippo signaling

YAP and TAZ are central to the Hippo signaling pathway, initially detailed in Drosophila in 2003 [43,44]. This pathway's core consists of MST1/2 and LATS1/2 kinases and its key effectors, YAP/TAZ [45]. Activation of Hippo leads to the phosphorylation of YAP/TAZ by LATS1/2, prompted by MST1/2 with MOB1's help, resulting in YAP/TAZ's cytoplasmic retention and degradation [46–48]. MAP4K4 also acts upstream, facilitating LATS1/2 phosphorylation [49,50]. When the Hippo pathway is deactivated, YAP/TAZ migrate into the nucleus to regulate transcription [51,52]. Interestingly, MST1/2 can influence bone cells like osteoblasts and osteoclasts independently of YAP/TAZ, contributing to bone homeostasis [53,54]. The study of the Hippo signaling pathway through high-pressure models provides strong evidence to support this [55].The effect of LATS1/2 on bone tissues remains unreported, yet YAP/TAZ are known to manage bone health outside the Hippo pathway's influence.

2.2. YAP/TAZ in non-Hippo signaling

Beyond the Hippo pathway, YAP and TAZ are crucial in various non-Hippo signaling pathways, especially those involving growth factors critical for skeletal regulation. Growth factors activate YAP/TAZ, influencing bone cell fate and skeletal health.

TGFβ1 enhances TAZ and Smad to promote bone remodeling [56]. BMP-2 promotes osteogenic differentiation through the Smad1/5/8-YAP/TAZ complex [57]. VEGF and BMP2 activate TAZ together to enhance bone regeneration [58], IGF1 increases TAZ to promote osteogenic differentiation of mesenchymal stem cells [59], while FGF-2 does the opposite, inhibiting mineralization and reducing TAZ [60]. TNFα decreases TAZ [56], and regulates the NF-κB pathway through YAP, affecting the expression of IL-6, RANKL, and osteoprotegerin [61]. Endocrine factors like glucocorticoids upregulate TAZ, promoting osteoblastogenesis over adipogenesis [62,63]. LPA and S1P, through GPCRs, suppress LATS1/2, activating YAP/TAZ [64]. ESR1, or estrogen receptor alpha (ERα), is crucial in modulating YAP/TAZ activity by preventing YAP's nuclear entry. Downregulation of ERα′s c-terminal activation function (AF) domain-2 enhances YAP expression [65]. However, ERα retains YAP/TAZ in the cytoplasm, leading to degradation via LATS1/2 or MST1/2 kinases [66–68]. The soluble biological signals that can regulate YAP/TAZ expression are summarized in Fig. 1.

3. Role of YAP/TAZ in mechano-sensing

Bone cells navigate a complex landscape of mechanical signals from various sources, including neighboring cells, tissue fluids, and the extracellular matrix (ECM). These signals, encompassing ECM protein composition, stiffness, viscoelasticity, substrate topology, and fluid shear [69], are crucial for the regulation of bone cell behavior. According to Wolff's law and the bone homeostasis theory, bone cells possess the innate ability to detect and respond to these mechanical

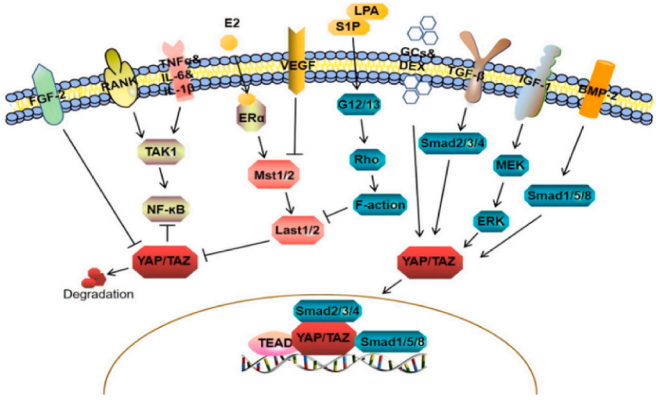

Fig. 1. Role of YAP/TAZ in soluble biological signals in bone. The localization of YAP/TAZ is influenced by various soluble signaling factors. For example, molecules such as FGF-2, RANK, ERα, VEGF, and S1P/LPA can regulate the fate of YAP/TAZ through direct action or the classical Hippo signaling pathway, causing it to remain in the cytoplasm or be degraded by the proteasome. Conversely, upstream signals from BMP-2, IGF-1, TGF-β, GC, and DEX drive YAP/TAZ to the nucleus, where they interact with the TEAD and Smad protein families.

stimuli, although the precise molecular mechanisms remain partially understood. Recent evidence supports a unified model where YAP/TAZ serve as central mediators in translating mechanical cues into cellular responses, affirming their indispensable role in mechanosensing and subsequent cellular adaptation [70,71]. These mechanical signals are summarized as mechanosensing in Fig. 2.

3.1. Surface topography

Surface topography plays a pivotal role in modulating the behavior of bone cells. Research demonstrates that the microenvironment, particularly the surface roughness, significantly influences human mesenchymal stem cells (MSCs) and their osteogenic potential. For instance, MSCs grown on hydroxyapatite discs with specific surface roughness exhibit enhanced osteogenic differentiation. This process is closely tied to the organization of F-actin fibers and correlates with the expression levels of YAP/TAZ, suggesting a direct link between cellular structure and gene expression [72].

Moreover, the architecture of the substrate surface, such as those found on silk fibroin substrates with high β-sheet content, can lead to increased cell spreading, more organized cytoskeletal structures, and larger focal adhesion areas. These physical cues are not just passively experienced by cells but actively transduce signals that result in the nuclear translocation and activation of YAP/TAZ along with RUNX2, a key transcription factor in bone development [73].

Additionally, advanced manufacturing techniques like lithography or electrospinning that create specific topographical features can direct the orientation of MSCs and their differentiation into chondrocytes, further underscoring the mechanosensitive nature of these cells [74]. Interestingly, while certain topographical cues such as oriented grooves and specific ranges of topography are shown to promote osteogenic differentiation, they do not universally affect YAP/TAZ expression, indicating a complex interaction between physical stimuli and cellular response mechanisms [75].

This nuanced understanding highlights the significance of surface topography in guiding stem cell fate and emphasizes the critical role of YAP/TAZ as mediators of mechanotransduction in bone cells.

3.2. Stiffness

Tissue stiffness is a critical factor in maintaining homeostasis, with its disruption leading to conditions like osteoarthritis [76] and osteoporosis [77] *In vitro* studies reveal that the stiffness of the culture matrix significantly affects cell fate decisions.

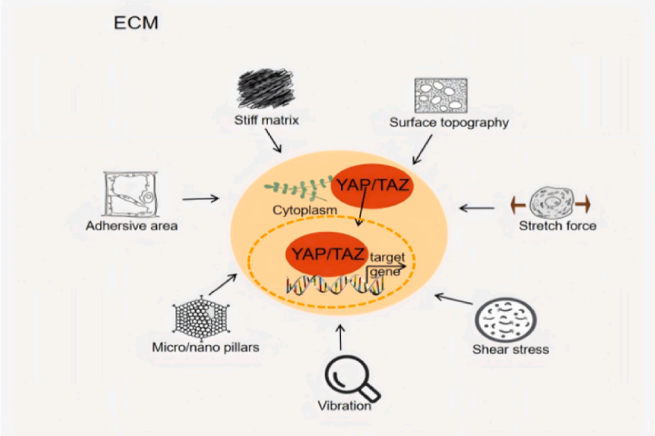

Fig. 2. Role of YAP/TAZ in mechanosensing. When cells are subjected to mechanical stimulation, YAP/TAZ senses this change and translocates to the nucleus to regulate the expression of target genes. Such mechanical stimulations include various factors, such as the surface of the topography, stiff matrix, adhersive area, micro/nano pillars, stretch force, shear stress and vibration.

In matrices with high stiffness (15–40 kPa), YAP/TAZ predominantly localizes in the nucleus, facilitating osteogenic differentiation. Conversely, on softer matrices (0.7–1 kPa), YAP/TAZ shifts to the cytoplasm, altering cell morphology to a smaller and rounder shape. This dynamic suggests that ECM stiffness modulates YAP/TAZ activity [35], thereby influencing cell fate independently of the Hippo pathway.

Enhancing the stiffness of scaffolds [78], such as mineralized collagen glycosaminoglycan (MC-GAG) scaffolds, leads to increased osteogenic differentiation in a YAP/TAZ-dependent manner [79]. Similarly, guided bone regeneration techniques that increase membrane stiffness also promote bone formation through YAP/TAZ activation [80].

The degradability of matrix materials, alongside stiffness, plays a vital role in mesenchymal stem cell (MSC) behavior. MSCs show enhanced spreading and nuclear YAP/TAZ localization on stiffer, non-degradable hydrogels. This effect is inverted in degradable matrices, indicating that both stiffness and degradability dictate YAP/TAZ localization and, consequently, cell differentiation pathways [80].

MSCs exhibit varied responses to matrix stiffness based on cell volume. In different stiffness conditions, appropriate cell volume allows for the formation of stress fibers and focal adhesions, crucial for YAP/TAZ nuclear localization and osteogenic differentiation. This observation underscores the complexity of the mechanotransduction process, involving multiple factors like cell size, matrix stiffness, and material properties.

Recent models have further elucidated the relationship between matrix stiffness, cell behavior, and YAP/TAZ dynamics, introducing concepts like "memory stiffness" in MSCs. These models predict how changes in substrate stiffness over time can influence MSC fate, offering insights into the mechanobiological regulation of bone cell differentiation [81].

In summary, the stiffness of the cellular environment plays a crucial role in dictating cell fate through the modulation of YAP/TAZ localization. This relationship between mechanical cues and cellular responses is pivotal for understanding and manipulating bone tissue engineering and regeneration strategies.

3.3. Adhesion area/micro-patterning

The manipulation of adhesion areas and micro-patterning significantly influences bone cell functions, particularly impacting mesenchymal stem cell (MSC) commitment. A constrained adhesion area reduces cell spreading and alters the cytoskeletal configuration, leading to a state characterized by denser cortical actin and fewer stress fibers. This environmental cue directly regulates the subcellular localization and activity of YAP/TAZ, with expanded cells showing enhanced nuclear YAP/TAZ presence and transcriptional activity, while restricted ones exhibit cytoplasmic localization of these factors [70]. Micro-patterned fibronectin islands demonstrate that the adhesive area available to MSCs dictates their spreading behavior [35,82]and, under 3D culture conditions, the YAP/TAZ activity of C-MSC is reduced, which promotes the differentiation of cells into fat and cartilage [83]. Consequently, YAP/TAZ localization—ranging from nuclear in well-spread cells to cytoplasmic in more confined ones [84]. Furthermore, designing isotropic micropatterns has allowed for precise control over cell adhesion and spreading, highlighting the adhesion area's dominant role over spreading in influencing YAP/TAZ nuclear localization and osteogenic differentiation.

3.4. Micro/nano pillars

The structure and organization of micro- and nano-pillars significantly affect MSC spreading and differentiation [85]. MSCs navigating between fibronectin-coated micropillars display preferential nuclear localization of YAP/TAZ, which correlates with enhanced osteogenic

differentiation [35]. Specifically, micropillars designed with particular dimensions encourage MSCs to adopt osteogenic pathways, further evidenced by increased YAP nuclear localization and RUNX2 expression [86]. In addition, the elastic modulus of the surface of micro nano columns can affect the mechanical response of cells, promote the nuclear localization of YAP/TAZ, and thus promote the differentiation of MSCs into osteoblasts [87].

3.5. Stretch

Applying stretch forces to cells results in cytoskeletal deformation, significantly affecting YAP/TAZ localization and activity [88]. Experiments with dynamic stretching, applying a 3 % strain at a frequency of 1 Hz, have shown to transfer cytoskeletal strain to the nucleus, prompting YAP/TAZ nuclear localization in MSCs [89,90]. This mechanical cue enhances osteogenic differentiation, as evidenced by experiments with human periodontal ligament cells and MSCs subjected to cyclic stretching [90]. Such mechanical stimuli not only inhibit MSC proliferation but also bolster osteoblastic differentiation through mechanisms involving the YAP/BMP2 axis [91]. Inflammatory macrophages, when exposed to cyclic stretching, promote MSC osteogenesis by activating YAP, demonstrating the synergy between mechanical forces and cellular signaling in bone cell differentiation.

3.6. Shear stress

Shear stress, a prevalent mechanical force in vivo, influences bone cell behavior and fate, including osteogenic differentiation and chondrocyte activity [92,93]. YAP/TAZ, acting as mechanical sensors, respond to shear stress, modifying their activity and localization within the cell [94]. Fluid flow shear stress (FFSS) and substrate stiffness have been identified as promoters of osteogenic activity in osteosarcoma cells via YAP activation [95]. Moreover, low-intensity shear stress, as generated in microfluidic systems, activates TAZ, enhancing MSC osteogenic differentiation [96]. The application of oscillatory fluid shear stress (FSS) has been shown to increase osteogenic differentiation in bone marrow stem cells (BMSCs) by upregulating YAP levels [80]. Interestingly, the absence of the mechanosensitive ion channels Piezo1/2 diminishes the osteogenic response to FSS, highlighting the integral role of mechanical signaling pathways in bone cell physiology [97].

3.7. Vibration

Exposure to low-magnitude, high-frequency vibrations, especially in the presence of estrogen, has been shown to suppress YAP/TAZ expression in vitro. These specific vibration conditions ($\leq$1 g magnitude and $\geq$30 Hz frequency) lead to the dephosphorylation of YAP, which correlates with a reduction in osteocyte apoptosis [98]. Additionally, such low-intensity vibrations have been observed to mitigate the effects of microgravity on MSCs, particularly the nuclear shuttling of YAP, suggesting a potential therapeutic avenue for maintaining bone health in environments characterized by reduced mechanical loading [99].

4. Role of YAP/TAZ in mechano-transduction (upstream mechanical signals)

This section delves into the mechanisms through which extracellular mechanical signals are relayed to the cell interior, affecting YAP/TAZ activity and localization, which is summarized in Fig. 3. In previous reviews, we mentioned that RASSF2, MST2, and Ajuba, as well as LATS1/2, can influence downstream YAP/TAZ [100]. However, after reviewing the literature, we found no evidence that these factors modulate YAP/TAZ to affect osteocytes under mechanical stimulation. Therefore, we focus only on the regulatory role of LATS1/2.

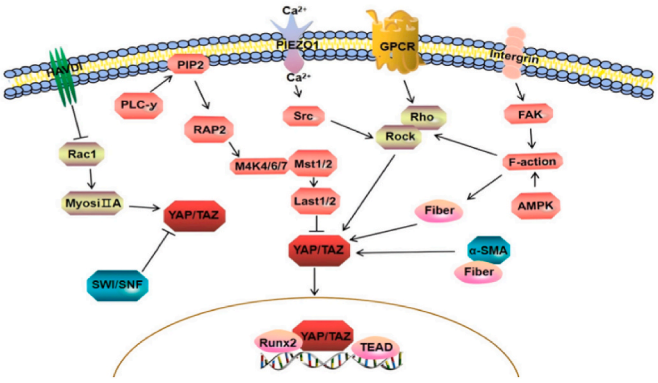

Fig. 3. Role of YAP/TAZ in mechanotransduction. This illustration shows how mechanical signals from outside the cell are converted into intracellular responses, affecting both the activity and positioning of YAP/TAZ. It reveals that stimulation through HAVDI and SWI/SNF suppresses YAP/TAZ activity, causing it to remain in the cytoplasm. In contrast, mechanical stimuli involving PLC-γ, PIEZO1, GPCR, integrin, AMPK, and α-SMA promote the movement of YAP/TAZ into the nucleus.

4.1. Stiffness/N-cadherin(HAVDI l)-YAP/TAZ

N-cadherin serves as a critical link between the extracellular matrix and the cytoskeleton, playing a pivotal role in cartilage and bone development [99]. Under mechanical tension, N-cadherin interacts with actin filaments, facilitating the transduction of mechanical signals [101]. In environments where matrix stiffness is moderate (10–15 kPa), the exposure of N-cadherin's HAVDI adhesion motif leads to alterations in cytoskeletal tension and Rho signaling [102], culminating in increased YAP/TAZ phosphorylation and reduced nuclear presence of RUNX2. Further observations reveal that MSCs cultured on substrates that mimic this stiffness experience a decrease in Rac1 activity, myosin IIA expression, and focal adhesion formation, alongside a significant reduction in cell proliferation [103].

4.2. Stiffness-αSMA-YAP/TAZ

Alpha-smooth muscle actin (α-SMA) plays a crucial role in cellular response to mechanical stress, interacting closely with actin to modulate cell contractility [104]. This interaction significantly influences the activity and localization of the mechanosensitive factors YAP/TAZ. In environments with low matrix stiffness (3 kPa), α-SMA is notably absent from stress fibers, leading to increased YAP phosphorylation and its cytoplasmic retention, thereby reducing MSC contractility. Conversely, the presence of α-SMA within stress fibers on stiffer matrices enhances YAP/TAZ nuclear localization and promotes the formation of mineralized nodules, indicating a direct link between cytoskeletal dynamics, α-SMA expression, and osteogenic activity mediated by YAP/TAZ [105].

4.3. Stiffness/energy-AMPK-YAP/TAZ

AMP-activated protein kinase (AMPK) is a key regulator of cellular energy balance, responding to changes in mechanical forces such as shear stress [106]. Activation of AMPK leads to an increase in ATP production and actin polymerization, which in turn enhances stress fiber formation and stretches the cytoskeleton [107]. This mechanical feedback results in the nuclear translocation of YAP from the cytoplasm, indicating a mechanism where cellular energy status and mechanical cues converge to regulate YAP/TAZ localization and activity. Studies have shown that hMSCs cultured on stiffer substrates exhibit increased glucose uptake, mitochondrial activity, and YAP/TAZ nuclear presence, promoting osteogenic differentiation [108]. Conversely, inhibiting AMPK activity results in decreased stress fiber formation and reduced nuclear presence of YAP/TAZ, highlighting the critical role of AMPK in

mediating the effects of mechanical stiffness on YAP/TAZ signaling and osteogenesis.

4.4. Integrin-FAK-F-actin-RhoA-Rock-YAP/TAZ

The cell's extracellular environment significantly influences fate decisions by transforming mechanical stimuli into biochemical signals via cell–cell adhesion mechanisms [109]. The process begins with increased substrate stiffness, prompting integrins to cluster and activate focal adhesion kinase (FAK) [110,111]. This activation leads to the reorganization of the actin cytoskeleton (F-actin), which is further modulated by the Rho/ROCK pathway [111]. RhoA, upon activation by GTP binding, enhances mechanical force transmission to the cytoskeleton, while ROCK phosphorylation facilitates the remodeling of skeletal proteins. This cascade not only mediates mechanical signal transduction but also propels YAP/TAZ into the nucleus, thereby boosting the osteogenic differentiation potential of mesenchymal stem cells (MSCs) [35,112]. This sequence of events underscores the critical role of the integrin-FAK-F-actin-RhoA-ROCK pathway in modulating MSC fate through mechanical cues.

4.5. PLC-PIP2-PA-PDZGEF1/2-RAP2-RhoA-MST1/2/M4K4/6/7-LATS1/2-YAP/TAZ

Phospholipase Cγ (PLCγ) plays a pivotal role in cytoskeletal remodeling, facilitated by its interaction with phosphatidylinositol 4,5-bisphosphate (PIP2) and phosphatidic acid (PA) [33]. Under conditions of low matrix stiffness (1 kPa), PLCγ activates the RAP2 GTPase through a cascade involving PIP2, PA, PDZGEF1, and PDZGEF2. This activation triggers MAP4K4/6/7 and Arhgap29, leading to a decrease in cytoskeletal tension and a reduction in YAP/TAZ activity. Interestingly, eliminating LATS1/2 or MST1/2 alongside MAP4Ks nullifies RAP2's influence on YAP/TAZ, indicating a complex regulatory network. This discovery highlights how YAP/TAZ are integral to the mechano-transduction processes initiated by PLCγ and its downstream effectors, affecting cell behavior in response to varying mechanical environments [32].

4.6. PIEZO1-YAP/TAZ

PIEZO1, a cation channel sensitive to mechanical changes in the extracellular environment, is vital for maintaining bone homeostasis. It functions by sensing and relaying mechanical signals through its distinct trimer helix structure [113]. The absence of PIEZO1, as seen in knockout mice, leads to reduced bone mineral density and impaired healing of fracture calluses, underlining its critical role in bone strength and repair [114]. Additionally, silencing PIEZO1 in MLO-Y4 cells decreases the expression of the YAP/TAZ target gene CYR61, alongside a blockade of calcium influx, highlighting the interplay between PIEZO1 activity, calcium signaling, and YAP/TAZ-mediated gene expression [115]. Conversely, activating PIEZO1 enhances YAP's nuclear localization and osteogenic differentiation, mediated through the activation of RUNX2, indicating PIEZO1's potential as a therapeutic target for bone regeneration strategies [116].

4.7. SWI/SNF-YAP/TAZ

The SWI/SNF complex, a significant player in chromatin remodeling, acts as a canonical mechanotransductor. ARID1A, a component of this complex, serves as a mechanical switch [117,118]. In conditions of low mechanical stress or disrupted mechanical signaling, ARID1A-bound SWI/SNF directly interacts with YAP/TAZ, preventing their association with TEAD transcription factors and leading to their cytoplasmic retention. In contrast, under high mechanical force, SWI/SNF dissociates from YAP/TAZ, facilitating their nuclear translocation and subsequent transcriptional regulatory functions [119]. This mechanism demonstrates the SWI/SNF complex's pivotal role in modulating YAP/TAZ activity in response to mechanical cues.

4.8. GCPR- YAP/TAZ

G protein-coupled receptors (GPCRs) modulate YAP/TAZ activity in a G protein-specific manner. The activation of YAP/TAZ is primarily mediated through Gα12/13 proteins, triggered by external signals like lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P). This activation pathway facilitates the closure of the Hippo signaling cascade and promotes the nuclear localization of YAP/TAZ, enhancing their transcriptional output [32]. Conversely, the Gαs subunit acts to inhibit YAP/TAZ activity; signaling molecules such as glucagon and adrenaline activate Gαs, leading to YAP/TAZ cytoplasmic sequestration and degradation [120]. This intricate regulation by GPCRs illustrates the diverse mechanisms through which YAP/TAZ activity can be finely tuned in response to various extracellular signals.

5. Role of YAP/TAZ in mechano-response (downstream biological signals)

After outlining how bone cells sense mechanical signals and their transmission to YAP/TAZ, we delve into how YAP/TAZ convert these signals into specific cellular responses. This process, pivotal for bone homeostasis and development, encompasses several downstream biological signals triggered by YAP/TAZ activity. The downstream biological signals are summarized as mechanoresponses in Fig. 4.

5.1. YAP/TAZ-RUNX2

YAP/TAZ, upon nuclear entry, associate with RUNX2, a key transcription factor in bone metabolism [23]. YAP's nuclear localization is facilitated by its interaction with the PY motif of RUNX2 [121], whereas TAZ connects to RUNX2 via its WW domain [122]. This interaction can either stimulate or inhibit RUNX2's transcriptional activity, depending on the context [123]. Mechanical stress leads to the nuclear translocation of the YAP/RUNX2 complex, enhancing osteogenic differentiation and bone formation. Interestingly, YAP and TAZ can exhibit competitive dynamics in binding to RUNX2, with potential implications for osteocalcin expression and osteogenesis regulation [124]. TAZ's direct interaction with RUNX2 particularly augments osteocalcin

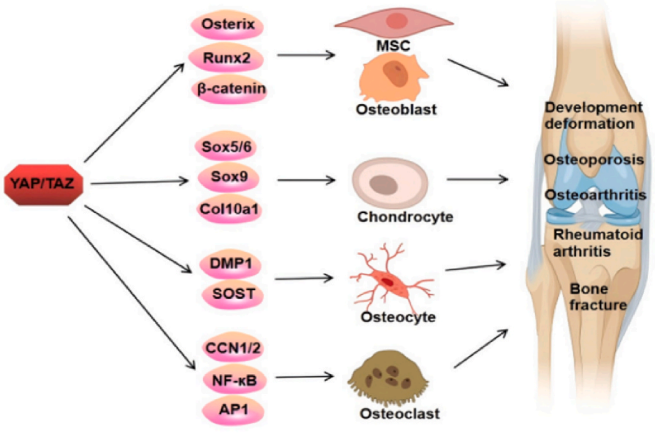

Fig. 4. Role of YAP/TAZ in mechanoresponse. This figure depicts how YAP/TAZ regulates bone diseases by entering the nucleus and binding with specific target genes. These genes are associated with mesenchymal stem cells, osteoblasts, chondrocytes, osteocytes, and osteoclasts, influencing their proliferation and apoptosis. As a result, this regulation plays a crucial role in bone development and conditions such as osteoporosis, osteoarthritis, bone tumors, and fractures.

promoter activity, underscoring TAZ's role in promoting bone formation under mechanical tension [125].

5.2. YAP/TAZ-SOX9

SOX9, crucial for cartilage formation, works alongside SOX5/6 to boost its function. The deletion of MOB1 leads to YAP overexpression and a corresponding decrease in SOX9, SOX5, and SOX6 levels, hinting at YAP's role in modulating cartilage-related gene expression. Overexpressed YAP/TAZ in chondrocytes results in diminished SOX9 expression, suggesting that YAP/TAZ may directly influence cartilage morphology by binding to the SOX9 promoter [17,126]. This interaction underscores the complex regulatory network involving YAP/TAZ in cartilage development and disease processes such as achondroplasia.

5.3. YAP/TAZ-WNT/β-catenin

The relationship between the Wnt/β-catenin and YAP/TAZ signaling pathways plays a critical role in regulating cellular processes crucial for bone health. Research has shown that YAP/TAZ activation is contingent upon the status of the classical WNT/β-catenin pathway; YAP/TAZ become active when this pathway is engaged, but are sequestered in a destruction complex when the pathway is inactive [26,27]. These dynamic underscores the integral role of YAP/TAZ within the Wnt signaling framework, influencing osteoblast proliferation and differentiation [127,128]. Moreover, YAP/TAZ activation by Wnt3a and Wnt5a/b through a non-classical signaling route emphasizes their versatility as downstream effectors in Wnt signaling, contributing to bone formation and angiogenesis, and affecting fracture healing processes [28,129]. This evidence suggests that YAP/TAZ serve as pivotal nodes at the intersection of classical and non-classical Wnt signaling pathways, influencing bone physiology.

5.4. YAP/TAZ-NF-κB

YAP/TAZ are significantly involved in modulating the NF-κB signaling pathway, particularly within the context of chondrocyte regulation in osteoarthritis and osteoclast activity in osteoporosis. TAZ's interaction with TAK1 serves as an inhibitory mechanism against the NF-κB pathway, reducing osteoclast differentiation and bone resorption. Conversely, the absence of TAZ activates the TAK1/NF-κB axis, exacerbating osteoporosis conditions [16]. In the realm of osteoarthritis, YAP's ability to suppress NF-κB activity by modulating TAK1 and IKKs phosphorylation highlights its potential as a therapeutic target for mitigating cartilage degradation [17]. These observations delineate the critical roles of YAP/TAZ in skeletal disease pathology through their influence on NF-κB signaling, offering insights into potential strategies for disease management and treatment.

5.5. YAP/TAZ-AP1

The AP1 complex, composed of transcription factors c-Jun and c-Fos, plays a crucial role in osteoclast differentiation [130]. Although AP1 does not directly bind to YAP/TAZ, it forms a functional complex with YAP/TAZ and TEAD, significantly enhancing the expression of YAP/TAZ target genes [94]. This interaction, particularly notable at active enhancer sites where c-Jun is present, underscores the regulatory influence of the YAP/TAZ/TEAD/AP1 complex on osteoclastogenesis and bone resorption [130,131]. The use of verteporfin to inhibit YAP activity also leads to a decrease in AP1 and RANKL activities, showcasing a therapeutic pathway to modulate bone resorption processes [94].

5.6. YAP/TAZ-CCN1/2

YAP/TAZ activities drive the expression of the CCN family of proteins, including CCN1 and CCN2, which are pivotal in bone biology [132]. CCN1, known for its role in angiogenesis (Cyr61), is essential for bone formation, with its knockdown leading to diminished bone formation in vivo [133,134]. Conversely, overexpressing CCN1 can suppress osteoclastogenesis [134]. CCN2, or connective tissue growth factor (CTGF), acts as an osteolytic factor and is prominently expressed in the context of bone invasion by breast cancer cells, leading to significant bone destruction [135]. The application of anti-CCN2 antibodies in such models has been shown to reduce osteoclast numbers and inhibit tumor progression, highlighting CCN2's role in bone resorption [136,137]. Abnormalities in CCN1 and CCN2 expression implicate YAP/TAZ dysregulation in bone and cartilage disorders, including cartilage dysplasia, pointing to their critical roles in maintaining bone integrity and signaling pathways involved in bone diseases.

6. Role of YAP/TAZ in bone diseases

YAP/TAZ's influence extends beyond cellular functions to impact various skeletal diseases. Their roles in bone diseases highlight the broad implications of their dysregulation, which summarized in this section and in Table 1.

6.1. Development deformities

In bone development, YAP and TAZ also play significant roles. Knocking out YAP and TAZ in mice leads to severe skeletal developmental defects. When YAP and/or TAZ knocked in Osx-Cre mice, the mortality rate of newborn mice is extremely high, and surviving mice exhibit issues such as spinal curvature and cranial deformities [138]. Similarly, knocking out YAP and TAZ in Prx1-Cre or Osx-Cre mice, result in embryonic lethality [38]. Furthermore, knockout of TAZ in Col2-Cre mice results in growth retardation and incomplete skeletal development in newborn pups [139]. Double knockout of YAP/TAZ in Col2α1-cre^{+ve} mice, embryo specimens exhibit skeletal deformities such as barrel-shaped chest, abnormal sternum, and nasal bone morphological abnormalities [140]. However, there are no relevant reports on the role of YAP and TAZ in clinical bone developmental disorders.

Table 1
The role of YAP/TAZ in various bone diseases.

Bone diseases	Specific knockout	Phynotype	References
Developmental deformities	YAP$^{f/f}$; TAZ$^{f/f}$ Osx-Cre	Skeletal deformity	(138)
	YAP$^{f/f}$; TAZ$^{f/f}$ Prx1-Cre	Embryonic death	(38)
	YAP$^{f/f}$; TAZ$^{f/f}$ Osx-Cre	Developmental abnormalities	(38)
	TAZ$^{f/f}$ Col2-Cre	Skeletal dysplasia	(139)
	YAP$^{f/f}$; TAZ$^{f/}$ Col2α1-Cre $^{+ve}$	Skeletal deformity	(140)
Osteoporosis	YAP$^{f/f}$; TAZ$^{f/ff}$ Prx1-Cre	Increase in bone mass	(38)
	YAP$^{f/f}$; TAZ$^{f/f}$ Osx-Cre	Decrease in bone mass	(38)
	YAP$^{f/f}$; TAZ$^{f/f}$ Dmp1-Cre	Decrease in bone mass	(38)
	YAP$^{f/f}$; TAZ$^{f/f}$ Osx-Cre	Decrease bone resorption	(138)
	TAZ$^{f/f}$ Col2-Cre	Decrease in bone mass	(139)
	TAZ$^{f/f}$ RANK-Cre	Decrease in bone mass	(16)
Osteoarthritis	YAP$^{f/f}$ Col2-Cre	Inhibit osteoarthritis	(39)
	YAP$^{f/f}$ Col2-Cre	Exacerbate osteoarthritis	(17)
Bone fracture	YAP$^{f/f}$; TAZ$^{f/f}$ Osx-Cre	Spontaneous long bone fractures	(142)
	YAP$^{f/f}$; TAZ$^{f/f}$ Osx-Cre	Inhibit fracture repair	(138)
	YAP$^{f/f}$; TAZ$^{f/f}$ Dmp1-Cre	Increase bone fragility	(143)
	TAZ$^{f/f}$ Col2-Cre	Delay fracture healing	(139)

Table 2
Effective regulatory drugs of YAP/TAZ.

Bone disease	Target	Compound	References
Osteoporosis	TAZ	TM-25659	(148)
Osteosarcoma	YAP	CA3	(152)
Osteosarcoma	YAP-TEAD	Verteporfin	(151)
Osteoarthritis	YAP-TEAD	Verteporfin	(39)
Developmental deformities	YAP-TEAD	VGLL4	(153)
Osteoarthritis	MST1/2	XMU-MP-1	(154)
Osteoporosis	MST1/2	XMU-MP-1	(155)
Osteoporosis	SETD7	(R)-PFI-2	(156)

6.2. Osteoporosis

The roles of YAP and TAZ have attracted significant attention in osteoporosis. Deletion of YAP/TAZ in Prx1-Cre mice during the MSCs stage increases bone mass. However, deletion of YAP/TAZ during the osteoblast and osteocyte stages with Osx-Cre and Dmp1-Cre mice, results in a decrease in bone mass [138]. In the Col2-Cre mouse model, conditional knockout of TAZ resulted in a decrease in bone mass [139]. Conditional knockout of TAZ in osteoclasts using RANK-Cre mice lead to osteoporosis [16]. Importantly, there is currently no reported in vivo data on the conditional knockout of YAP in osteoclasts. In addition, we found a decrease in TAZ expression in clinical osteoporosis bone tissues and osteoclasts, suggesting that TAZ may be a potential therapeutic target for osteoporosis and osteolytic diseases.

6.3. Osteoarthritis

YAP/TAZ play important and complex roles in the occurrence and treatment of osteoarthritis. Conditional knockout of YAP in chondrocytes with Col2-Cre exacerbated cartilage destruction in osteoarthritis [39]. Interestingly, $YAP^{f/f}$ Col2-cre mice were no significant cartilage damage when there was not undergone inflammatory stimulation [17]. Moreover, there is evidence to suggest that upregulation of TAZ can inhibit inflammation and to some extent promote the repair of osteoarthritis [141]. Further research reveals that YAP/TAZ participates in the process of cell matrix hardening in synovial cells of osteoarthritis patients, forming a vicious cycle [137]. With the aggravation of the severity of osteoarthritis, the number of YAP positive chondrocytes gradually decreased in articular cartilage of human patients. Therefore, YAP/TAZ is expected to become a potential target for the future treatment of osteoarthritis.

6.4. Bone fracture

YAP/TAZ are pivotal in the process of fracture healing. Conditional knockout of YAP/TAZ with Osx-Cre leads to impaired fracture healing [142] and spontaneous long bone fractures [138]. Additionally, conditional knockout of YAP/TAZ in osteocytes with Dmp1-Cre reduces bone mechanical properties, which are crucial for bone repair [143]. However, another study indicated that overexpression of YAP in Col2-Cre mice inhibits osteogenesis within cartilage, potentially delaying fracture repair [124]. In contrast, conditional knockout of TAZ in the same mouse model inhibits fracture healing [139]. It is worth mentioning that the role of YAP/TAZ in different types of cell mediated osteoporotic fracture healing has not been reported. These findings provide important insights into understanding the molecular mechanisms of fracture healing and lay a foundation for further translating research results from animal models into clinical applications.

6.5. Osteosarcoma

In the progression of osteosarcoma, the nuclear localization of YAP/TAZ plays a crucial role [144]. Deletion of Trp53 and Rb1 genes in mice leads to spontaneous osteosarcoma, which is closely related to the presence of YAP/TAZ in the nucleus. In addition, the disease progression caused by these gene defects can be delayed through VP intervention [145]. Overexpression of TAZ accelerates the development of osteosarcoma [146]. Notably, using three-dimensional scaffolds with adjustable mechanical properties for osteosarcoma cell culture, revealing the correlation between matrix hardness, cell growth, and YAP/TAZ nuclear translocation [147]. These findings are consistent with Rothzerg's view, pointing to a new possibility of YAP/TAZ as a potential therapeutic target for osteosarcoma [144].

7. Effective regulation drugs of YAP/TAZ

Considering the significant role of YAP/TAZ in bone disease regulation, we summarize the related drugs in Table 2. We also have a review that delves into the agonists and inhibitors of YAP/TAZ, while this review focuses on drugs with specific effects on bone regulation. TM-25659 can directly activate TAZ to promote bone formation [148–150]. Verteporfin not only alleviates osteoarthritis by inhibiting YAP [39] but also significantly suppresses osteosarcoma growth in vitro [151]. CA3 shares similar effects [152]. Moreover, VGLL4 influences bone development [153], and XMU-MP-1 effectively alleviates osteoarthritis symptoms [154]. In osteoporosis models, XMU-MP-1 enhances TAZ in osteoclasts, reducing bone loss and slowing osteoporosis progression [155]. Similarly, Xu et al. demonstrated that (R)-PFI-2 activation of TAZ effectively inhibits osteoclastogenesis, preventing osteoporosis [156].

8. Summary and questions

YAP/TAZ are at the heart of biological signal mechanics, encompassing mechanosensing, mechanotransduction, and the subsequent cellular responses. They are adept at being activated by a plethora of extracellular mechanical stimuli through diverse signaling pathways and translating these into signals that dictate the behavior of bone cells.

In the realm of mechanosensing, YAP/TAZ exhibit sensitivity to a wide array of mechanical stimuli, including but not limited to vibration, fluid shear, tensile forces, surface morphology, matrix stiffness, cell adhesion, and the geometry of micro- or nano-structures. Mechanotransduction processes see these mechanical signals relayed to YAP/TAZ through various pathways, such as HAVDI, α-SMA, AMPK, PIEZO1, SWI/SNF, and integrin-FAK-F-actin-RhoA-ROCK, among others. In the phase of mechanoresponse, YAP/TAZ act to convert these upstream mechanical cues into downstream biological signals, interacting with crucial biomolecules like RUNX2, SOX9, β-catenin, NF-κB, AP1, and CCN1/2, to modulate cellular activities.

Proper regulation of YAP/TAZ activity is essential for the maintenance of physiological functions in bone-associated cells. Dysregulation, manifesting as either inactivation or hyperactivation, can disrupt this balance, potentially leading to bone diseases. The absence or malfunction of YAP/TAZ is linked to developmental anomalies, osteoporosis, exacerbated osteoarthritis, and compromised fracture healing, showcasing their protective role in bone health.

Given their pivotal role in bone physiology and pathology, YAP/TAZ emerge as promising therapeutic targets for bone-related conditions. Strategies aimed at modulating YAP/TAZ activity could offer new avenues for treating osteoporosis, osteoarthritis, and fractures. However, given the association of YAP/TAZ overexpression with tumorigenesis, their therapeutic manipulation requires precision to avoid unwanted oncogenic effects. The nuanced roles of YAP and TAZ in bone biology underscore the need for targeted approaches in leveraging their potential for bone disease therapies.

However, the role of YAP/TAZ in bone-related diseases is complex and not fully understood, and there are still many questions. In most bone cells and diseases, both have similar functions, but different roles have also been reported in almost every type of bone cell, especially YAP.

When YAP/TAZ have the same function, how do their contributions compare and is there any compensation between them? When their functions are opposite, who takes the dominant position? Further comparison of the phenotypes of YAP, TAZ, and YAP/TAZ knockouts is still of scientific significance in the field. Due to the more complex structure of YAP, does it mean that the unique structural domain of YAP is playing a role? Evaluating the phenotype after YAP mutation or specific domain deletion may be a strategy to solve this problem. Answering this question clearly may also bring a possible solution for targeting YAP or TAZ alone and avoiding the simultaneous regulation of YAP/TAZ.

As key molecules in mechanobiology signaling, YAP/TAZ have only been reported for their phenotypes after knockout. In the mechanical environment, does YAP/TAZ participate in the progression of bone diseases, such as osteoporosis, osteoarthritis, and fracture healing? Whether the opposing functions between YAP and TAZ are related to mechanical signals remains to be further studied? In mechanical environments, such as tail suspension unloadinng or running loading stimulation models, evaluating the impact of YAP or TAZ on bone-related diseases may unveil the role of YAP/TAZ-mediated mechanotransduction in vivo, further solidifying the pivotal position of YAP/TAZ in the regulation of bone mechanics.

Furthermore, in MSCs, YAP/TAZ promotes osteogenic differentiation, but knocking out YAP/TAZ in Prx1-Cre mice shows an increase in bone mass, showing opposite results in vivo and in vitro, which deserves further research.

TAZ inhibits osteoclasts to maintain bone mass, whereas YAP is reported to be necessary for osteoclast differentiation in vitro, but its phenotype in vivo is not yet known, warranting further clarification of its role in diseases such as osteoporosis. It may once again prove that YAP and TAZ have different functions and regulatory mechanisms in the same cell.

Osteoporotic fracture is an extremely complex pathological state, which is not simply the sum of osteoporosis and fracture. In this case, the role of YAP/TAZ in osteoporotic fracture healing is still unknown. Further research on the role of YAP/TAZ in different modes of osteoporotic fracture healing is expected to fill this gap.

YAP/TAZ plays an important role in almost all kinds of bone cells, even bone tumor cells, suggesting that YAP/TAZ is a potential target for the treatment of bone diseases. However, how to accurately target YAP/TAZ in bone cells is a difficult problem. Based on existing research findings, activating YAP/TAZ in osteoblasts, osteoclasts, and chondrocytes may be a potential and feasible strategy for treating osteoporosis, fractures, and osteoarthritis. However, activating YAP/TAZ also has the risk of causing bone tumors. How to accurately control the amount of activation has become a key point and difficulty for future research. When inhibiting YAP/TAZ activity for the treatment of bone tumors, precisely targeting tumor cells and preventing off-target effects are also key points that require attention in future research.

Clinically, mechanical stimuli like exercise are crucial for maintaining homeostasis in the skeletal system and treating diseases. Exercise-induced activation of YAP/TAZ holds potential for treating osteoporosis, osteoarthritis, fractures, and other ailments. However, in practical scenarios, factors such as old age, illnesses, or fractures can lead to decreased mobility, making exercise therapy challenging for treating these conditions. Fortunately, direct drug activation of YAP/TAZ can circumvent these issues, bypassing mechanosensing and mechanotransduction, and directly engaging in mechanoresponse, thereby enabling precise regulation of the skeletal system and effective disease treatment.

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Declarations of competing interest

The author(s) have no conflicts of interest relevant to this article.

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