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Review

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Mechanosignaling Promotes Osteogenic-Angiogenic Coupling in Bone Tissue

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Abstract: Osteogenesis-angiogenesis coupling is the bidirectional interaction between osteogenic and angiogenic processes. This coupling is the fundamental prerequisite for successful bone formation and post-fracture healing. While soluble biofactors are well-known mediators, mechanical stress has recently emerged as a potent driver of this coupled regeneration. However, the precise mechanotransduction cascades that translate physical forces into synchronized tissue growth remain to be fully elucidated. This review systematically summarizes the mechanisms by which mechanical stimuli activate and augment osteogenesis-angiogenesis coupling. Specifically, we detail the critical crosstalk within key mechanosensory networks. We highlight how the Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) nuclear translocation, Piezo1-mediated calcium influx, and Integrin-triggered Wnt/β-catenin signaling pathway synergistically synchronize endothelial neovascularization with osteoblast differentiation. Furthermore, we explore the clinical translation of these mechanisms. We emphasize how engineered biomaterials, particularly digitally customized 3D-printed smart scaffolds, can actively modulate these pathways *in vivo*. This material-driven modulation can maximize the therapeutic efficacy of osteogenesis-angiogenesis coupling. Ultimately, by linking macroscopic physical cues with microscopic biochemical cascades, this review offers highly translational perspectives for the personalized management of complex bone defects.

Keywords: osteogenesis-angiogenesis coupling; mechanosignaling; YAP/TAZ; Piezo1; integrins; VEGF; Wnt/β-catenin

1. Introduction

Osteogenesis-angiogenesis coupling is a synergistic relationship between bone formation and regeneration with the development of neovasculature and microvascular networks. Bone tissue is highly vascularized, and angiogenesis is one of the earliest events in the organogenesis of various organs [1]. Therefore, the formation of blood vessels determines the integrity and feasibility of bone formation. A multitude of studies have indicated that various factors and pathways can exert the same directional effects on both osteogenesis and angiogenesis, thereby positively promoting osteogenesis-angiogenesis coupling [2]. In addition to purely biochemical signals and factors such as vascular endothelial factors [3,4], there is a significant type of signaling pathways that regulate their own and downstream channel expression by sensing external mechanical stress stimuli, thus modulating osteogenesis-angiogenesis coupling [5]. These pathways are often reflected in both macroscopic and microscopic biological manifestations, such as the widely recognized distraction osteogenesis, weight-bearing rehabilitation healing after

fracture, and the resorption and regeneration of alveolar bone during orthodontic treatment [6], as well as the generation of different types of blood vessels within the neo-bone microenvironment, and the migration of various cells and factors in specific environments, all of which are closely related to these signaling pathways that sense mechanical stress and simultaneously promote bone and blood vessel formation. Building upon the fundamental understanding of these mechanosensory mechanisms, modern regenerative medicine has increasingly leveraged engineered biomaterials, particularly 3D-printed smart scaffolds [7]. By precisely tailoring the intrinsic biomechanical properties of these constructs, including matrix stiffness, pore architecture, and surface topography, researchers can actively emulate physiological physical microenvironments to stimulate these mechanosensitive pathways *in vivo* [8]. Consequently, these digitally fabricated materials serve not merely as passive structural supports but as active modulators that maximize osteogenesis-angiogenesis coupling within bone defect milieus. This article reviews the role of these mechanical stress-sensing signaling pathways in osteogenesis-angiogenesis coupling, and further explores how 3D-printed biomaterials translate these biomechanical principles into advanced clinical therapeutics.

2. Osteogenesis-Angiogenesis Coupling

Bone tissue is characterized by its high degree of vascularization, and the formation of new bone is inextricably linked to angiogenesis. The complete development of the skeleton necessitates a close spatiotemporal association between vascular endothelial cells and osteoblasts [9]. The generation of new blood vessels is a prerequisite and crucial component in the processes of bone growth, development, and repair, with the bone vascular system playing a significant role in skeletal development, remodeling, and the maintenance of bone mass equilibrium. Signaling pathways for new blood vessel formation can also activate osteogenic signaling pathways, interacting with each other, such as bone morphogenetic proteins (BMPs) and Transforming Growth Factor-beta (TGF-β), which can stimulate bone repair and regulate bone formation [10]. Table 1 systematically summarizes these key cellular interactions and biofactors.Furthermore, the newly formed bone vasculature assists in the migration of osteoblast precursors and osteoclasts to their appropriate locations and environments [11]. This illustrates that bone formation is a vascular-dependent process, and the intimate relationship between neovascularization and bone formation is termed “osteogenesis-angiogenesis coupling.”

In recent years, with the advancement of scientific and technological research, it has been discovered that the generation of microvasculature within the bone and the bone microenvironment also play a significant role in osteogenesis and the maintenance of bone mass [12]. Researchers have identified various morphologies of blood vessels, such as H-type vessels, and the expression of various cell surface pathways that can secrete factors and transmit signals to regulate bone growth and homeostasis [13], thereby further strengthening the interrelationship between bone formation and angiogenesis.

Osteogenesis and angiogenesis exhibit precise spatiotemporal coordination. During the early stages of bone repair, endothelial cells initially invade the defect site to establish a primary vascular network. These invading endothelial cells continuously secrete specific angiocrine factors. These critical factors include platelet-derived growth factor BB and Notch ligands. These local biochemical signals actively recruit mesenchymal stem cells and vascular-associated osteoblast precursors to the perivascular niche. Subsequently, these recruited precursor cells physically align along the capillaries and differentiate into mature osteoblasts [9]. Mature osteoblasts then actively secrete vascular endothelial growth factor. This potent factor further promotes capillary branching and stabilizes the newly formed blood vessels. This bidirectional communication forms a highly organized spatiotemporal sequence. Consequently, mechanical signaling pathways do not merely act on isolated cells. Instead, external physical forces precisely modulate this established cellular crosstalk to accelerate synchronized tissue regeneration [14].

Elucidating the intricate coupling mechanisms between osteogenesis and angiogenesis is of profound clinical significance. Patho-logical states such as osteoporosis (characterized by diminished bone mass) and diabetes mellitus (which severely compromises vascular integrity) can significantly disrupt this delicate interplay. Furthermore, in dental and maxillofacial clinical settings, osteo-genesis-angiogenesis coupling is indispensable for post-extraction alveolar bone regeneration [15], implant-associated osseointegration [16], post-surgical maxillofacial reconstruction [17], and the prevention of osteonecrosis. Consequently, therapeutic strategies tailored to augment this coupling process are emerging as a focal point in regenerative medicine, offering promising avenues to enhance clinical outcomes in fracture healing, bone grafting, and the comprehensive management of skeletal pathologies.

Table 1. Summary of key cellular interactions and biofactors in osteogenesis and angiogenesis coupling.

Biological Context	Key Cells Involved	Major Biofactors	Primary Function in Coupling
Endochondral ossification	Chondrocytes, endothelial cells	VEGF, Hypoxia-inducible Factor 1-alpha (HIF-1α)	Stimulates vascular invasion into cartilage to initiate bone formation.
Fracture healing	Mesenchymal stem cells, osteoblasts	BMP-2, TGF-β	Recruits osteoprogenitors and guides new vessel formation at the callus.
Distraction osteogenesis	Endothelial cells, osteoprogenitors	Platelet-derived Growth Factor BB (PDGF-BB), Angiopoietins	Promotes rapid vascular network expansion to support high metabolic demands.
Alveolar bone regeneration	Periodontal ligament cells, osteoblasts	Fibroblast Growth Factor (FGF), Notch ligands	Synchronizes bone remodeling with capillary growth during local tissue repair.

3. Signaling Pathways Sensing Mechanical Stress Stimuli

In various macroscopic developmental processes of organisms, rehabilitation, as well as in microscopic cellular development and disease regulation, mechanical forces play a pivotal role. It was not until 1892, with the proposal of Wolff's Law, that the positive effects of mechanical loading on bone formation and healing were explicitly recognized [18]. At the macroscopic level, the assistance of mechanical forces in bone healing has been acknowledged and applied since earlier times, such as postoperative rehabilitation exercises and weight-bearing training for fracture patients [19]. However, research on the micro-level impact of mechanical forces on cells or the microenvironment has been relatively scarce. Nowadays, investigators have conducted more in-depth explorations into the role of mechanical stress at the micro level. With the advancement of research standards and medical progress, it has been confirmed that mechanical stress is an important factor in inducing new bone formation at sites of bone injury [20].

Physical stimuli such as mechanical forces are crucial external signals that regulate cell fate and function. The stiffness of the extracellular matrix, cell adhesion, and the limitations of the physical space in which cells reside are all significant sources of mechanical force stimulation. Physical stimuli within the bone microenvironment can be fundamentally categorized into two distinct modalities: static mechanical microenvironments and dynamic force stimuli. Static mechanical cues, such as the stiffness of the extracellular matrix, surface topography, and the structural constraints of the cellular niche, provide continuous basal biophysical signals [21]. These static elements primarily regulate cell behavior by modulating focal adhesion assembly and sustaining steady cytoskeletal tension. In contrast, dynamic force stimuli, including fluid shear stress, cyclic mechanical stretching, and macroscopic weight-bearing loads, deliver rhythmic, time-dependent signals that rapidly trigger mechanosensitive ion channels and acute intracellular kinase cascades [22].

It is imperative to emphasize that these two modalities govern cellular mechanotransduction through mutually irreplaceable and distinct mechanisms. While static microenvironments often pre-condition cell lineage commitment and structural adaptation through mechanisms such as sustained YAP/TAZ nuclear retention, dynamic forces typically elicit immediate functional responses, well exemplified by the Piezo1-mediated transient calcium influx [23]. Together, they operate synergistically rather than redundantly, providing a comprehensive mechanical framework that drives osteogenesis-angiogenesis coupling [24]. Regarding their specific action trends, static biophysical cues establish a permissive baseline for cell attachment and morphology, which guides the initial alignment of endothelial cells and the osteogenic commitment of mesenchymal stem cells. On the other hand, dynamic forces act as potent, on-demand accelerators that actively drive the secretion of angiocrine and osteogenic factors. In the context of osteogenesis-angiogenesis coupling, static matrix stiffness primarily influences the early stages of bone regeneration by promoting osteoblast differentiation and focal adhesion kinase activation [25]. In contrast, dynamic force stimuli, particularly fluid shear stress and cyclic physiological stretching, show a stronger trend in accelerating the formation of functional type H vessels and subsequent matrix mineralization [26].

Among these diverse modalities, dynamic mechanical forces, especially moderate cyclic compression and physiological shear stress, are considered the most effective for accelerating bone healing [27]. These specific dynamic forces closely mimic the physical loading of natural locomotion. Consequently, they can effectively prevent bone fatigue, stimulate transient intracellular calcium oscillations, and maximize the synergistic crosstalk between endothelial cells and osteoblast precursors within the fracture callus [28]. In addition to the known roles of various angiogenesis-related factors and endothelial cells, recent studies have found that mechanical stress signals actively promote both angiogenesis and osteogenesis [29], and can also interact with osteogenesis-angiogenesis coupling. Specialized blood vessels mediate the remodeling of the cartilage matrix and position vasculature-associated osteoblast precursors (VOPs) to support the formation of new bone [30]. During vascular invasion, these precursors either support angiogenic vessels or mature into osteoblasts to form bone. In adult bone

homeostasis, osteoblastic Lepr+ mesenchymal cells in the perivascular niche respond to mechanical stimuli and are maintained by such stimuli.

3.1. YAP/TAZ

Among the various mechanosensors that translate physical cues into biological responses, the YAP/TAZ signaling axis acts as a central nuclear relay. YAP (Yes-associated protein) is a transcriptional activator downstream of the Hippo pathway. It functions as a primary cellular modulator in response to mechanical signals and is widely expressed in various bone-related cells, such as chondrocytes, osteoblasts, and osteocytes [31]. The regulation of YAP/TAZ requires the activity of Rho GTPases and the tension of the actin cytoskeleton, but is independent of the Hippo/LATS signaling cascade. Importantly, YAP/TAZ is essential for the differentiation of mesenchymal stem cells induced by the stiffness of the cellular matrix and for the survival of endothelial cells regulated by cellular geometry [32]; conversely, the expression of active YAP can override physical constraints and determine cellular behavior. In addition to matrix stiffness and rigidity, the flow of fluid around cells [33] and cytoskeletal tension [34] can also affect the activity and expression levels of YAP/TAZ. It has been reported in the literature that culturing mesenchymal stem cells on a stiff extracellular matrix significantly promotes their differentiation into osteoblasts, while culturing on a soft extracellular matrix favors their differentiation into adipocytes [35]. These findings establish YAP/TAZ as sensors and mediators of mechanical signals in the cellular microenvironment. As illustrated in Figure 1, YAP and TAZ also coordinate osteogenesis with angiogenesis during skeletal development and growth-plate reconstruction. In the invading blood vessels, YAP/TAZ-dependent regulation of CXCL12 and collagen–integrin signaling promotes both the recruitment and osteogenic activity of osteoblast precursors and the accompanying vascular response [36]. This coordinated mobilization of osteogenic progenitors and blood vessels facilitates osteogenic–angiogenic crosstalk and contributes to growth-plate remodeling and fetal limb skeletogenesis.

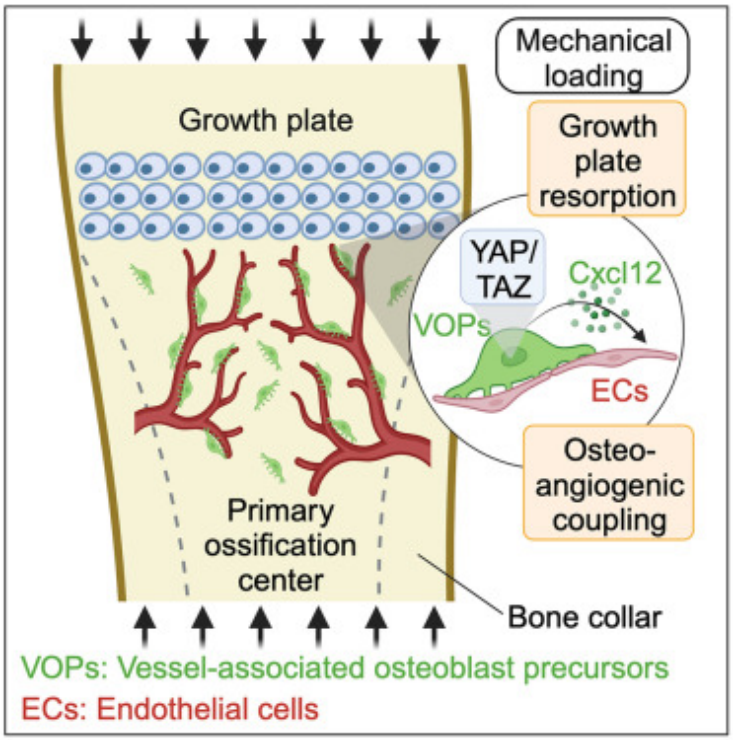

Figure 1. YAP/TAZ coordinate osteogenesis and angiogenesis during skeletal development [36], © 2023 Elsevier Inc.

YAP and the PDZ-binding motif-containing transcriptional co-activator (TAZ) can spatially mobilize osteoblast precursor cells and integrate with angiogenesis, thereby regulating the occurrence of vascular morphogenesis and further controlling bone formation and regeneration. They regulate the transcriptional program that guides vascular invasion through collagen-integrin interactions and C-X-C motif chemokine ligand 12 (CXCL12). Functionally, in 3D human cell co-cultures, CXCL12 treatment can rescue angiogenesis impaired by the depletion of stromal cell YAP/TAZ [36]. The absence of YAP/TAZ affects the normal mobilization of osteoblast precursors and subsequent cartilage and new bone formation, particularly the endochondral bone formation in the neck of the bone, while also significantly reducing the overall bone cell density and the density

of Osx-GFP+ cells [37]. At the gene expression level, the expression of Cxcl12 mRNA in osteoblast lineage cells is also significantly reduced due to the absence of YAP/TAZ, which limits the formation of the bone's microvascular network and the generation of osteoblasts.

The regulation of osteogenesis-angiogenesis coupling by YAP and TAZ is highly context-dependent. Previous sections established YAP and TAZ as positive regulators driving this initial coupling. However, their constitutive overexpression can occasionally yield contradictory outcomes. Continuous YAP activation maintains cells in a highly proliferative progenitor state. This constant activation actively prevents the terminal differentiation of both osteoblast precursors and endothelial cells. Therefore, tissues require dynamic and transient YAP activation rather than continuous overexpression. Furthermore, YAP functions differently across distinct tissue microenvironments. In the epidermis, YAP overexpression decreases the Notch transcriptional response. Conversely, conditional YAP knockout triggers Notch signaling to promote cell differentiation [38]. In specific pathological contexts, targeted YAP inhibition can uniquely benefit vascularization. Metformin treatment can inhibit YAP1 and TAZ expression in hypoxic human microvascular endothelial cells. This targeted inhibition subsequently increases HIF-1α expression to promote type H vessel formation. Consequently, optimal bone healing requires a precise temporal balance of YAP and TAZ activity.

The regulatory role of YAP/TAZ in osteogenesis-angiogenesis coupling has attracted the attention of researchers, who have begun to explore the macro and micro effects that YAP/TAZ can exert under mechanical stress stimulation. During distraction osteogenesis, activation of TAZ/transcriptional coactivators associated with PDZ binding motifs specifies H-type endothelial cells (THECs) via a Notch positive feedback loop. Important molecules involved in this loop are enriched in exosomes during cell-to-cell transmission of regeneration signals, which can be used to promote segmental bone regeneration through THEC activation [39] (Figure 2).

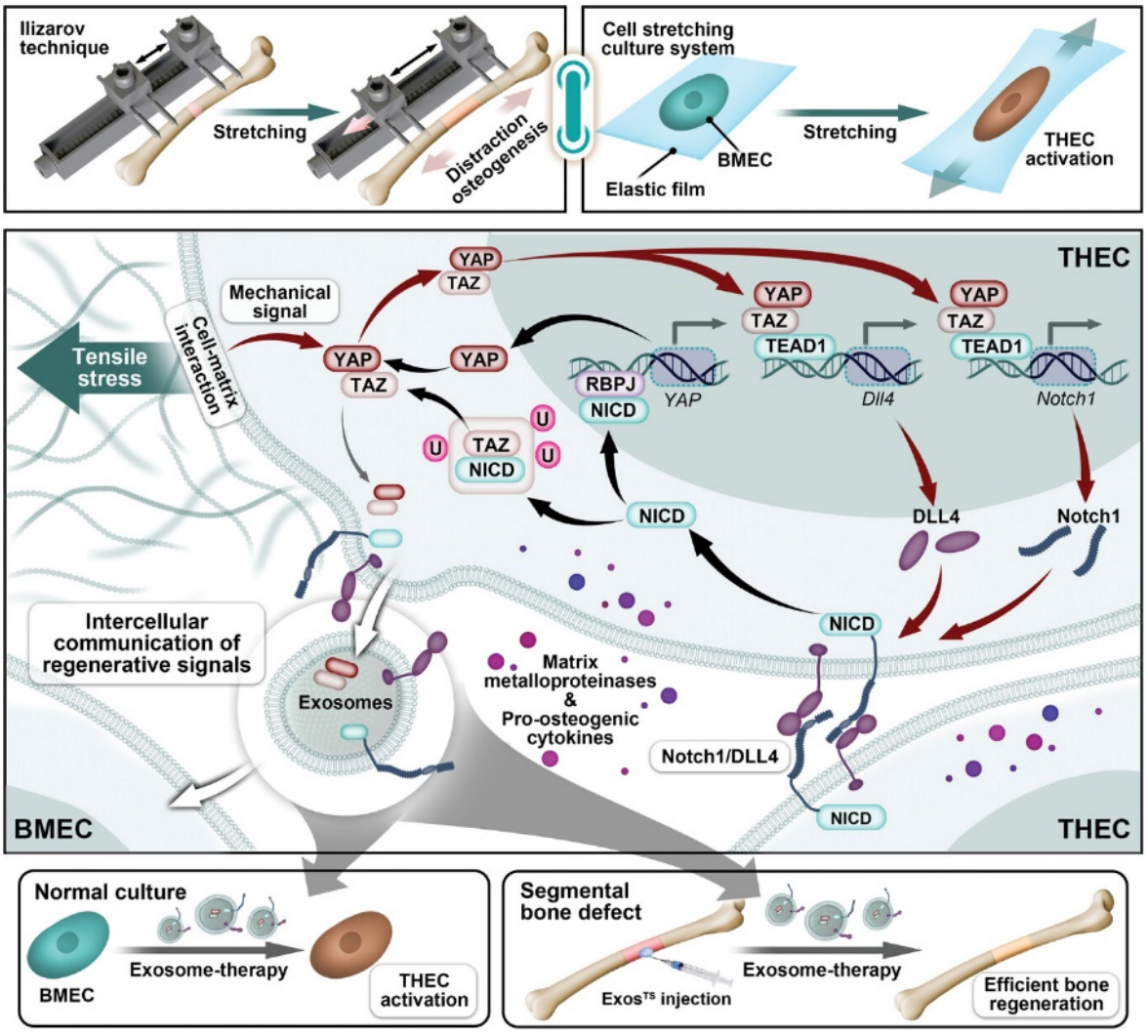

Figure 2. YAP/TAZ promote H-type vessel formation during distraction osteogenesis [39], © 2024 The Authors. Advanced Science published by Wiley-VCH GmbH

Importantly, this positive feedback signal cascade can be propagated through exosomes, thereby bringing additional therapeutic effects. Zhu et al. found that radial extracorporeal shock waves (r-ESW) can promote the self-renewal of chondrocytes/subchondral osteocytes/precursors and the formation of new blood vessels through the YAP/TAZ pathway, thereby increasing the rate of *in vivo* repair [40]. At the same time, YAP/TAZ can also enhance the synergistic effects with other growth factors when subjected to mechanical stimulation, such as when YAP/TAZ is activated by mechanical forces, the growth factor bone morphogenetic protein-2 (BMP-2) also synergistically stimulates the further activation of YAP/TAZ, integrating the biological and mechanical pathways to enhance the effects of osteogenesis-angiogenesis coupling [41].

Furthermore, recent evidence indicates that beyond macroscopic external mechanical loading, the microscopic intrinsic biomechanical cues presented by implantable biomaterials can robustly activate the YAP/TAZ signaling pathway [42]. Cytoskeletal tension fundamentally drives the mechanotransduction process, while the biophysical properties of implantable materials—such as matrix stiffness [43], pore architecture, and surface topography—act as sustained "passive" mechanical stimuli to govern cell fate determination via the YAP/TAZ axis [44]. In a notable study, Wu et al. applied 3D-printed porous scaffolds with functionalized nanocoatings to bone defects, demonstrating that cell adhesion to the scaffold induces cellular stretching tightly dependent on the strut diameter [45]. This physical elongation successfully triggers the *in vivo* activation of the YAP/TAZ pathway and its downstream effectors [46], thereby effectively promoting neovascularization and bone repair within the defect milieu. Moreover, scaffolds with distinct pore sizes and strut diameters elicited significantly divergent stimulatory effects on focal adhesion [47], further substantiating that finely-tuned mechanotransduction directly dictates the activation landscape of downstream signaling networks.

3.2. Piezo1

While the YAP/TAZ pathway primarily relies on cytoskeletal tension to regulate gene transcription, cells concurrently require immediate mechanisms to sense dynamic physical forces. The mechanosensitive non-selective cation channel Piezo1 fulfills this critical role. Piezo1 exhibits high calcium permeability and is widely recognized as a rapid sensor of dynamic mechanical signaling. In the context of bone development and osteoblast differentiation, Piezo1 serves a mechanosensory role, where mechanical stress, through Piezo1 signaling transduction, can activate multiple downstream signals and factors. For instance, in osteocytes, Piezo1 can promote the expression of Wnt1 to enhance bone formation when subjected to shear stress, while also activating the Akt signaling pathway to stimulate angiogenic capabilities.

Piezo1 is highly expressed in endothelial cells, thereby playing a crucial role in the regulation of angiogenesis. Predominantly expressed in non-sensory tissues, Piezo1 mediates mechanical responses in various cell types, including endothelial cells, astrocytes, smooth muscle cells, pancreatic acinar cells, and erythrocytes [48]. It is enriched in stem cells and their osteogenic and chondrogenic derivatives and is upregulated during the fracture healing process, indicating a close association with bone repair. Recent studies have also shown that Piezo1 is a key determinant in bone homeostasis and metabolism. Piezo1 exhibits selective permeability to Na^+, K^+, Ca^{2+}, and Mg^{2+}. Under mechanical stimulation, particularly shear stress, its permeability to Ca^{2+} slightly increases. This mechanical activation triggers a Ca^{2+} response, which subsequently upregulates the osteogenic activity of osteoblasts and promotes the angiogenic function of endothelial cells [49]. Recent biophysical studies have quantified the specific activation thresholds required to initiate these responses. Piezo1 is extremely sensitive to direct cellular membrane tension. Researchers determined that its half maximal activation tension is approximately 1.4 mN/m [50]. In standard cell patch clamp experiments, the half maximal activation pressure for Piezo1 ranges from negative 15 to negative 40 mmHg. Furthermore, fluid shear stress as low as 1.1 dyn/cm^2 can effectively activate Piezo1 channels to trigger intracellular calcium elevation [51]. During direct physical cell compression, Piezo1 requires a membrane stretch ratio of approximately 1.9 to initiate robust calcium signaling [52]. These precise quantitative thresholds highlight the high mechanosensitivity of Piezo1 in diverse physiological environments. In addition to separately activating the osteogenic and angiogenic capabilities of cells, when activated in vascular endothelial cells, Piezo1 can enhance angiogenesis while promoting osteogenesis-angiogenesis coupling. Piezo1 can regulate YAP-β-catenin signaling transduction, thereby upregulating the expression of BMP2 and VEGFA in hematopoietic stem cells, two of the most potent molecules for osteogenesis and angiogenesis. The Piezo1 channel is positively correlated with the phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) pathway and CD31 and Notch signaling in the processes of bone vascularization and ossification. When Piezo1 is absent in endothelial cells, the abnormal entry of Ca^{2+} inhibits the cells' response to shear stress, making it difficult to induce neovascularization. It also leads to the downregulation of calpain activity and inhibition of osteogenic differentiation, thus limiting the function of fracture repair [53]. As illustrated in

Figure 3, endothelial Piezo1 links mechanical stimulation to local vascular growth during fracture repair. Mechanical forces, particularly fluid shear stress, activate Piezo1 in endothelial cells and induce Ca^{2+} influx, which promotes endothelial activation and neovascularization. Conversely, endothelial-specific suppression of Piezo1 weakens mechanically induced Ca^{2+} signaling and impairs the vascular response required to support callus formation and bone regeneration. Similarly, downregulation of Piezo1 can impair the healing process, while treatment with the Piezo1 agonist Yoda1 can promote chondrogenesis and osteogenesis in PSCs through the activation of the YAP-β-catenin signaling pathway, thereby accelerating fracture healing [54].

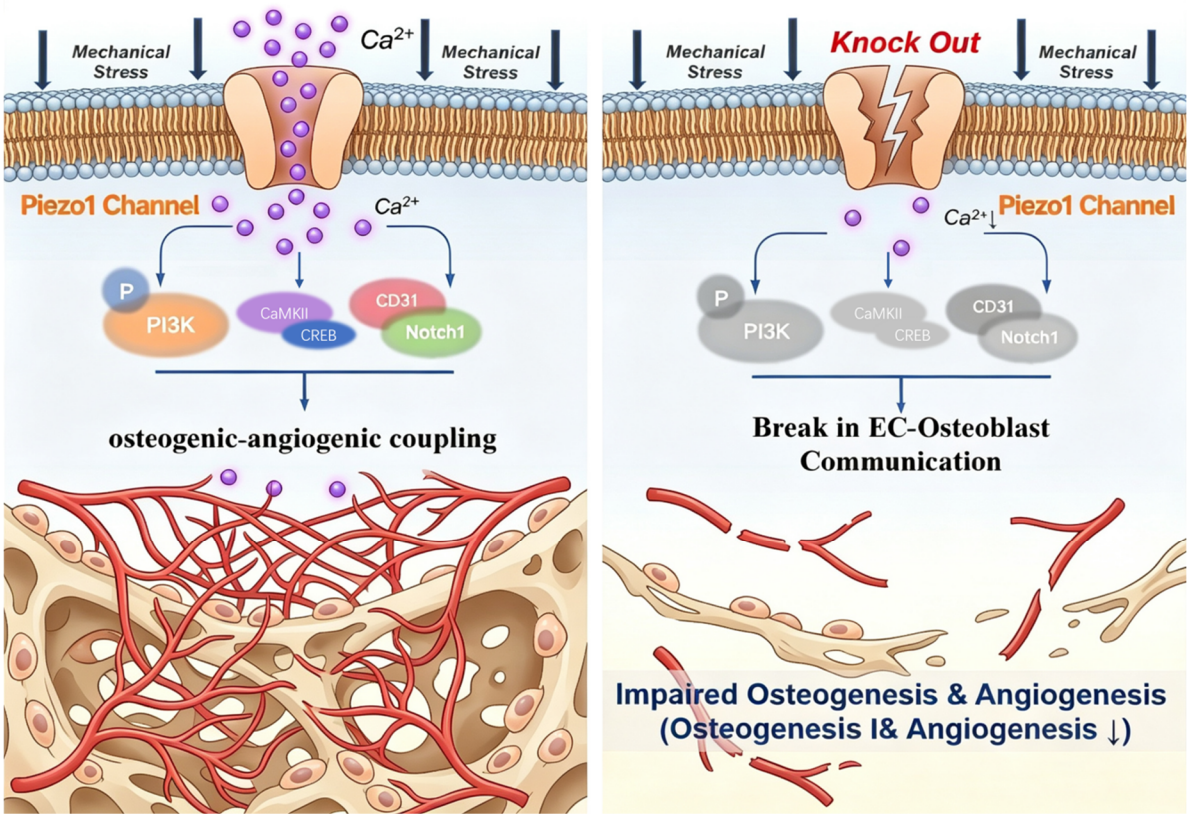

Figure 3. Piezo1 channels promote angiogenesis and play a key role in vascular biology. EC-specific suppression of Piezo1 is associated with Ca^{2+} signaling that regulates local vascular growth, which is important to support fracture repair.

Furthermore, as illustrated in Figure 3, Piezo1 also regulates Notch1, a vascularization factor unique to the mammalian skeletal system. The absence of Piezo1 downregulates the expression of Notch1, thereby inhibiting angiogenesis, callus formation, and bone mineralization during bone injury. Downregulation of Piezo1 in the callus can impair fracture healing, while activation of its specific agonist can promote fracture healing by stimulating chondrogenesis and osteogenesis regulated by periosteal stem cells (PSCs) and accelerating the transformation of cartilage to bone.

Therefore, Piezo1 holds promise as a potential target for developing clinical strategies to improve fracture healing and treat delayed or non-union fractures. Wang et al. utilized electrospinning technology to create a bilayer membrane containing the Piezo1 channel agonist Yoda1, thereby accelerating bone formation and neovascularization [55]. A previous study showed that Piezo1 is downregulated in aged bone marrow mesenchymal stem cells (BMSCs) and can respond to electrical stimulation mediated by wearable pulsed triboelectric nanogenerators, promoting osteogenic differentiation in aged BMSCs and enhancing angiogenesis in human umbilical vein endothelial cells (HUVECs) [56]. Zhou et al. also attempted mechanical stimulation with low-intensity pulsed ultrasound and found that the expression of piezo1 in periodontal ligament stem cells was activated, promoting their endothelial vascularization [57]. In osteoporotic BMSCs (SOP-BMSCs), radial extracorporeal shock waves (r-ESW) can significantly stimulate the expression of Piezo1 and activate the expression of the Piezo1 ion channel and CaMKII/CREB signaling pathway, enhancing the osteogenic differentiation and angiogenic functions of SOP-BMSCs [58].

In the macroscopic field, whole-body vibration therapy has significant therapeutic effects on bone formation, even for steroid-induced femoral head necrosis, which is achieved by enhancing the HIF-1α/VEGF axis and

activating the Piezo1 ion channel to regulate H vessel generation [59]. The sensitivity of Piezo1 to mechanical stimulation has also been applied in the field of orthodontics. Kang used a BioDynamic cyclic mechanical stretching device to perform cyclic stretching (CS) experiments on MC3T3-E1 cells treated with Piezo1 channel blockers and channel agonists, finding that blocking the Piezo1 channel led to a significant downregulation of BMP-2, Runt-related transcription factor 2 (Runx2), and osteocalcin (OCN) expression, while CS initially increased the expression of these factors, which was inhibited after Piezo1 channel blockade. In contrast, the use of the Piezo1 channel agonist led to a significant increase in Yoda1 expression, and both osteogenic differentiation and the proliferation of alveolar bone cells were significantly enhanced [60].

Given the pivotal role of the Piezo1 channel in driving osteogenesis-angiogenesis coupling, recent endeavors have focused on fabricating biomimetic scaffolds via 3D printing to provide a precise biomechanical microenvironment, thereby enabling the targeted regulation of this mechanosensitive pathway. For instance, Yu et al. developed a hydrogel-integrated 3D-printed titanium scaffold platform. This system not only facilitates the in situ sustained release of Piezo1-engineered exosomes but also reconstructs a biomimetic trabecular topological architecture at the site of osteonecrosis of the femoral head (ONFH) [61]. This dual structural-biological synergistic strategy significantly restores bone mineral density and trabecular microarchitecture, exhibits tremendous therapeutic potential for ischemic bone defects. Notably, moving beyond static mechanotransduction cues dictated by scaffold topography, cutting-edge 3D-printed scaffolds are increasingly integrating magnetic-responsive technologies with intrinsic self-mineralizing capabilities. Following the implantation of these smart scaffolds into the bone defect milieu, an external magnetic field is employed to remotely actuate the construct [62]. Through this precise, on-demand magnetic modulation, researchers can accurately manipulate the intensity, frequency, duration, and spatial vector of mechanical stimuli generated in situ. This capability allows for the controllable, dynamic activation of the Piezo1 pathway *in vivo*, establishing an innovative spatiotemporal regulatory paradigm that synergizes biomechanical stimulation with the scaffold's self-mineralization to maximize osteogenic and angiogenic efficacy [63].

3.3. Integrins

Both the Piezo1 channel and the YAP/TAZ nuclear relay rely heavily on the direct physical connection between the cell membrane and the surrounding extracellular matrix to perceive mechanical stress accurately. Integrins serve as these essential structural bridges. Integrins are a family of transmembrane adhesion receptors that consist of heterodimers of alpha and beta subunits. They play a crucial role in structurally tethering the cytoskeleton to the extracellular matrix [64]. Integrins serve as mechanoreceptors in bone tissue, transducing mechanical signals into biochemical responses within osteocytes [65]. The integrin family, with its numerous members, senses mechanical stress stimuli on the cell surface and subsequently participates in intracellular signal transduction. Integrin β1 can mediate osteogenic differentiation through the glycogen synthase kinase 3 beta (GSK-3β)/β-catenin signaling pathway [66], BMP2/Smad signaling pathway, and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway [67]. Integrin αVβ3 can upregulate the phosphorylation of FAK and nuclear Yap to participate in osteogenesis and indirectly promote osteogenesis by affecting angiogenesis, while integrins α5β1 and αV can promote the opening of connexin 43 hemichannels (Cx43 HCs) through the PI3K/Akt signaling pathway [68]. The integrin family plays a significant role in regulating bone regeneration and is a direction that cannot be overlooked in related research.

Studies have shown that integrins α5β1 and αvβ3 can regulate vascular morphogenesis in polymeric matrices, particularly having a significant regulatory effect on the construction and regeneration of terminal microvascular networks [69]. Furthermore, integrins not only adhere to the cytoskeleton and extracellular matrix but also establish signaling pathways between the two, thereby regulating cell behavior [70].

Integrin αvβ3 mediates cell adhesion to several extracellular matrix proteins in the bone microenvironment, thus playing a significant role in promoting endothelial cell migration and the formation of new microvascular networks at the bone termini [71]. After inhibiting the expression of integrin αvβ3, the regulation of the FAK/ERK pathway by integrin αvβ3 is suppressed, leading to the obstruction of endothelial cell migration, preventing the necessary nutritional support for osteogenesis, and inhibiting both osteogenesis and angiogenesis [72]. Jiang et al. found that after stimulating BMSCs with fluid shear stress (FSS) for 1–4 h per day, the expression of the integrin β1-FAK-ERK signaling pathway was enhanced, and under these conditions, the mRNA levels of alkaline phosphatase, Runx2, and osteocalcin (OCN), as well as the protein levels of osteocalcin and osteopontin (OPN) in BMSCs, were all increased. Additionally, FSS and co-culturing with HUVECs synergistically increased the expression of integrin β1 in BMSCs and further activated cell adhesion kinase (FAK) and downstream extracellular signal-related kinase (ERK), thereby enhancing the expression of Runx2 [73].

However, research has found that the junctional markers on endothelial cells significantly change depending on the type of activated integrin; αvβ3 stimulation leads to fewer organized connections, while the α5β1 pathway integrins can provide a broader range of neovascular networks [69]. When the α5β1 pathway integrins are stimulated by mechanical stress, they can also activate angiopoietin-2 (Angpt2) in angiopoietins, thereby inducing endothelial cell migration and promoting blood vessel formation [74]. In addition to forming better-organized blood vessels than integrin αvβ3, the α5β1 pathway can also regulate osteogenesis-angiogenesis coupling. Compared to αvβ3, the α5β1 pathway is more sensitive to pressure sensing, and Pan et al. found that after high-pressure oxygen treatment at the site of a cranial bone flap implant, there was a significant increase in the gene expression level of the α5β1 pathway [75], which led to more mature osteoblasts and endothelial cells, along with high-level expression of genes related to adhesion and migration, and a significant increase in the number of OSX^+ osteoblasts and $EMCN^+$, $CD31^+$ endothelial cells [76]. Furthermore, integrin αvβ3 does not mediate the angiogenic effects of exosomes, while αvβ5 can interact with exosomes to promote endothelial cell migration and angiogenesis [77].

3.4. Wnt/β-Catenin

Once integrins establish a solid physical connection with the extracellular matrix and sense external mechanical stress, they must transmit these signals inward to dictate cell fate. The Wnt signaling family frequently acts as a critical downstream biochemical effector for these integrin-mediated mechanosensory signals. This family is widely present in various vertebrates and plays an essential role in physiological processes such as early embryonic development, organ formation, and tissue regeneration [78]. It regulates osteogenesis-angiogenesis coupling through two distinct mechanisms, which include the canonical and non-canonical pathways. The canonical pathway relies on the stabilization of β-catenin to drive osteoblast differentiation. Mechanical stimulation inactivates glycogen synthase kinase 3 β through phosphorylation [79]. This inactivation allows β-catenin to translocate into the nucleus and activate osteogenic genes [80]. In contrast, the non-canonical Wnt pathways operate independently of β-catenin. Mechanical stress triggers these non-canonical cascades to stimulate intracellular calcium release. This calcium elevation then activates downstream kinases to enhance endothelial cell migration and neovascularization. Together, the canonical pathway establishes the osteogenic baseline, while the non-canonical pathway accelerates the angiogenic response during bone repair [81].

These two Wnt pathways respond to entirely different mechanical environments. Recent biological studies utilizing tunable hydrogels explicitly demonstrate the canonical mechanism. Researchers cultured mesenchymal stem cells on highly rigid extracellular matrices. This static mechanical environment directly suppressed GSK-3β. The specific suppression induced massive β-catenin nuclear translocation to drive continuous osteoblast differentiation. In contrast, separate microfluidic experiments highlight the non-canonical pathway [82]. Researchers applied pulsatile fluid shear stress to bone cells. This highly dynamic physical stimulation immediately upregulated the expression of Wnt5a protein [83]. The Wnt5a protein subsequently triggered massive intracellular calcium oscillations without affecting β-catenin. These acute calcium signals rapidly promoted endothelial cell migration and angiogenesis [84]. Therefore, cells utilize the canonical Wnt pathway to sense stable extracellular matrix stiffness. Conversely, cells utilize the non-canonical Wnt pathways to rapidly adapt to sudden mechanical shocks and fluid shear variations.

During the process of distraction osteogenesis, the epidermal growth factor-like domain-containing protein 6 (EGFL6) activates the Wnt/β-catenin pathway upon tensile mechanical stimulation, inducing the migration and proliferation of various endothelial cells. This enhances angiogenesis while promoting the osteogenic differentiation of BMSCs [85]. He et al. also found that under hypoxic conditions during distraction osteogenesis, the expression of Wnt/β-catenin can be further increased, particularly in promoting angiogenesis, leading to an increase in bone formation and further supporting the synchronous occurrence of osteogenesis and angiogenesis [86]. In contrast, under sustained static mechanical stress, such as the continuous application of 100 kPa pressure by Zhang et al. on periodontal ligament stem cells, a significant increase in the expression of the Wnt/β-catenin pathway was observed, which enhanced osteogenic differentiation while suppressing the expression of osteoclastic differentiation [87]. In addition, macroscopic systemic exercise, which aids in bone formation, also involves the Wnt/β-catenin signaling pathway. A protein sensitive to mechanical stimulation, Antxr1, is downregulated during exercise, thereby promoting an increase in bone mass and the number of newly formed blood vessels in osteoporotic patients, as the expression of Antxr1 inhibits the Wnt/β-catenin signaling pathway [88].

In fact, the response of the Wnt/β-catenin signaling pathway to mechanical stimulation is not static. After continuous exposure to cyclic tensile stress, the expression level of Wnt/β-catenin initially increases and then decreases [89]. This may be because early mechanical stimulation inactivates negative regulatory factors of Wnt/β-

catenin such as GSK-3β, but with sustained mechanical stress, there is no new inactivation of negative regulatory factors, while some agonists may lose function due to phosphorylation, leading to a decrease in Wnt/β-catenin expression [90]. However, the Wnt/β-catenin signaling pathway can also respond to ultrasonic mechanical stimulation. For example, low-intensity pulsed ultrasound can activate the Wnt/β-catenin signaling pathway, upregulate the expression of osteogenic and angiogenic factors such as Runx2 and VEGF proteins, and even mitigate the downregulation of osteogenic function caused by long-term mechanical stress-induced bone fatigue [91]. Therefore, utilizing the Wnt/β-catenin pathway to promote osteogenesis-angiogenesis coupling by applying mechanical stimulation of appropriate duration and various types may be a feasible strategy.

3.5. Other Mechanosensitive Pathways

The previously mentioned major pathways form the core mechanotransduction network. Several other signaling cascades also play essential roles. These additional pathways specifically regulate cytoskeletal dynamics and intercellular communication. They function synergistically to enhance the overall osteogenesis and angiogenesis coupling process. Table 2 systematically compares the mechanosensor functions in diverse bone and vascular mechanical environments.

The RhoA/ROCK signaling pathway acts as a major regulator of intracellular tension. Mechanical forces directly activate the small GTPase RhoA. Activated RhoA subsequently stimulates Rho-associated protein kinase [92], commonly known as ROCK. The activation of ROCK generates substantial cytoskeletal contractile forces. These mechanical forces strongly promote the osteogenic differentiation of mesenchymal stem cells. Simultaneously, the RhoA/ROCK pathway strictly controls the migration and spatial organization of endothelial cells [93]. This coordinated regulation fundamentally drives the formation of functional microvascular networks during bone repair.

Furthermore, the Notch signaling pathway governs direct cell-to-cell communication under mechanical stress. Physical forces including fluid shear stress can activate Notch receptors on the surface of endothelial cells. This specific activation promotes the proliferation of type H endothelial cells [94]. Type H vessels are specialized capillaries strictly associated with active bone formation. Moreover, the Notch pathway intimately interacts with other primary mechanosensors [95]. Prior sections noted that YAP/TAZ activation can upregulate Notch ligands such as DLL4. This critical crosstalk establishes a positive feedback loop. This loop significantly accelerates the synchronized development of blood vessels and bone tissue.

Additionally, the Hypoxia-Inducible Factor 1-alpha (HIF-1α) pathway closely responds to mechanical stimulation. The HIF-1α pathway is traditionally recognized as a hypoxia sensor [96]. However, recent studies indicate that dynamic mechanical loading can also stabilize HIF-1α proteins independently of oxygen levels. This stabilization directly upregulates the expression of vascular endothelial growth factor [97]. The increased secretion of this potent growth factor robustly stimulates local angiogenesis and supports subsequent osteoblast activity. Ultimately, integrating these diverse pathways provides a highly comprehensive perspective on mechanically driven bone regeneration.

Table 2. Comparison of mechanosensor functions in diverse bone and vascular mechanical environments.

Mechanosensory Pathway	Primary Mechanical Stimulus	Target Cells	Osteogenic Effect	Angiogenic Effect
YAP/TAZ	Matrix stiffness, cytoskeletal tension	Osteoblasts, endothelial cells	Promotes osteoblast differentiation through nuclear translocation.	Regulates vascular morphogenesis and maintains endothelial survival.
Piezo1	Fluid shear stress, membrane stretch	Osteocytes, endothelial cells	Upregulates Wnt1 to enhance bone formation.	Triggers calcium influx to stimulate neovascularization.
Integrins (α5β1)	Cell adhesion, extracellular matrix tension	Mesenchymal stem cells	Activates focal adhesion kinase to support bone regeneration.	Guides endothelial cell migration to build microvascular networks.
Wnt/β-catenin	Cyclic mechanical stretching	Osteoblast precursors	Stabilizes β-catenin to activate essential osteogenic genes.	Synergizes with calcium signaling to accelerate vessel growth.
RhoA/ROCK	Matrix rigidity, physical compression	Mesenchymal stem cells	Generates cytoskeletal contractile forces to drive osteogenesis.	Controls the spatial organization of growing capillaries.

4. Conclusions

Osteogenesis-angiogenesis coupling is a complex biological process that depends on a highly integrated mechanosignaling network [98]. Rather than operating in isolation, key mechanosensors such as YAP/TAZ, Piezo1, integrins, and the Wnt/β-catenin pathway engage in continuous intracellular crosstalk [99]. For example, integrin activation and subsequent cytoskeletal tension provide the structural baseline that allows Piezo1 channels

to open efficiently under fluid shear stress. The resulting calcium influx activates downstream kinases that directly interact with the YAP/TAZ transcription complex [100]. Simultaneously, mechanical activation suppresses negative regulators of Wnt signaling, which stabilizes β-catenin and promotes the transcription of essential osteogenic and angiogenic factors [101]. This synergistic network ensures that endothelial neovascularization and osteoblast differentiation occur with precise spatiotemporal synchronization [102]. As summarized in Figure 4, mechanical stimuli are sensed through an interconnected network involving integrins, Piezo1, YAP/TAZ, and Wnt/β-catenin signaling. Integrin-mediated adhesion and cytoskeletal tension provide the structural basis for force transmission, whereas Piezo1 rapidly converts membrane deformation into Ca^{2+} signals. These upstream mechanical inputs subsequently converge on transcriptional regulators such as YAP/TAZ and β-catenin to coordinate osteogenic differentiation, endothelial activation, and vascular formation. In addition, digitally customized 3D-printed biomaterials can reproduce or modulate these biomechanical cues, thereby enabling more precise regulation of osteogenesis–angiogenesis coupling for personalized bone regeneration.

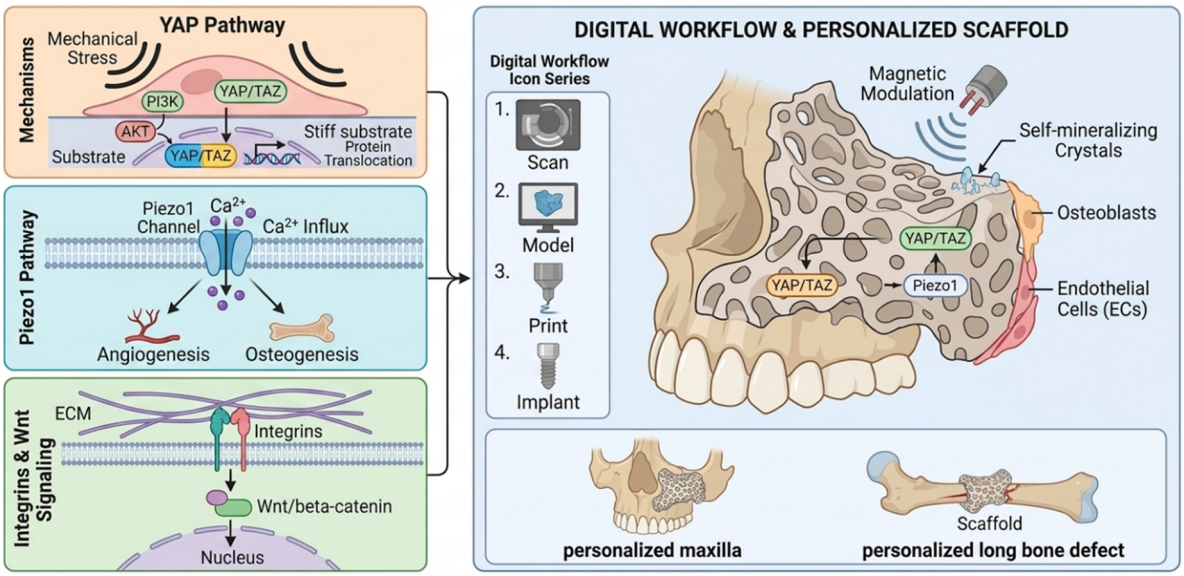

Figure 4. Integrated mechanotransduction networks and biomaterial-based regulation of osteogenesis–angiogenesis coupling.

Despite recent progress, several limitations persist in current mechanotransduction research. Most existing studies rely heavily on two-dimensional cell cultures or simplified static models, which cannot fully replicate the complex in vivo loading environment [103]. Furthermore, isolating the specific effects of a single mechanical force remains technically challenging because cells simultaneously experience multiple physical cues in the bone niche [104]. Current research also lacks advanced methodologies for the real-time, non-invasive tracking of mechanosignaling activation within living tissues. Additionally, the exact molecular thresholds required to trigger distinct pathways in different cell types remain poorly defined, which creates gaps in our understanding of cell-specific responses [105].

Translating these mechanobiological principles into advanced clinical therapeutics faces significant roadblocks. Although digitally customized 3D-printed smart scaffolds offer excellent anatomical matching, their long-term degradation kinetics and mechanical stability under dynamic physical loading require further optimization [106]. Achieving precise, uniform, and safe remote magnetic modulation within deep human tissues represents another major bioengineering challenge [107]. Furthermore, the standardization of digital dentistry and orthopedic workflows remains incomplete. Current challenges include high manufacturing costs, long processing times for personalized modeling, and a lack of clear regulatory guidelines for bioprinted smart implants.

Finally, certain limitations of this review must be explicitly acknowledged. This article systematically addresses key mechanotransduction networks and several vital auxiliary cascades. These pathways include the YAP/TAZ, Piezo1, integrin, Wnt/β-catenin, RhoA/ROCK, and Notch signaling systems. However, the cellular mechanobiology landscape is remarkably vast. Other emerging mechanosensors and complex epigenetic regulatory mechanisms remain beyond the scope of this discussion. Furthermore, this review focuses extensively on the direct interaction between endothelial cells and osteoblast precursors. It does not fully address the critical role of systemic physiological environments. Factors including immune regulation and macrophage polarization

significantly influence the mechanical microenvironment during bone healing. Future studies must address these interdisciplinary gaps to broaden therapeutic strategies for complex bone defects.

Author Contributions

Conceptualization, E.L. and H.L.; methodology, Z.Z.; software, S.L.; validation, E.L. and H.L.; formal analysis, L.L.; investigation, Z.Z.; resources, E.L.; data curation, S.L.; writing—original draft preparation, Z.Z.; writing—review and editing, Z.Z., L.L. and W.Y.; supervision, E.L.; project administration, W.Y. and S.L.; funding acquisition, H.L. and E.L. All authors have read and agreed to the published version of the manuscript.

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No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest

The authors declare no conflicts of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, we used Gemini to improve the English language quality and readability. After using this tool, we reviewed and edited the content as needed and take full responsibility for the content of the published article.

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