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REVIEW ARTICLE

Advancing bone and cartilage regeneration with three-dimensional-printed piezoelectric biomaterials: Current progress and future outlook

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Abstract

Bone and cartilage defects resulting from trauma, degenerative diseases, or congenital malformations remain a significant clinical challenge due to the limited intrinsic healing capacity of these tissues, often leading to unsatisfactory outcomes. Piezoelectric biomaterials, which are capable of generating localized electrical signals under mechanical stimulation, have attracted considerable attention as they could mimic the electromechanical microenvironment of native tissues and modulate key cellular processes. However, conventional fabrication strategies have usually failed to meet the personalized requirements of bone and cartilage regeneration. Three-dimensional (3D) printing offers powerful tools for producing patient-specific scaffolds with complex architectures and controlled functionality. In this review, we firstly introduce the piezoelectric properties of the natural bone and cartilage tissue, and then discuss the characteristics of piezoelectric materials in regenerative medicine, with particular emphasis on the advantages and limitations of using 3D printing techniques in the fabrication of the piezoelectric biomaterials. Finally, we summarize the recent advances in 3D-printed piezoelectric scaffolds for bone and cartilage regeneration. Consequently, this review highlights the significant potential and practical value of 3D-printed piezoelectric scaffolds as the next generation of osteochondral implants.

Keywords: Bioactive materials; Biofabrication; Bone regeneration; Cartilage regeneration; Piezoelectric biomaterials; Three-dimensional printing

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1. Introduction

Bone and cartilage defects represent a significant clinical challenge due to their intrinsically limited regenerative capacity and the structural and functional complexity of osteochondral tissues.[1-4] Conventional clinical interventions, including autografts, allografts, and synthetic substitutes, often fail to achieve long-term functional recovery and are frequently associated with donor site morbidity, immune rejection,

or insufficient integration. Electrical stimulation has long been recognized as a potent and effective modality for regulating cell migration, proliferation, and lineage differentiation. Many exogenous electrical stimulation methods have been explored to enhance bone and cartilage regeneration.[5] Despite their therapeutic potential, these methods require external power sources and implanted electrodes, which can cause discomfort, infection, and poor patient compliance.[6,7] These limitations have prompted growing interest in piezoelectric biomaterials capable of generating electrical cues without external devices.

Piezoelectric biomaterials have emerged as a promising alternative, as they convert physiological mechanical forces into localized electrical signals, thereby recreating the native electromechanical microenvironment required for bone and cartilage regeneration.[8] This electromechanical conversion closely mimics the natural bioelectric environment in bone and cartilage, where collagen fibrils exhibit inherent piezoelectricity that contributes to tissue remodeling. Compared with conductive or electroresponsive materials, piezoelectric materials offer the advantage of autonomous stimulation driven by normal physical activity. The resulting electrical cues are spatially constrained, mechanically responsive, and biologically relevant, making piezoelectric materials particularly well-suited for bone and cartilage repair, where dynamic loading continuously activates and sustains their therapeutic function.

At the same time, the rapid development of additive manufacturing has transformed the fabrication of biomaterial scaffolds. Three-dimensional (3D) printing technology precisely controls the architecture, porosity, and composition of piezoelectric biomaterials, which could be designed according to predictable mechanical behavior and spatial organization of native bone or cartilage.[9] Such design flexibility is essential for piezoelectric biomaterials, as the printing process strongly influences crystal orientation, dipole alignment, and the resulting electrical output. The combination of 3D printing and piezoelectric materials has opened new opportunities for creating smart scaffolds that respond to the mechanical environment of bone and cartilage.

Although the relevant investigation about piezoelectric biomaterials is expanding rapidly, several critical gaps remain. Previous studies have mainly focused on general material categories or printing technologies, but a general review of the interaction between piezoelectric materials and 3D-printed architectures is absent. Moreover, little attention has been devoted to the distinct electromechanical and mechanical requirements of the bone, cartilage, and their osteochondral interface, which may require a comprehensive understanding of material chemistries, piezoelectric coefficients, stiffness levels, and architectural designs.

To address these gaps, this review provides a focused and integrated overview of 3D-printed piezoelectric biomaterials for bone, cartilage, and osteochondral regeneration. Fundamental principles of piezoelectricity and their biological relevance are briefly introduced, followed by an overview of inorganic, organic, and composite systems with their respective advantages and limitations. The use of advanced 3D printing techniques, including fused deposition modeling (FDM), vat photopolymerization (VPP), inkjet printing, powder bed fusion (PBF), and bioprinting, in fabricating piezoelectric scaffolds is then discussed. Finally, key challenges and future directions are highlighted to guide the clinical translation of 3D-printed piezoelectric scaffolds for next-generation osteochondral implants.

2. Piezoelectricity in bone and cartilage

2.1. Native cartilage

Cartilage is a specialized connective tissue that lacks vascular and lymphatic supply, resulting in a limited regenerative potential. Nutrient exchange primarily relies on the slow diffusion from the synovial fluid.[10,11] Natural cartilage is composed of chondrocytes, water, collagen type II, and proteoglycans. Under compression or shear stress, the dipole components within collagen molecules undergo reorientation and produce charge separation, generating weak bioelectric signals.

Since the Nobel Prize in Physiology or Medicine was awarded to Ardem Patapoutian in 2021 for the discovery of Piezo channels, increasing attention has turned toward their role in cartilage regeneration. Piezo1 and Piezo2, belonging to the mechanoreceptor family, are capable of sensing mechanical stimuli such as pressure, stretch, and shear forces, and subsequently convert these physical signals into intracellular bioelectric signals. These channels, together with collagen-based piezoelectricity, trigger the influx of calcium ions (Ca^{2+}) and regulate intracellular calcium homeostasis, subsequently activating downstream signaling cascades such as calmodulin (CaM) and calcineurin. These molecular events collectively enhance extracellular matrix synthesis, promote chondrocyte proliferation, and facilitate tissue repair. Therefore, the combined contribution of collagen-based piezoelectricity and Piezo channel-mediated mechanotransduction provides a synergistic mechanism that enables cartilage to sense and adapt to its mechanical microenvironment.

2.2. Native bone

Compared with cartilage, bone demonstrates stronger piezoelectric properties, which might be attributed to both

structural and compositional features. Bone is primarily composed of collagen (~22 wt%) and hydroxyapatite (HAp; ~69 wt%). Collagen fibers are encapsulated into the collagen matrix and then embedded in HAp crystals. This interwoven structure endows bone tissue with its remarkable compressive strength.[12] The piezoelectricity of bone was first reported by Yuan *et al.*,[13] which is mainly attributed to the asymmetric structure of collagen molecules. Type I collagen, the dominant form in bone, exhibits strong piezoelectricity due to its highly ordered triple-helical arrangement. According to Wolff's law, when bone is subjected to mechanical loading, the dipole moments within collagen fibers rearrange and lead to charge separation, generating an electric field.[14]

Several factors contribute to the superior piezoelectric behavior of bone compared with cartilage. The piezoelectric coefficient of type I collagen is reported to be 28–32% higher than that of type II collagen.[15] Moreover, collagen fibers in bone tissue exhibit a more organized arrangement compared with the loose structure in cartilage, forming structures with an organized pattern (such as bone plates) that efficiently generate piezoelectricity under stress. In addition, HAp crystals themselves exhibit intrinsic piezoelectricity, further enhancing the electromechanical responsiveness of bone tissue.[7]

Beyond the matrix-level mechanism, Piezo1 and Piezo2 play an important role in bone mechanotransduction. These channels respond to external forces by regulating the influx of ions such as Ca^{2+}, sodium ions, potassium ions, and magnesium ions (Mg^{2+}). Among these ions, Ca^{2+} functions as a second messenger and plays a dominant role in the activation of kinases (e.g., calcium/CaM-dependent protein kinase II [CaMKII]) and phosphatases (e.g., calcineurin), which further trigger downstream signaling cascades, such as the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), Wnt/β-catenin, and Hippo/Yes-associated protein signaling pathways. The coordinated activation of these pathways modulates gene expression, regulates osteoblast activity, and guides tissue remodeling. In the process of bone repairing, Piezo1 not only enhances osteoblast responsiveness to mechanical loading but also promotes cell migration toward injury sites, thereby accelerating fracture healing and localized regeneration.[16]

2.3. Piezoelectric biomaterials

The term "piezoelectric" originates from the Greek word "*piezein*," meaning "to press." Piezoelectric materials generate electrical signals in response to mechanical deformation (direct piezoelectric effect) and conversely deform under an electric field (converse effect). The origin of piezoelectricity lies in the intrinsic non-centrosymmetric structure of materials, arising from the asymmetric arrangement of ions in inorganic crystals, such as zinc oxide (ZnO), or oriented molecular dipoles in organic polymers, such as polyvinylidene fluoride (PVDF) and poly-L-lactic acid (PLLA). Mechanical loading distorts these asymmetric structures and induces charge separation, producing localized electric fields. Similar electromechanical behavior also exists in biological tissues such as bone and cartilage, where collagen fibrils exhibit inherent piezoelectricity that contributes to mechanotransduction, tissue remodeling, and regeneration.[17,18]

The most common method for calculating the piezoelectric properties of materials is the piezoelectric strain constant d_{ij}, which quantifies the polarization generated per unit mechanical stress (Coulomb/Newton). According to the piezoelectric theory, there is a linear relationship between stress and generated charge, expressed as **Equation (1)**:

$$P = d \times T \quad (1)$$

where P is the polarization vector and d and T are the piezoelectric strain coefficient and the imposed stress, respectively. Since piezoelectric responses are direction-dependent, different coefficients are used to describe axial, transverse, and shear modes. The longitudinal coefficient d_{33} measures charge generated parallel to the applied stress and is the most widely used parameter in biomedical research due to its relevance to compressive loading in bone. The transverse coefficient d_{31} captures polarization generated perpendicular to the applied force. Shear coefficients, such as d_{14}, describe electromechanical coupling under shear deformation, a mode more prominent in cartilage, where fibrillar rotation and sliding dominate the mechanical environment.[19] These coefficients directly influence scaffold performance: d_{33} is dominant in bone under compressive loading, whereas d_{31}/d_{15} are more relevant to cartilage, which primarily experiences shear and tensile forces.

3. Classification of piezoelectric biomaterials

Injury or degeneration disrupts bioelectric balance in bone and cartilage tissues, leading to impaired natural repair capacity. Given that both tissues inherently possess piezoelectric properties, biomimetic design strategies are essential for fabricating scaffolds that recapitulate their native electromechanical cues. By reproducing the piezoelectricity of native bone and cartilage tissues, the

tissue-engineered scaffolds could functionally restore their structural and physiological functions.

Before exploring their biomedical applications, it is crucial to first understand the classification, properties, and functional mechanisms of piezoelectric biomaterials. These materials can be broadly divided into inorganic, organic, and composite systems (Table 1). Understanding their respective advantages and limitations provides a framework for tailoring scaffolds to bone and cartilage regeneration.

3.1. Inorganic piezoelectric material

Inorganic piezoelectric materials include natural crystals and synthetic ceramics. Natural piezoelectric crystals typically show low piezoelectric coefficients, which limit their biomedical applicability. Hence, research has shifted toward synthetic ceramics and semiconductors, which offer tunable electromechanical behavior and improved biocompatibility.

Synthetic ceramics comprise lead-based and lead-free systems. Due to the significant toxicity of the lead-based piezoelectric materials, lead-free ceramics such as barium titanate (BT), potassium sodium niobate (KNN), and bismuth sodium titanate are preferred for biomedical applications. Additionally, semiconductor materials like boron nitride (BN), aluminum nitride (AlN), gallium nitride (GaN), and black phosphorus have drawn attention. Among them, BT, ZnO, and lead zirconate titanate remain the most studied owing to their high piezoelectric constants and mechanical stability. However, despite these advantages, inorganic ceramics are intrinsically brittle and poorly degradable, which limits their direct clinical translation.

3.1.1. Barium titanate

Barium titanate is the first lead-free piezoelectric ceramic discovered and is perhaps the most studied piezoelectric ceramic. It is a lead-free perovskite oxide that typically adopts a tetragonal ferroelectric phase near room temperature. When an external force is applied to BT, the internal ions within the material are displaced, causing a redistribution of charges within its perovskite structure. This piezoelectric polarization facilitates the adsorption of Ca^{2+} ions and promotes apatite nucleation, thereby supporting osteoconductivity. In addition, the biocompatibility of BT has been demonstrated in multiple *in vitro* and *in vivo* studies, making it a widely used piezoelectric additive or active phase in composite scaffolds to enhance osteogenic performance.[36]

There are several recent advances in 3D-printed BT-based scaffolds, typically through polymer–ceramic composite strategies. By incorporating BT nanoparticles into printable polymer matrices such as polylactic acid (PLA) or hydrogels, spatially programmed electromechanical cues and improved integration with host tissue can be achieved, highlighting the advantages of 3D printing in overcoming the intrinsic brittleness and poor processability of bulk BT ceramics. Consequently, BT-based 3D-printed scaffolds are particularly suited for bone and subchondral applications that require strong electromechanical coupling and patient-specific structural design, whereas their limited degradability still restricts direct use in cartilage-dominated regions.[37]

3.1.2. Potassium sodium niobate

Potassium sodium niobate is a lead-free perovskite oxide in which potassium oxide/sodium oxide occupies the A-site, and niobium ion occupies the B-site, with the oxygen atoms at the vertices. It combines environmentally friendly, high piezoelectric coefficient, and thermal stability across −20 to 100°C. Notably, its Young's modulus ($E \approx 104$ GPa) is slightly lower than that of BT, but is still robust. Furthermore, polarized KNN exhibits antibacterial properties and supports cell adhesion and proliferation, suggesting potential utility in bone-related applications.[38] By integrating KNN particles into printable polymeric matrices and fabricating scaffolds with cartilage-mimetic architectures, such as lower stiffness regions, controlled porosity, and anisotropic microstructure, 3D printing enables the design of personalized, mechanically compliant constructs that better match the structural characteristics of cartilage. Such hybrid and architecturally optimized KNN-based scaffolds may reconcile the high piezoelectric output of ceramics with the mechanical requirements of cartilage, thereby expanding the applicability of KNN beyond purely bone-oriented regeneration.[39]

3.1.3. Boron nitride nanotubes

Boron nitride nanotubes (BNNTs) have a structure similar to that of carbon nanotubes, but the substitution of boron and nitrogen atoms introduces high polarity and enhanced piezoelectricity. They are biocompatible, thermally stable, and mechanically strong ($E \approx 1.3$ TPa). Incorporating BNNTs into polymers or ceramics significantly improves mechanical reinforcement and piezoelectric response, making them promising reinforcement phases in tissue engineering composites.[6] The high aspect ratio and surface polarity of BNNTs facilitate efficient stress transfer and electrical signal generation under physiological loading, thereby amplifying piezoelectric output at relatively low filler concentrations. These properties make BNNTs particularly effective in bone-oriented scaffolds, where high stiffness and strong electromechanical coupling are advantageous. Nevertheless, the ultra-high modulus of BNNTs may result in excessive stiffness when used at high

Table 1. Piezoelectric constants of different piezoelectric materials and native tissues

Piezoelectric biomaterial	Piezoelectric coefficient, d_{33} (pC/N)	References
Polyvinylidene fluoride	34	20,21
		20
		20
		21
		21
		20
Poly(vinylidene fluoride-co-trifluoroethylene)	38	22
		22
		21
		22
		21
		22
		22,23
		22
		21
Poly-L-lactic acid	10.7 (d_{14})	23
		22
		23
		22
		23
		23
		22
Polyhydroxybutyrate	1.6–2 (d_{14})	23
		23
		25
		23
Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)	1.3 (d_{14})	23
		22
		23
		22
		23
		23
		22
Chitin	4	24–26
		24,25
		24,25
		24
		24,25
		24
		24
		25,26
		24,25
		24
Chitosan	2.54	28
		27
		28
		27
		28
		29
		28
Cellulose	0.1 (d_{31})	27
		30
		26
		27
		27
		25,28
		27
		26

Table 1. Piezoelectric (Continude...)

Piezoelectric biomaterial	Piezoelectric coefficient, d_{33} (pC/N)	References
Barium titanate	191	28,29
		28,29
		28,29
		27,28
		28,29
		27,28
		28,29
		29,30
		28,29
		27,28
Hydroxyapatite	1.5–2.4	30,31
		29,30
		30,31
		29,30
		30,31
		29,30
		30,31
		31,32
		30,31
		29,30
Zinc oxide	12.4	32
		31
		32
		31
		32
		31
		32
		33
		32
		31
Potassium sodium niobate	63	33
		32
		33
		32
		33
		32
		33
		34
		33
		32
Human bone	0.7–2.3 pC/N	34
		33
		34
		33
		34
		33
		34
		35
		34
		33
Articular cartilage	0.2–0.7 pC/N	35

loadings, leading to mechanical mismatch with cartilage tissue. As a result, BNNTs are most suitable as reinforcing additives rather than standalone matrices, and their application in osteochondral regeneration requires careful compositional control and hierarchical structural design to balance stiffness and compliance.[40]

3.1.4. Zinc oxide

Zinc oxide exhibits excellent piezoelectric properties due to its AB-type composition with tetrahedral coordination. In addition, ZnO has good biocompatibility and low toxicity, which makes it a popular piezoelectric material. Zinc and oxide ions are alternately distributed in the hexagonal structure. When an external force is applied, the centers of positive and negative charges are separated, generating a piezoelectric potential. It could release zinc ions, which may prevent bacterial infection and promote osteogenic differentiation by influencing Yes-associated protein expression along with the nuclear envelope protein Lamin A/C, further promoting the expression of the nuclear transcription. However, the main obstacle to the application of ZnO is its poor mechanical strength and low fracture toughness, causing it to fracture easily under mechanical stress. A common strategy used to overcome this limitation is doping, which can effectively enhance its piezoelectric properties and mechanical strength.[41] In piezoelectric composite systems, ZnO provides bioactive ion release and piezoelectric stimulation, while the surrounding matrix ensures structural integrity.

3.1.5. Aluminum nitride

Aluminum nitride is another tetrahedrally coordinated piezoelectric ceramic with enhanced hardness, compressive strength, and excellent chemical stability. AlN exhibits good cytocompatibility, supports cell adhesion, and demonstrates a degree of antimicrobial activity, making it potentially attractive for bone-related biomedical applications.[42] However, similar to other ceramic piezoelectrics, AlN is intrinsically brittle and difficult to process into complex architectures. Moreover, its relatively high manufacturing cost and limited degradability restrict large-scale biomedical translation. As a result, while AlN may be advantageous for rigid bone implants or surface coatings, its application in cartilage repair or gradient osteochondral constructs remains limited.[12]

3.2. Organic piezoelectric material

Compared with inorganic piezoelectric ceramics, organic piezoelectric polymers offer superior flexibility, deformability, and processability, which are particularly advantageous for soft tissue engineering and additive manufacturing. They can be broadly classified as natural polymers (e.g., chitosan, collagen, cellulose, silk fibroin) and synthetic polymers, such as PVDF, poly(vinylidene fluoride-co-trifluoroethylene) (PVDF-TrFE), and PLLA.

3.2.1. Collagen

Collagen, the primary extracellular matrix protein in bone and cartilage, exhibits intrinsic but relatively weak piezoelectricity arising from its ordered triple-helical molecular structure. Its excellent biocompatibility, biodegradability, and low immunogenicity make collagen particularly attractive for cartilage repair and soft tissue interfaces. In addition, the triple helix structure of collagen contributes to its excellent flexibility. However, collagen-based scaffolds are susceptible to degradation under the influence of environmental factors (such as temperature, humidity), limiting their stability in long-term applications.[18,43] As a result, collagen is more commonly employed as a bioactive component in composite systems or as the cartilage-mimicking layer in osteochondral constructs, rather than as a standalone piezoelectric scaffold for bone repair.

3.2.2. Cellulose

Cellulose consists of repeating glucose units connected by β-1,4-glycosidic bonds. The piezoelectricity of cellulose arises from the polar hydroxyl groups and the anisotropy of molecular orientation. It has good compatibility for orthopedic applications and can be used to enhance the properties of other polymers, such as poly(vinyl) alcohol (PVA), silk fibroin, and others.[44] Due to its tunable stiffness and mild electromechanical response, cellulose-based materials are well-suited for cartilage-like environments and soft osteochondral interfaces. Nevertheless, their relatively low piezoelectric coefficients limit their ability to induce strong osteogenic responses, making them less effective for standalone bone regeneration unless reinforced with ceramic fillers or combined with higher-output piezoelectric phases.

3.2.3. Chitosan

Chitosan, a deacetylated derivative of chitin, contains abundant amino and hydroxyl groups that generate piezoelectricity under mechanical deformation. Its natural origin, biodegradability, and bioactivity support cell adhesion and extracellular matrix deposition, particularly in cartilage and osteochondral tissues. Moreover, chitosan can be processed into hydrogels, membranes, and porous scaffolds, offering flexibility in scaffold design. However, the intrinsic mechanical weakness of chitosan severely limits its use in load-bearing bone applications. Without reinforcement, chitosan-based scaffolds cannot sustain physiological stresses or provide sufficient mechanical cues for osteogenesis. Consequently, chitosan is most effective when used in combination with stiffer polymers

or inorganic fillers, serving primarily as a bioactive and cartilage-compatible component rather than a structural backbone.

3.2.4. Polyvinylidene fluoride

Polyvinylidene fluoride and its copolymer PVDF-TrFE exhibit strong piezoelectricity linked to molecular dipole alignment. Depending on the position of dipoles, PVDF can be classified into five crystal phases as follows: α, β, γ, δ, and ε. Among them, the β phase shows the highest piezoelectricity. Common ways to increase the β-phase include polarization and chemical modification. TrFE is added to PVDF to stabilize its β-phase, resulting in PVDF-TrFE. However, neither PVDF nor PVDF-TrFE is degradable and requires a secondary surgery for removal. Moreover, their strong integration ability makes it difficult to remove them completely, as the boundary with the surrounding tissue is not clearly defined. In addition, prolonged retention in the body may trigger inflammation.[6] Their high piezoelectricity benefits bone regeneration under mechanical loading, though their non-degradability and long-term retention limit clinical applicability unless used as transient stimulatory membranes or in removable constructs.

3.2.5. Poly-L-lactic acid

Poly (L-lactic acid) is a Food and Drug Administration-approved polymer, widely recognized for its biodegradability and low toxicity. Though naturally non-polar (α-phase), mechanical or electrical treatment can induce a piezoelectric β-phase. The unique structure of PLLA results in a specific polarization direction, enhancing its application in regenerating bone tissue. The collagen composition of bone tissue imparts a shear-responsive characteristic, highly relevant to the shear piezoelectricity observed in PLLA. This correlation is crucial because the piezoelectric response to shear stress can significantly influence cellular behaviors such as attachment, proliferation, and differentiation.[45]

Although the piezoelectric coefficients of polymers are lower than those of ceramics, these materials compensate with excellent processability, tunability, and biocompatibility, making them ideal for complex structural designs. For instance, PVDF-based scaffolds fabricated by 3D printing achieve precise architectures and tailored mechanical properties while retaining piezoelectric responsiveness.[1] Orientation and poling of polymer chains during fabrication further enhance their piezoelectric performance. Importantly, organic scaffolds can provide low-level electrical stimulation to regulate neuronal growth, tendon repair, and angiogenesis.[46] Thus, beyond serving as substitutes for ceramics, they offer soft, dynamic platforms for tissue engineering applications. Its degradability and shear-responsive piezoelectricity align well with bone regeneration, though the relatively low piezoelectric output compared with ceramics may limit its use in large defects without reinforcement.

3.3. Piezoelectric composite material

Piezoelectric composites combine organic and/or inorganic biomaterials to optimize their functional performances. Unlike the single-component piezoelectric materials, composites retain their intrinsic piezoelectricity while enhancing electromechanical conversion efficiency, structural stability, and biological tolerance.

3.3.1. Polymer blends

Blending of piezoelectric polymers is a common method of modifying polymers, as these polymers tend to interpenetrate due to their polarity, which facilitates the achievement of comprehensive performance. Using chemical polymerization, Sui *et al.*[47] combined polypyrrole (PPy) in the form of nanocones on a PVDF membrane. When mechanical stimuli are applied, PVDF generates a piezoelectric stimulus, which is locally conducted through PPy, transforming PPy into a dynamic environment. Additionally, the nanotopography of PPy can better mimic the physiological microenvironment. The results demonstrated the osteogenesis-promoting effect of the mixture on BMCSs. Wu *et al.*[1] constructed blended bilayer hydrogels of PVA and PVDF, with the PVDF content correlating with enhanced piezoelectric properties and the PVA content correlating with improved mechanical properties. The β-phase of the cartilage layer of the PVDF was improved by doping it with silver, while the mechanical properties of the bone layer were enhanced by adding HAp. Ultimately, better repair results were obtained compared to the non-piezoelectric group. Li *et al.*[23] reported a 0.7 poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV; 70% PHBV and 30% PLLA, wt%), which utilized its similar piezoelectric origin, resulting in piezoelectric properties that were 2–2.5 times higher than those of conventional PLLA. The 0.7 PHBV scaffold constructed using 3D printing showed excellent repair results in rabbit knee cartilage defects. These blends enable simultaneous tuning of mechanical flexibility and electrical output, making them suitable for cartilage and osteochondral applications, though achieving uniform properties remains a challenge.

3.3.2. Polymer and ceramic

Piezoelectric ceramics are known for their piezoelectric properties, but they are hard and brittle, whereas piezoelectric polymers can withstand greater deformation when subjected to force. Composites constructed from these two materials combine the strengths of both,

making them highly promising for bone and cartilage regeneration. PVDF and BT are the classic combinations of polymer–ceramic hybrids. Lei *et al.*[48] innovatively used supersonic spraying to prepare PVDF/BT membranes. The open-circuit voltage of the PVDF/BT membrane was 37.5 V under the 14-hour program conditions. Bhaskar *et al.* obtained a high-performance composite by doping PVDF with 3 wt% of multiwalled carbon nanotubes (MWCNT) and 30 wt% of BT. The doping of 30BT/3MWCNT increased the β-phase content of the PVDF, thereby improving its piezoelectricity. Zheng *et al.*[49] constructed PVDF membranes loaded with boron nitride nanosheets/HAp using electrostatic spinning, where the incorporation of the polymer improved the ferroelectric/piezoelectric properties of PVDF, resulting in higher adhesion and osteogenic properties of human osteosarcoma cells on the surface. Blending of other polymers with piezoelectric ceramics has also yielded excellent composite results. Liu *et al.* reported a PLLA nanofiber doped with calcium/manganese and barium titanate with enhanced osteogenic and antimicrobial properties.[49] These hybrids are ideal for bone regeneration due to their high stiffness and strong piezoelectricity, but excessive ceramic content can reduce toughness and printability, necessitating careful composition control for osteochondral designs.

3.3.3. Polymer and oxide

The incorporation of metal oxides helps to improve the electrical properties of piezoelectric materials. Liu *et al.* reported an electrostatically spun membrane of titanium dioxide and PVDF, increasing the β-phase of PVDF. *OCN* expression in bone marrow stem cells (BMSCs) was six times higher than in PVDF alone. Zhang *et al.* constructed an FeOOH/PVDF electrospinning membrane, which was activated by ultrasound. PVDF provided local electrical signals, and iron(III) oxide-hydroxide released iron(III) ions, which synergistically promoted neuronal differentiation of BMSCs, resulting in the significant upregulation of neural-specific genes (*Nestin*, *Tuj1*, and *MAP2*). They provide enhanced electrical activity and biofunctionality, yet the risk of nanoparticle agglomeration can compromise mechanical uniformity and limit applicability in fine cartilage structures.

4. Three-dimensional printing approaches for piezoelectric scaffolds

Piezoelectric biomaterials provide promising options for constructing electroactive materials for bone and cartilage regeneration, yet their application effects critically depend on how they are processed into functional architectures. The fabrication methods for the piezoelectric biomaterials are summarized as follows.

4.1. Fused deposition modeling

Fused deposition modeling is one of the earliest and most widely used additive manufacturing techniques. Through a controlled extrusion of thermoplastic filaments, the molten polymer is extruded via a heated nozzle and solidifies layer-by-layer, forming the 3D construct.

Fused deposition modeling offers several advantages in regenerative medicine. It enables the fabrication of highly porous scaffolds with precisely controllable pore architectures and interconnectivity, supporting cell adhesion, proliferation, and nutrient diffusion. Moreover, it eliminates the need for organic solvents and produces complex geometries at a relatively low cost. Importantly, thermoplastic piezoelectric polymers such as PVDF and PVDF-TrFE have been successfully processed via FDM to generate scaffolds that produce electrical cues under mechanical stress, thereby replicating the electromechanical microenvironment of the native piezoelectric tissues.

Beyond architectural control, FDM processing exerts a direct influence on material properties. The elevated temperature and shear stress during extrusion promote partial molecular chain alignment, which can enhance β-phase formation and dipole orientation in piezoelectric polymers. As a result, FDM-fabricated scaffolds often exhibit anisotropic mechanical stiffness and directional piezoelectric responses, features that can be exploited to mimic the load-dependent electromechanical behavior of native bone. However, FDM suffers from relatively low resolution, visible layer lines, limited polymer choices, and mechanical anisotropy of printed constructs. In addition, its inability to directly print living cells restricts its broader biomedical application.[55]

4.2. Vat photopolymerization

Vat photopolymerization techniques, including stereolithography, digital light processing, and two-photon polymerization, rely on spatially controlled light to selectively solidify liquid photopolymers, providing high resolution and intricate geometries.

Stereolithography has been employed to fabricate hydrogel-based scaffolds with tunable mechanics and porosity. Digital light processing offers faster printing speeds and higher resolution, facilitating vascular-like designs. Two-photon polymerization achieves submicron precision, enabling scaffolds with heterogeneous microstructures and tailored piezoelectric responses. Piezoelectric properties can be introduced by dispersing ceramic nanoparticles (e.g., BT) into photocurable resins and producing hybrid scaffolds that generate electromechanical signals under stress. Despite these advantages, challenges remain, including limited printable

materials, the need for biocompatible photoresins, and difficulties in scaling up production.

Due to rapid photopolymerization, VPP-fabricated scaffolds generally exhibit uniform microstructures and smooth surfaces, which favor homogeneous stress distribution and consistent electrical output. However, photopolymerized polymers are often amorphous or weakly crystalline, limiting intrinsic piezoelectricity unless reinforced by ceramic phases.

Mechanically, VPP-fabricated scaffolds exhibit tunable stiffness that can be adjusted through resin chemistry and crosslinking density, making them particularly suitable for cartilage regeneration and osteochondral constructs. Their high resolution also enables the creation of gradient or zonal architectures, which is advantageous for replicating the depth-dependent properties of osteochondral tissue.

4.3. Inkjet printing

Inkjet-based 3D printing, derived from traditional two-dimensional inkjet techniques, deposits microscale droplets of bioink in a layer-by-layer manner, offering high resolution and precise spatial deposition. This method has been used to print bioinks containing piezoelectric ceramics (e.g., BT, lead zirconate titanate) or polymer nanofibers with electroactive properties.

Nevertheless, inkjet printing is limited by its narrow range of printable viscosities, which restricts the diversity of usable bioinks. The relatively low printing speed and difficulties in maintaining stability during large-scale printing also hinder its translation into clinical applications. Careful optimization of particle dispersion and droplet ejection stability is required to achieve uniform piezoelectric responses across printed constructs.

Consequently, inkjet-printed scaffolds are more suitable for cartilage regeneration, soft tissue interfaces, or secondary patterning in osteochondral systems, rather than for standalone load-bearing bone scaffolds.

4.4. Powder bed fusion

Powder bed fusion, including selective laser sintering and selective laser melting, employs a high-energy laser to selectively sinter or melt powdered materials into a 3D scaffold layer-by-layer. This method provides mechanically robust scaffolds with excellent precision and design flexibility.

Selective laser sintering has been applied to fabricate polymer–ceramic composite scaffolds, where bioactive or piezoelectric fillers are incorporated into thermoplastic matrices to improve their osteoconductivity and electrical responsiveness. In contrast, the dense metallic scaffolds produced by selective laser melting can be further functionalized with piezoelectric coatings. The main challenges associated with PBF include the generation of powder residues, the need for high processing temperatures that may degrade sensitive biomaterials, and the current lack of printable biocompatible piezoelectric inks.[56]

The high processing temperature in PBF promotes ceramic crystallinity, benefiting piezoelectric performance, but restricts polymer selection and biological compliance. As a result, PBF is best suited for bone regeneration and subchondral support, while its application in cartilage repair is limited.

4.5. Three-dimensional bioprinting

Conventional methods such as electrospinning and freeze-drying often lack the spatial precision and structural complexity required to fully harness piezoelectricity. In contrast, 3D printing allows precise regulation of key aspects of scaffold architecture, including pore geometry, filament orientation, and filler distribution, thereby generating spatial gradients in mechanical stiffness and electrical output. According to the American Society for Testing and Materials classification, 3D printing encompasses seven categories. The most relevant technologies for bone and cartilage tissue engineering include FDM, VPP, inkjet-based printing, and PBF. More recently, bioprinting, which employs living cells or bioactive hydrogels as printing inks, has expanded the scope of this field, providing platforms for creating cell-loaded and electrically active constructs.[57]

Bioprinting has emerged as a distinctive branch of 3D printing, characterized by the direct incorporation of living cells into printable inks, thereby enabling scaffolds with both structural and biological functionality. It supports the recreation of extracellular matrix-like environments and multicellular architectures, making it particularly promising for cartilage and osteochondral regeneration.[58]

However, precise construction of the piezoelectric scaffolds needs stringent printing parameters such as temperature, viscosity, and crosslinking conditions. Moreover, the limited repertoire of bioinks and the relatively low printing speed also hamper the application of bioprinting technology in fabricating piezoelectric scaffolds. Moreover, sole bioink often lacks sufficient mechanical strength for load-bearing scaffolds, necessitating the reinforcement with polymeric or ceramic materials. Therefore, hybrid strategies that combine bioprinting with conventional additive manufacturing methods are a promising strategy to enhance their mechanical properties and address the associated challenges.

From a tissue-specific perspective, bioprinting is well-suited for cartilage regeneration and osteochondral constructs. For bone or load-bearing applications,

bioprinting is most effective when combined with stiffer printed frameworks, enabling hierarchical scaffolds that integrate biological activity with mechanical and electromechanical support.

4.6. Combination printing

Based on the above-mentioned contents, each 3D printing approach offers distinct advantages or disadvantages for the fabrication of piezoelectric scaffolds. FDM is cost-effective and polymer-compatible. However, the resolution of the polymer precursor is limited. Inkjet printing enables precise deposition of precursors, yet the mechanical robustness of the resulting scaffold hinders its wide usage. Although PBF is energy-intensive, the scaffolds fabricated by PBF exhibit excellent mechanical strengths and complex structures. VPP offers the highest printing precision and surface quality among polymer-based techniques; however, its applicability is restricted by the narrow range of photocurable resins and potential cytotoxicity of residual monomers. Bioprinting allows the incorporation of cells but often exhibits insufficient mechanical performance.[59]

In consideration of the advantages and disadvantages of the different 3D printing approaches, emerging approaches increasingly focus on combining multiple printing modalities to leverage the strengths of each. For instance, Lou *et al.*[61] fabricated triphasic osteochondral scaffolds through both ink-based and bioink-based printing methods, achieving region-specific architectures and robust compressive stability. Similarly, coupling melt electrowriting with FDM has yielded microfiber-incorporated scaffolds with a rigid shell, balancing structural reinforcement with microenvironmental cues.[60] Although these multi-technology fabrication methods provide unique opportunities for creating complex and biomimetic scaffolds, the technical difficulties in processing time and operational complexity of scaffold manufacturing are also increased. Future efforts should weigh whether similar outcomes might be achieved through optimized single-technique approaches, which would simplify the fabrication processes and enhance their clinical translatability. Such integrated strategies would be essential to recover the full potential of piezoelectric scaffolds in bone and cartilage regeneration.[61]

4.7. Distinctive advantages of three-dimensional printing over non-additive approaches

Traditional non-additive fabrication methods such as electrospinning, freeze-casting, and solvent casting have also been used to produce piezoelectric biomaterials. However, these approaches provide only limited control over macroscopic architecture and the spatial organization of functional phases, making it challenging to reproduce bone–cartilage structure. In contrast, 3D printing allows scaffold properties to be predetermined through computer-aided design and subsequently realized by controlling filament deposition paths, layer-by-layer orientation, and the localized incorporation of functional phases. Through this design-to-fabrication workflow, constructs with predictable mechanical behavior and tunable piezoelectric performance can be reliably produced. These capabilities make 3D printing uniquely suited for engineering complex, hierarchical, and patient-specific piezoelectric scaffolds. For this reason, our review focuses primarily on additive manufacturing strategies while acknowledging the complementary role of traditional approaches[62] (Table 2).

5. Application of piezoelectric scaffolds in bone regeneration

The regeneration of bone, cartilage, and the osteochondral interface relies on a complex interplay of biomechanical stimuli, biochemical signaling, and cellular responses. Piezoelectric biomaterials, capable of converting mechanical forces into localized electrical cues, have emerged as a unique class of materials that can directly interface with these physiological processes. Their ability to recapitulate the electromechanical microenvironment of native tissues, especially when combined with 3D printing, has opened new possibilities for the treatment of hard-to-heal bone defects, avascular cartilage injuries, and complex osteochondral lesions. Despite significant advances, the degree to which piezoelectric scaffolds can be optimized for tissue-specific demands remains an active area of investigation.

5.1. Bone regeneration

Bone regeneration is a highly orchestrated process that involves an initial inflammatory response, cartilaginous and bone tissue formation, and reconstruction. Endogenous piezoelectricity, largely arising from type I collagen, participates in this sequence by regulating cell adhesion, proliferation, differentiation, and extracellular matrix organization. Piezoelectric scaffolds, therefore, aim to restore this microenvironment by generating electrical potentials under physiological loading or ultrasound stimulation.[64]

Recent studies have shown that piezoelectric scaffolds exhibit potent antibacterial functions. Bacterial infection remained a major obstacle to bone regeneration, often leading to secondary bone loss, with rising treatment costs. Piezoelectric scaffolds have emerged as promising antibacterial platforms that not only suppress infection but also promote bone repair by generating localized electric fields under mechanical loading or ultrasound stimulation. For instance, Shuai *et al.*[65] fabricated a 3D porous PVDF/silver–polydopamine (PDA)-functionalized

Table 2. Properties of piezoelectric scaffolds and their effects on regeneration

Material	Fabrication methods	Electrical properties	*In vivo* outcomes	References
ZnO/BT/HA	DLP	d_{33} = 1.87 pC/N	Low-intensity pulsed ultrasound-activated piezoelectric effect promoted angiogenesis and effectively repaired infected bone defects	50 49 50 49 50 49 50 51 50 49 50 49 50
BT/titanium	BT coating on porous titanium alloy scaffolds	~3 pC/N	Enhanced macrophage M2 polarization and immunoregulatory osteogenesis of MC-3T3 cells	51 49 51 50 51 50 51 52 51 50 51 50 51
PVDF/BT/ polydopamine	SLS	-	Improved osteoconductivity and enhanced piezoelectric-driven cell responses (adhesion, proliferation, differentiation)	52 51 52 51 52 51 58 53 52 51 52 51 52
PVDF/BT/Ag	PBF	Output voltage 1.8–7.0 V	Promoted cell adhesion, proliferation, and osteogenic differentiation via Ag-enhanced piezoelectricity	53 52 53 52 53 52 53 54 53 52 53 52 53

Table 2. Properties (Continued...)

Material	Fabrication methods	Electrical properties	*In vivo* outcomes	References
PVDF-TrFE/ZnO	Electrospinning	-	Enhanced cell adhesion and angiogenesis	54 53 54 53 54 53 54 55 54 53 54 53 54
PHBV/PLLA	FDM	d_{33} = 2.0–2.5 × PLLA	Favorable biodegradability and improved piezoelectric performance for cartilage repair	23 22 23 22 23 23 22

Abbreviations: Ag, silver; BT, barium titanate; DLP, digital light processing; FDM, fused deposition modeling; HA, hydroxyapatite; PBF, powder bed fusion; PHBV, poly(3-hydroxybutyrate-co-3-hydroxyvalerate); PLLA, poly-L-lactic acid; PDA, polydopamine; PVDF, poly(vinylidene fluoride); PVDF-TrFE, poly(vinylidene fluoride-co-trifluoroethylene); SLS, selective laser sintering; ZnO, zinc oxide.

BT scaffold fabricated by selective laser sintering, in which silver nanoparticles were anchored onto PDA-modified BT via *in situ* nucleation. The resulting strawberry-shaped Ag-pBT nanostructures improved piezoelectric performance, producing an output current and voltage that were ~50% and ~40%, respectively, higher than PVDF/PDA-functionalized BT. The enhanced bioelectric cues accelerated MG-63 cell osteogenic differentiation under ultrasound stimulation, while conferring robust antibacterial activity against *Escherichia coli*. Similarly, Huang *et al.*[66] developed an ultrasound-driven, spatiotemporal cascade catalytic nanoreactor composed of copper(II) ions and PDA-modified BT. They then incorporated it into a 3D-printed polyetheretherketone scaffold. Upon ultrasound activation, the scaffold produced reactive oxygen species via hot carrier transfer and copper-catalyzed Fenton-like reaction, destroying bacterial membranes and DNA while simultaneously promoting angiogenesis and osteogenesis (Figure 1). Together, these findings highlight the dual antibacterial and pro-regenerative potential of piezoelectric scaffolds.

Beyond antibacterial activity, the immunomodulatory properties of piezoelectric materials have gained increasing attention as key drivers of bone healing.[67] The early inflammatory phase is dominated by pro-inflammatory M1 macrophages, which help recruit mesenchymal stem cells (MSCs) and osteoprogenitors through chemokines such as C-C motif ligand 2, C-X-C motif chemokine ligand 8, and stromal cell-derived factor 1.[68] During the later phase, the polarization shift toward the M2 phenotype promotes osteogenesis and mineralization. Liu *et al.*[69] reported that polarized BT-coated porous Ti6Al4V scaffolds significantly enhanced the recruitment of MSCs and human umbilical vein endothelial cells compared with either unpolarized or unmodified scaffolds (Figure 2A). Building upon these findings, Wu *et al.*[51] further showed that polarized BT/titanium achieved a high piezoelectric constant (d_{33} = 3.2 pC/N), promoted an immunoregulatory shift by downregulating the M1 marker CD86 and upregulating the M2 marker CD206. Mechanistic analysis revealed that piezoelectric stimulation suppressed the MAPK/c-Jun N-terminal kinase pathway while promoting adenosine triphosphate synthesis and osteogenic differentiation both *in vitro* and *in vivo*. Building on this, iron-doped BT nanoparticles responsive to magnetic and ultrasonic stimulation were engineered to activate Janus kinase 2–signal transducer and activator of transcription 3 signaling in Icam1$^+$ macrophages, restoring their oxidative phosphorylation and pro-regenerative capacity. When functionalized with curcumin and MSC membranes and incorporated into 3D-printed chitosan/tricalcium phosphate bioinks, these nanoparticles enabled targeted immunomodulation and accelerated infectious bone defect repair *in vivo* (Figure 2B).[70]

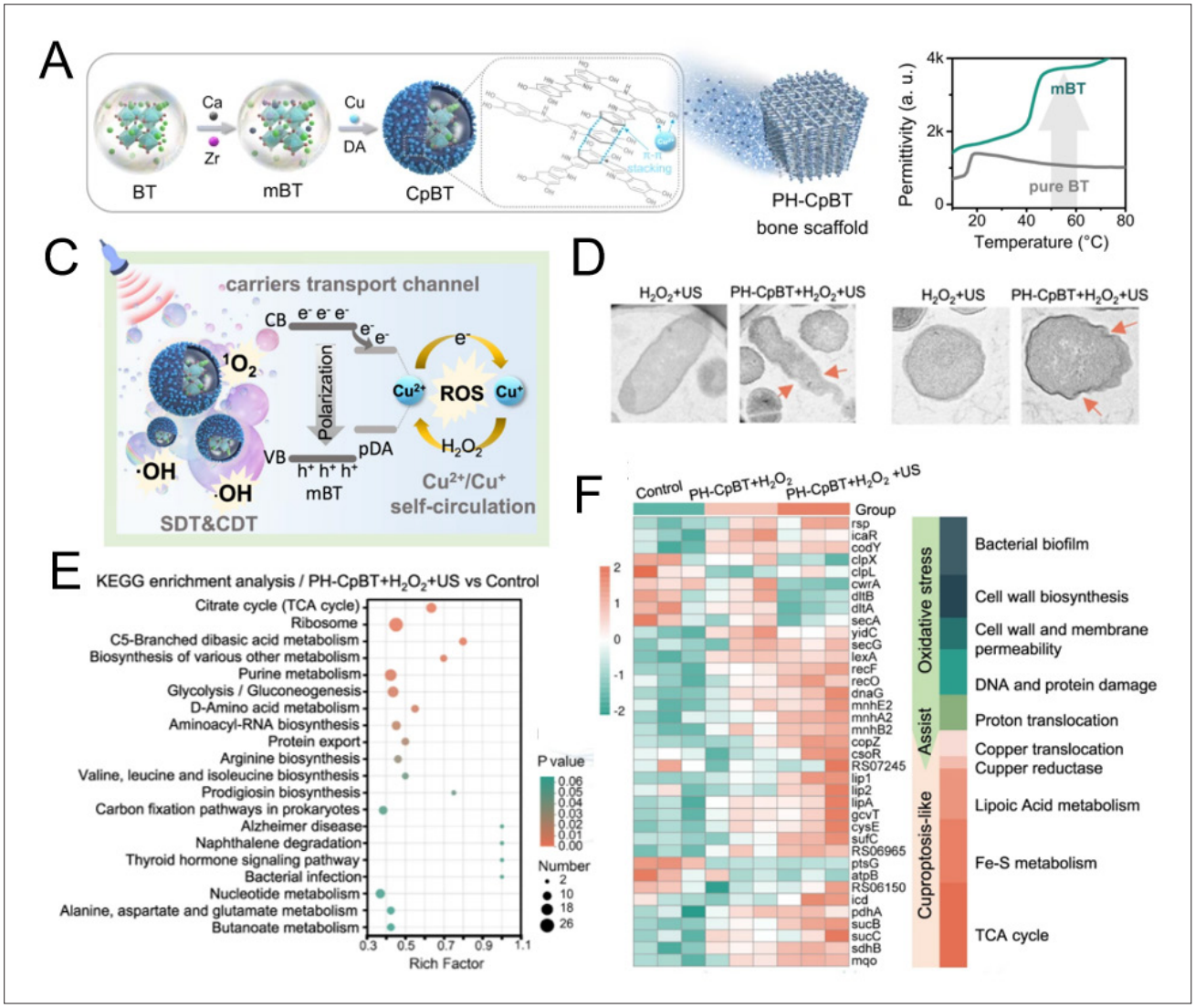

Figure 1. Piezoelectric antibacterial strategies. A synergistic sonodynamic and chemodynamic strategy was developed to prevent implant-associated infection. (A) Fabrication process of copper(II) ions modified BT (CpBT) nanoreactors and copper(II) ions and PDA-modified BT (PH-CpBT) scaffolds. (B) Enhanced piezoelectric properties of modified BT compared with pristine BT. (C) Mechanism of tandem catalysis under ultrasound activation, integrating sonodynamic and chemodynamic processes. (D) Strongest bactericidal effect achieved in the H-CpBT + H_2O_2 + US group. Scale bar: 500 nm. (E) Pronounced bacteriolysis-related gene expression changes in the PH-CpBT +H_2O_2 group. (F) Multiple metabolic pathways in *Staphylococcus aureus and Escherichia coli* were affected by PH-CpBT + H_2O_2 treatment. Reproduced from Pajarinen *et al.*[77] Abbreviations: BT, barium titanate; H_2O_2, hydrogen peroxide; PDA, polydopamine; US, ultrasound.

Effective bone regeneration also requires the reconstruction of a neurovascularized microenvironment, as revascularization and reinnervation ensure nutrient exchange and cellular communication.[71] Mechanically responsive 3D-printed piezoelectric scaffolds can simultaneously provide localized electrical cues and controlled ion release, fostering both angiogenesis and osteogenesis. Among bioactive ions, Mg^{2+} has emerged as a particularly critical regulator, with the ability to enhance endothelial cell migration, vessel formation, and osteogenic differentiation.[72] Fan *et al.*[75] fabricated piezoelectric whitlockite/polycaprolactone scaffolds via melt extrusion, which maintained stable piezoelectricity under physiological conditions and released Mg^{2+} to enhance vascularization and bone formation (Figure 3A). Biomimetic bilayer scaffolds have further advanced this strategy by mimicking the natural periosteum–bone interface. A PVDF-magnesium metal–organic framework/curcumin membrane as the periosteal layer provided sustained Mg^{2+} and curcumin release to promote angiogenesis and macrophage polarization, while a 3D-printed scaffold HAp@gelatin methacrylate as the

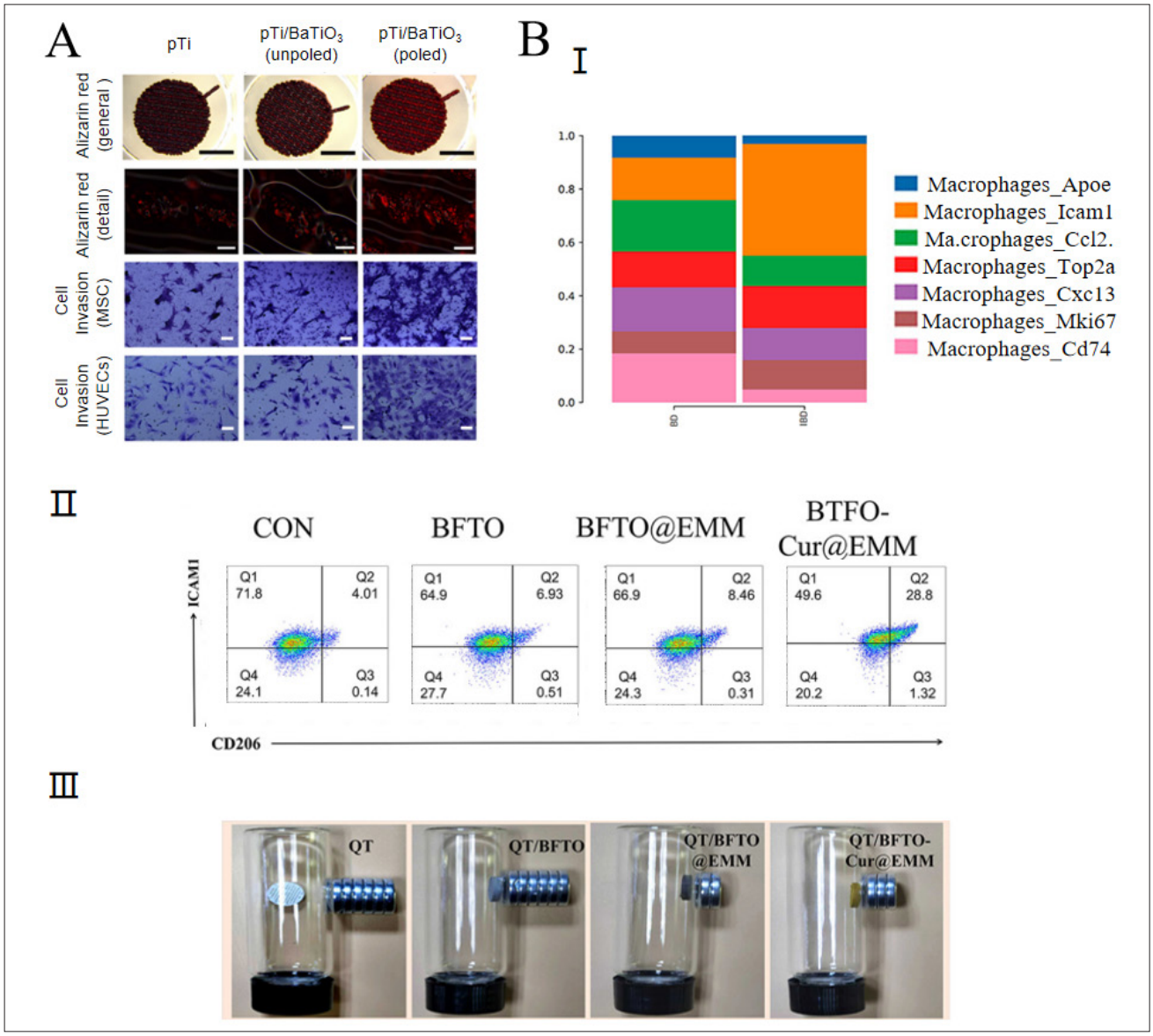

Figure 2. Immunomodulatory strategies. (A) Piezoelectric coating-modified scaffolds enhanced extracellular matrix mineralization and promoted cell migration. Scale bar: black = 5 mm, white = 100 μm. Reprinted with permission from Wang *et al.*[80] Copyright © 2020, American Chemical Society. (B) Engineered magneto-piezoelectric materials modulated Icam1$^+$ macrophages to promote bone defect regeneration. (I) Significant upregulation of Icam1$^+$ macrophage subsets in infected bone defects. (II) Polarization regulation of Icam1$^+$ macrophages via low-intensity pulsed ultrasound stimulation. (III) Magnetic attraction of magneto-responsive scaffolds under a static field. Reprinted with permission from Gao *et al.*[81] Copyright © 2024, American Chemical Society. Abbreviations: BFTO, iron-doped barium titanate; Cur, curcumin; EMM, mesenchymal stem cell membranes.

bone layer provided osteoconductivity and geometric adaptability (Figure 3B). Acting synergistically, these two layers not only mimic the biological functions of periosteum but also establish a regenerative microenvironment by regulating inflammation and promoting osteogenesis, thus offering a multifunctional platform for advanced bone defect repair.[73] Moreover, a 3D multi-channel scaffold fabricated from electrospun PLA/KNN@PDA nanofibers demonstrated potential for neuroregeneration under ultrasound exposure. By rolling aligned PLA microstrips into a cylindrical configuration, the scaffold reproduces key extracellular matrix features while simultaneously generating controllable *in situ* electrical signals. This stimulation has been shown to facilitate neuronal differentiation and functional neural recovery, underscoring the potential of piezoelectric constructs in neuroregenerative therapies.[39]

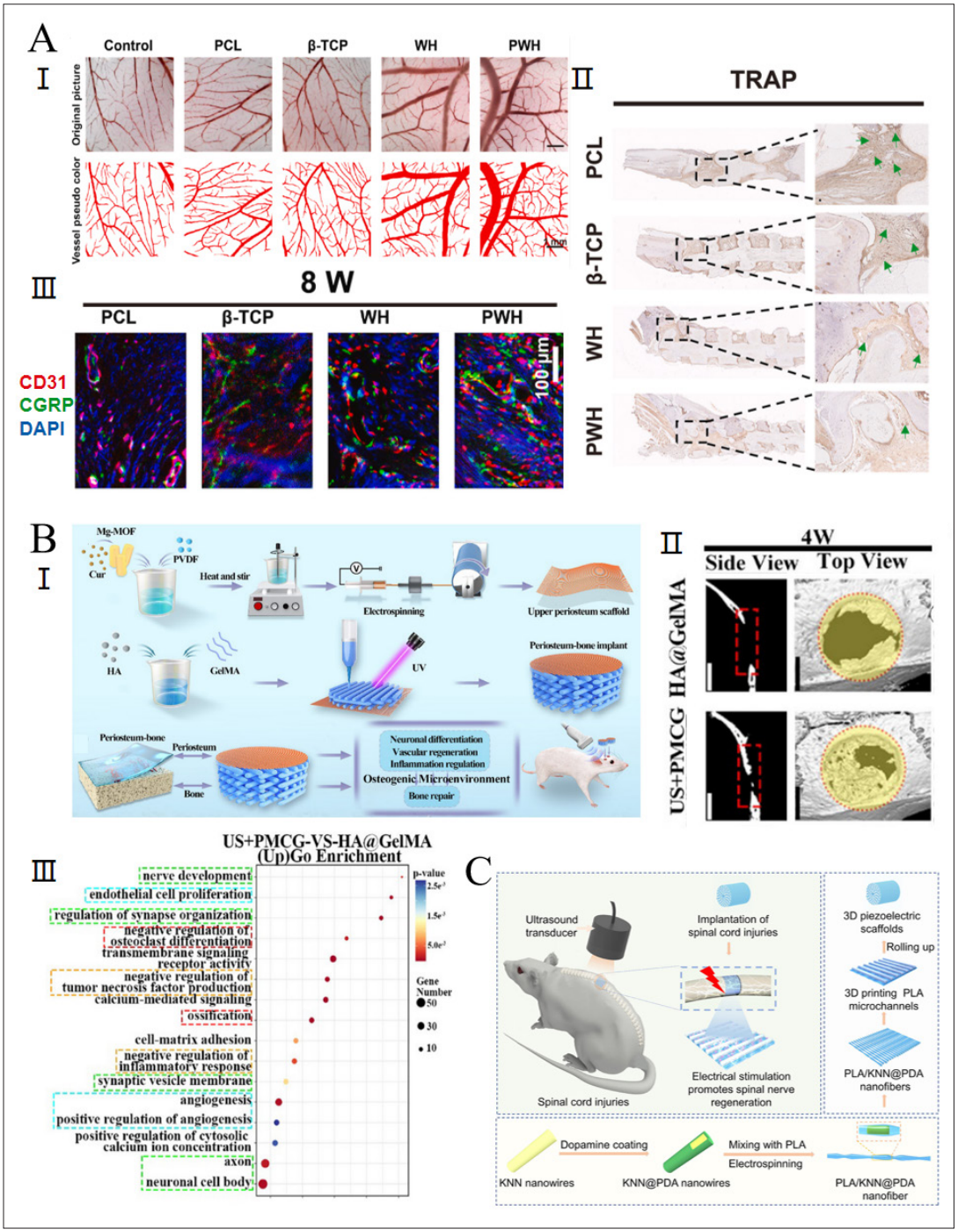

Figure 3. Neurovascularized microenvironment reconstruction. (A) Piezoelectric whitlockite (PWH) scaffolds promoted neurogenic and angiogenic differentiation, thereby enhancing bone regeneration. (I) Angiogenesis assays showing PWH-facilitated vascular formation. Scale bar: 1 mm, white = 100 μm. (II) Significantly enhanced osteogenesis by PWH scaffolds *in vivo*. Scale bar: 1 mm, white = 100. (III) Immunofluorescence of CGRP (green, neurogenesis) and CD31 (red, angiogenesis) confirming synergistic neural/vascular promotion by Mg^{2+} release and scaffold bioactivity. Scale bar: 100 μm. Reprinted from Fan *et al.*[84] (B) A biomimetic piezoelectric periosteum–bone integrated implant remodeled the osteogenic microenvironment and promoted bone defect repair. (I) Fabrication process of the bilayer periosteum–bone implant. (II) Significantly improved osteogenesis demonstrated *in vivo*. Scale bar: 2 mm. (III) Gene ontology (GO) analysis linking ultrasound (US)+PMCG to neurodevelopment, neuronal formation, axonal growth, angiogenesis, anti-inflammation, and ossification. Reprinted with permission from Chen *et al.*[85] Copyright © 2025, Wiley. (C) Wireless electrical stimulation using biodegradable 3D piezoelectric scaffolds facilitated spinal cord injury repair. Reprinted with permission from Chen *et al.*[43] Copyright © 2022, American Chemical Society. Abbreviation: HA@GelMA, hydroxyapatite@gelatin methacrylate; PMCG, polyvinylidene fluoride-curcumin-loaded magnesium metal–organic framework periosteum scaffold with a lower hydroxyapatite@gelatin methacrylate bone scaffold.

The optimization of piezoelectric biomaterials for bone repair increasingly depends on synergistic improvements in composition and structural design. Recent studies have shown that incorporating functional nanoparticles or modifying chemical components can markedly enhance biological activity and electromechanical properties. Li *et al.*[58] incorporated BT nanoparticles into polyethylene glycol–modified gelatin methacrylate and employed 3D bioprinting to fabricate piezoelectric scaffolds for BMSC delivery. Under low-intensity pulsed ultrasound stimulation, these scaffolds exhibited markedly enhanced osteogenic activity. Similarly, Chen *et al.*[50] developed ZnO-modified BT/HAp scaffolds processed via 3D printing, which increased the piezoelectric coefficient (d_{33}) from 0.65 to 1.87 pC/N, within the physiological range of natural bone (0.7–2.3 pC/N).[50] Moreover, these scaffolds not only promoted osteogenesis but also enhanced angiogenesis, with transcriptomic analysis identifying *EGR1* as a key regulatory gene.

Changes in the structural characteristics of piezoelectric materials can also further enhance their functional performance. For instance, 3D-printing 20 wt% BT/chitosan scaffold displayed superior antibacterial activity compared with conventionally pressed scaffolds. Owing to spatially controlled porosity and precise distribution of the functional phase, the inhibition rates against *E. coli* and *Staphylococcus aureus* increased from 80.7% to 88.1% and from 74.0% to 83.8%, respectively.[74] Another common strategy employed was piezoelectric coatings and conductive modifications. For example, 3D-printed BT-coated Ti6Al4V scaffolds composites generated electroactive implants that, when combined with ultrasound stimulation, significantly improved osteogenesis and bone fusion in large-segment bone defect models.[75] In another example, digital light processing 3D printing was applied to prepare covalently functionalized piezoelectric composites, in which silver-modified BT nanoparticles were uniformly dispersed in polymer matrices. The resulting porous scaffolds exhibited tailored architectures and enhanced electromechanical performance, while also allowing customization for irregular bone defects.[76]

Recent developments focus on multifunctional integration, combining shape–memory, immunomodulatory, photothermal, and self-powered properties into single piezoelectric systems. Li *et al.*[77] prepared PVDF and thermoplastic polyurethane using electric stirring and ultrasonic homogenization, and then processed composite scaffolds using selective laser sintering. In this system, thermoplastic polyurethane endowed shape–memory capability and PVDF provided electrical responsiveness, resulting in a dual combination stimulation. Li *et al.*[78] further designed an *in situ* self-powered shape–memory polyurethane elastomer/PVDF, which generated local charges during shape recovery to modulate the immune microenvironment during early healing, followed by activity-driven voltage output during rehabilitation. Likewise, Chen *et al.*[82] developed shape–memory polyurethane elastomer/CMBT nanofiber scaffolds that exhibited thermoresponsive polarization (−0.51 kV) (Figure 4A), driving M2 phenotype macrophage polarization via PI3K/Akt signaling, while also enhancing stem cell osteogenesis through focal adhesion kinase/ERK activation.[79] Beyond structural and immunomodulatory improvements, multifunctional piezoelectric systems now integrate anti-tumor and regenerative capabilities. Tang *et al.*[80] engineered BT/iron-coated Ti6Al4V scaffolds via hydrothermal synthesis, endowing them with both piezoelectric and photothermal properties (Figure 4B). Under near-infrared irradiation, iron induced localized hyperthermia to ablate residual tumor cells, while BT promoted angiogenesis and osteogenesis through mechano-electrical conversion. In another example, an acoustic-responsive four-dimensional biocomposite scaffold was developed, in which black phosphorus nanosheets and nitric oxide donors were incorporated into bioactive glass (Figure 4C). Upon ultrasound exposure, the scaffold generated piezoelectric reactive oxygen species and burst nitric oxide release, achieving effective tumor ablation. In the later stage, gradual degradation of black phosphorus released phosphate ions, while sustained low-dose nitric oxide promoted angiogenesis and osteogenesis. This time-dependent therapeutic transformation from tumor suppression to bone regeneration exemplifies the multifunctional adaptability of piezoelectric four-dimensional biomaterials.[81]

At the cellular level, piezoelectric cues modulate adhesion, migration, differentiation, and energy metabolism, thereby determining the ultimate regenerative outcome. Chen *et al.*[82] reported that simply tuning the preparation parameters of piezoelectric scaffolds significantly enhanced cell adhesion and migration. The resulting cells exhibited an approximately fivefold increase in aspect ratio compared with controls, and *in vivo* experiments confirmed effective repair of rat mandibular bone defects. Piezoelectric stimulation also elevated intracellular Ca^{2+} influx through L-type channels and upregulated CaV1.2 expression, strengthening osteogenic differentiation.[83,84] In addition to regulating cell–matrix interactions, piezoelectric scaffolds play a crucial role in cellular energy metabolism. Ultrasound-driven piezoelectric cues elevated both cytoplasmic and mitochondrial Ca^{2+} levels, promoting mitochondrial energy metabolism and stimulating cell activity. For instance, 3D-printed polyurethane–Hap/BT composite

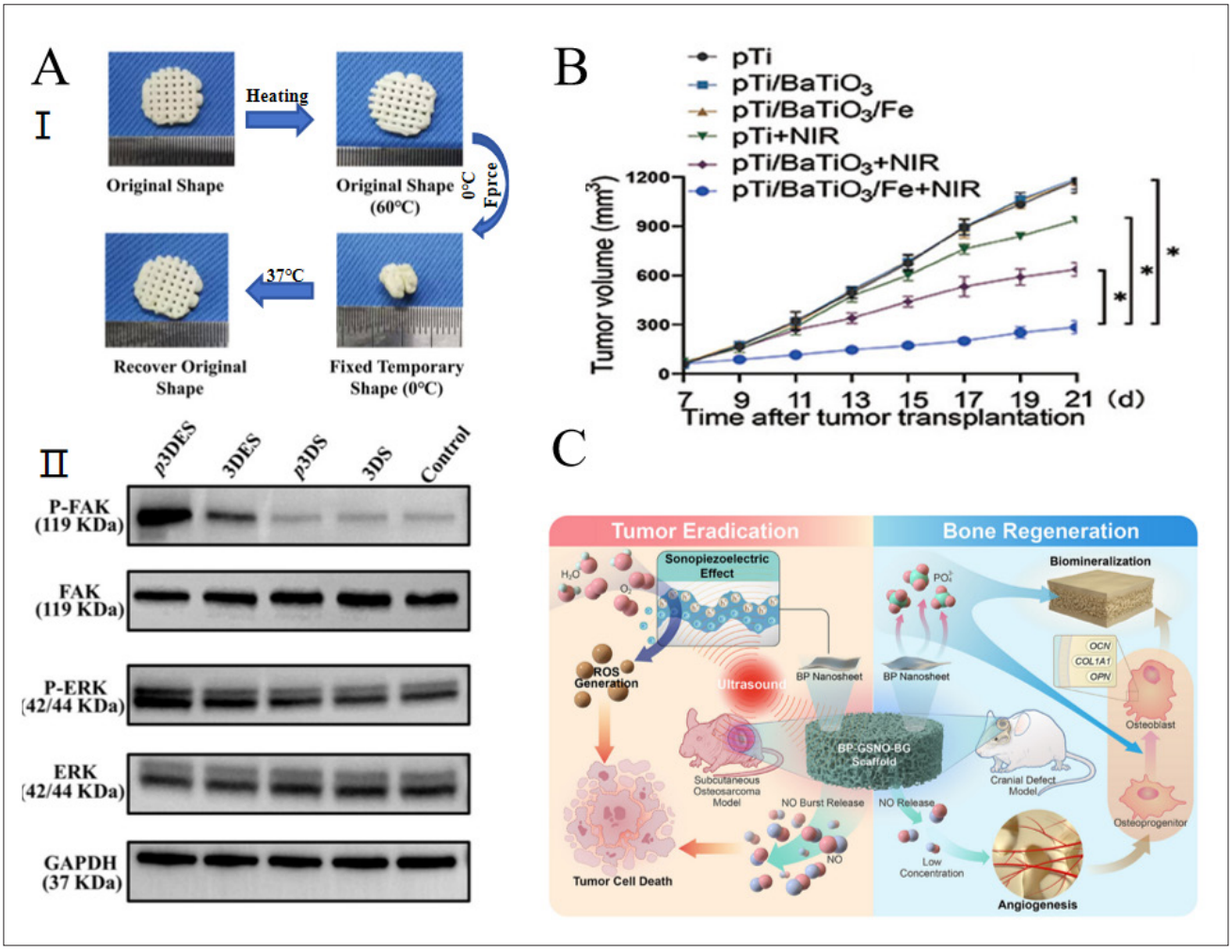

Figure 4. Multifunctional integration. (A) Shape–memory scaffolds regulated osteogenesis in multiple stages to promote bone defect regeneration. (I) *In vitro* shape–memory behavior of the scaffolds. (II) Focal adhesion kinase (FAK)/extracellular signal-regulated kinase (ERK) signaling activation, indicated by a polarized three-dimensional electrolysis system, enhances bone marrow stem cell osteogenic differentiation. (B) The barium titanate-containing iron-coated porous titanium alloy scaffolds (pTi/$BaTiO_3$/Fe) group achieved the strongest antitumor efficacy. Reprinted with permission from Atsuta *et al.*[92] (C) Ultrasound-assisted synergistic sono-electro-gas therapy suppressed tumor growth and simultaneously enhanced bone regeneration. Reproduced from Zhang *et al.*[93]

scaffolds restored intercellular Ca^{2+} signaling through L-type voltage-gated calcium channels under low-intensity pulsed ultrasound. Similarly, piezoelectric hydrogels doped with tetragonal BT were able to rescue impaired osteogenic capacity by modulating cellular bioenergetics. Under localized mechanical loading, these hydrogels generated piezoelectric potentials that stimulated adenosine triphosphate synthesis, promoted osteogenic differentiation of periodontal ligament stem cells, and induced the polarization of macrophages from the pro-inflammatory M1 to the pro-regenerative M2 phenotype.[27] Beyond energy metabolism, piezoelectric modulation can directly mitigate oxidative stress, another critical determinant of cell fate. Excessive reactive oxygen species can disrupt mitochondrial membrane potential, trigger cell death pathways, and impair cellular function. Vinikoor *et al.*[89] demonstrated that ultrasound-responsive iron/bismuth oxychloride piezoelectric nanosheets generated electrons under stimulation, consuming protons on the outer mitochondrial membrane and altering proton flux within the mitochondrial matrix. This process induced mitochondrial membrane potential depolarization and mitophagy in inflammatory regions, thereby reducing reactive oxygen species accumulation and reshaping mitochondrial fate.[85]

In summary, 3D-printed piezoelectric scaffolds have demonstrated integrated antibacterial,

immunomodulatory, neurovascular, and osteogenic functions that synergistically drive bone regeneration. However, challenges remain in achieving precise spatiotemporal control of piezoelectric responses, long-term stability *in vivo*, and large-scale clinical translation. Future research should focus on optimizing scaffold design through advanced 3D printing technologies, integrating immunomodulatory and bioactive functions, and exploring personalized fabrication strategies to address patient-specific bone defects.

5.2. Cartilage repair

Cartilage regeneration presents unique challenges due to the lack of blood vessels and nerves, which results in extremely limited self-healing capacity. Piezoelectric stimulation provides a promising strategy to overcome these limitations by activating stretch-activated and voltage-gated Ca^{2+} channels, and engaging downstream signaling pathways, such as transforming growth factor (TGF)-β and Wnt/β-catenin. In addition, piezoelectric materials provide a non-invasive strategy for promoting cartilage repair.

Current piezoelectric strategies for cartilage regeneration include both biodegradable and non-biodegradable systems.[86] These systems are fabricated in various morphological forms, including one-dimensional nanofibers, two-dimensional membranes and microspheres, and 3D scaffolds and hydrogels, which were administered either through invasive implantation or minimally invasive injection.[86] Early studies integrated silver nanowires into PVA/PVDF hydrogels to induce the β-phase of PVDF, thereby enhancing its piezoelectric response while also introducing antibacterial functionality.[87] However, the non-degradability of PVDF remains a significant limitation. To overcome these limitations, research has shifted to biodegradable piezoelectric materials, such as PLLA and PHBV, which exhibit favorable degradation profiles and improved biocompatibility. For instance, Liu *et al.*[88] engineered a PLLA–collagen "sandwich" scaffold that generated piezoelectric stimulation during motion, enhancing Ca^{2+} influx and TGF-β1 secretion, achieving effective repair of rabbit cartilage defects (Figure 5A). To address the risks of invasive implantation, injectable strategies have also been pursued. PLLA fiber–collagen composite hydrogels were developed as ultrasound-activated injectable scaffolds, enabling X-ray guided *in situ* formation tailored to cartilage defects (Figure 5B).[89] Similarly, microsphere systems incorporating barium titanate nanoparticles or KNN ceramics within hydrogels were shown to recruit endogenous stem cells, precisely regulate Ca^{2+} signaling, and direct lineage-specific differentiation.[90,91] These minimally invasive systems highlight the potential of piezoelectric hydrogels to achieve cell-specific control and promote functional chondrogenesis *in situ*.

Beyond hydrogels and microspheres, 3D printing has enabled the design of piezoelectric scaffolds with hierarchical structures and dynamic functionalities. Lin *et al.*[40] fabricated PVDF/ZnO/polycaprolactone scaffolds by using electrospinning writing techniques and rolling technology to mimic the hierarchical structure of wood (Figure 5C). These scaffolds displayed large surface area, robust mechanics, and enhanced expression of mechanoresponsive proteins linked to TGF-β signaling. Using homologous monomers and similar chiral carbon atoms of PHBV and PLLA, Li *et al.*[23] employed FDM to fabricate 0.7 PHBV scaffolds with a piezoelectric coefficient 2.0–2.5 higher than PLLA alone, achieving robust regeneration of rabbit cartilage defects. Further advances have introduced four-dimensional printing, exemplified by Liu *et al.*,[91] who developed a shape–memory, antibacterial scaffold with mechanical properties comparable to ligaments and cartilage, thereby providing adaptive functionality under physiological conditions.

5.3. Osteochondral regeneration

For osteochondral repair, where cartilage and subchondral bone demand distinct structural and electrical cues, multilayer scaffolds have been investigated. Liu *et al.*[92] designed multilayer piezoelectric PLLA/strontium-enriched silicate bioceramic scaffolds capable of generating controllable piezoelectric outputs while releasing strontium/silicon ions to synergistically activate purinergic receptor P2X 1/CaM-dependent protein kinase II Ca^{2+} signaling, thereby supporting both cartilage and subchondral bone repair. However, they did not take into account the differential mechanics and biological interfaces of osteochondral scaffolds. Building on this, Liu *et al.* combined piezoelectric amino acid-based self-assembly (diphenylalanine-modified decellularized extracellular matrix) with a conductive poly(3,4-ethylenedioxythiophene)-reinforced gelatin layer, achieving spatially distinct electrical cues that promoted bidirectional differentiation of MSCs. These scaffolds not only enhanced *in vitro* chondrogenesis and osteogenesis but also successfully repaired large osteochondral defects in a porcine model.[91]

Despite encouraging advances, several challenges remain. Conventional scaffolds often lack the gradient, anisotropic, or dynamic properties needed to replicate the complex osteochondral interface. Minimally invasive delivery is another key limitation. Although injectable hydrogels and microspheres show promise, achieving

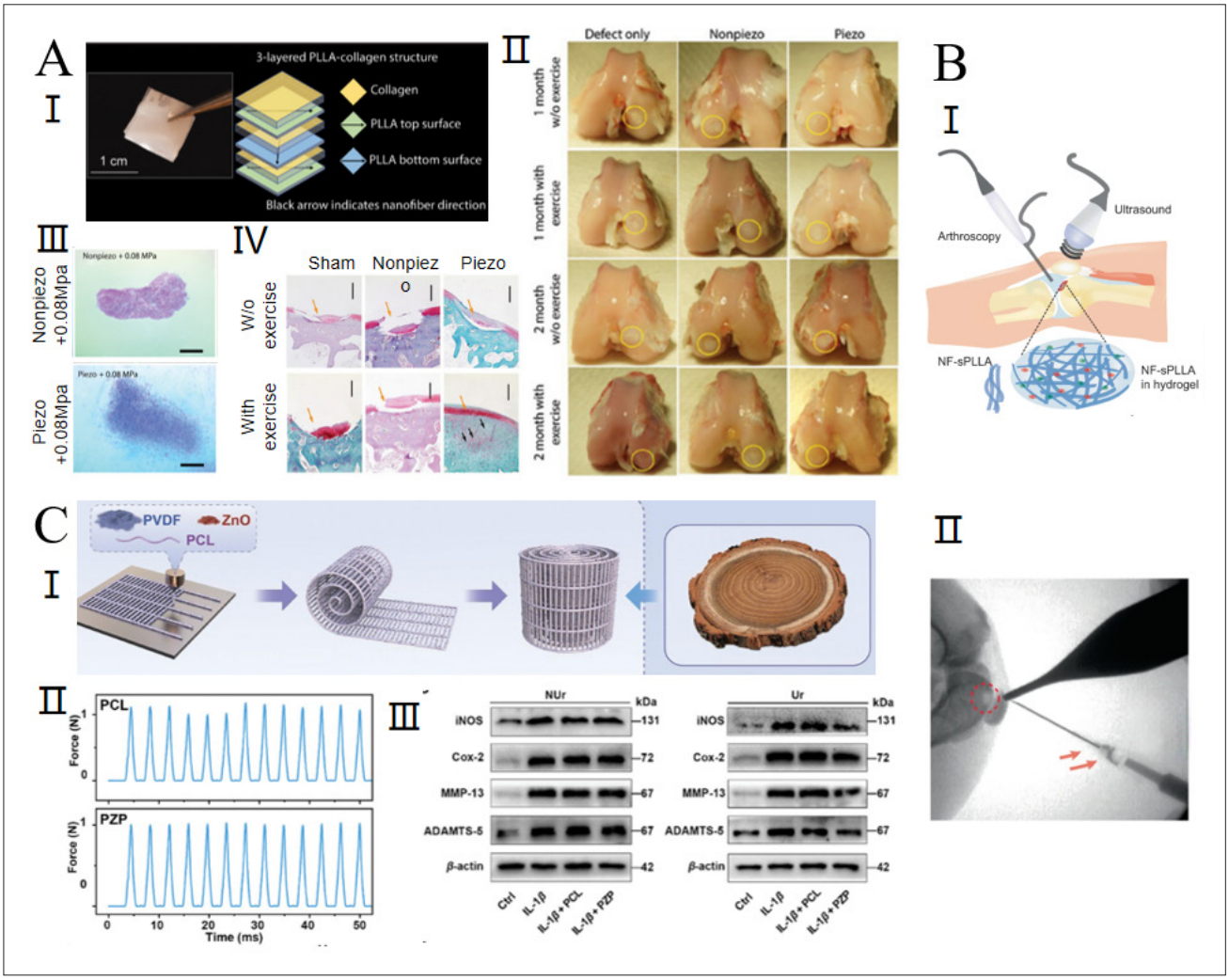

Figure 5. Current approaches and strategies for cartilage regeneration. (A) Biodegradable scaffolds combined with physical exercise promoted cartilage repair. (I) Assembly strategy of poly-L-lactic acid piezoelectric scaffolds. (II) Superior regeneration in exercise groups with piezoelectric scaffolds. (III) Enhanced chondrogenic differentiation under pressure shown by Alcian blue staining. Scale bar: 100 μm. (IV) Improved cartilage repair in the exercise group confirmed via Safranin O–Fast Green staining. Scale bar: 500 μm. Reprinted with permission from Liu *et al.*[92] Copyright © 2022, The American Association for the Advancement of Science. (B) Injectable biodegradable scaffolds facilitated cartilage regeneration. (I) Piezoelectric hydrogel design for osteoarthritis (OA) treatment. (II) X-ray-guided hydrogel injection into knee joint defects. Adapted from Liu *et al.*[91] (C) Piezoelectric scaffolds with tree-ring-inspired structures enhanced cartilage repair. (I) Fabrication process of tree-ring structured piezoelectric scaffolds. (II) Piezoelectric responses under mechanical stimulation in polyvinylidene fluoride (PVDF)/zinc oxide (ZnO)/polycaprolactone (PCL) (PZP) scaffolds. (III) Suppressed pro-inflammatory macrophage expression in PZP groups. Reprinted with permission from Lin *et al.*[44] Copyright © 2025, Wiley.

precise spatial control of bioelectrical stimulation *in situ* remains difficult. Biodegradable multilayer scaffolds such as PLLA/collagen composites can provide long-term surface potential, but the fine-tuning of mechanical and piezoelectric cues in a spatiotemporal manner is still limited.

Evidence suggests that higher-intensity piezoelectric stimulation favors osteogenesis, while lower levels promote chondrogenesis, underscoring the importance of precise signal regulation. This provides a strong rationale for the application of advanced 3D printing techniques. Unlike conventional fabrication methods, advanced 3D printing techniques allow spatially controlled modulation of pore size, layer thickness, and material composition, thereby enabling the construction of scaffolds with continuous gradients or multilayered structures that closely mimic the native osteochondral interface.[93,94] Moreover, these methods facilitate the incorporation of piezoelectric elements with tailored properties, making it possible to deliver localized and tunable bioelectrical cues.

Looking forward, combining biodegradable piezoelectric materials with advanced 3D printing holds great promise. On the one hand, personalized scaffolds can be designed based on patient-specific imaging data, ensuring anatomical fit and functional integration. On the other hand, dynamic and programmable architectures could be achieved, in which piezoelectric properties evolve with scaffold degradation, thereby providing time-dependent stimulation that matches the healing process. Additionally, integration with minimally invasive activation strategies, such as ultrasound or magnetic fields, may further enhance *in vivo* applicability, reducing surgical trauma while enabling remote regulation of bioelectrical signals.

5.4. Mechanisms of piezoelectric biomaterials in bone and cartilage regeneration

Piezoelectric biomaterials promote bone and cartilage regeneration by converting mechanical stimuli into localized bioelectric signals that activate a cascade of intracellular events. These electrical cues are sensed by membrane-associated receptors and ion channels, including mechanosensitive channels (e.g., Piezo), voltage-gated calcium channels (particularly L-type), and calcium-sensing receptors. Their activation triggers a rapid influx of extracellular Ca^{2+} together with the release of endoplasmic-reticulum Ca^{2+} via IP_3 receptors, establishing a spatiotemporally regulated calcium microdomain central to subsequent lineage-specific signaling.

The elevated cytoplasmic Ca^{2+} binds to CaM, initiating a network of downstream signaling pathways that coordinate both osteogenic and chondrogenic differentiation. The Ca^{2+}/CaM–calcineurin–nuclear factor of activated T-cells (NFAT) cascade dephosphorylates NFAT, facilitating its nuclear localization and transcriptional activation of lineage-specific genes. During osteogenesis, NFAT cooperates with runt-related transcription factor 2 and Osterix to enhance the transcription of matrix-related proteins such as collagen type I and osteocalcin. Simultaneously, activation of the Ca^{2+}/CaM–CaMKII axis stabilizes runt-related transcription factor 2, while Ca^{2+}-dependent MAPK phosphorylation of p38 and ERK amplifies osteogenic gene expression. In contrast, in chondrogenic differentiation, the same Ca^{2+} signaling network activates the Ca^{2+}/NFAT and Ca^{2+}/SRY-box transcription factor 9 pathways, where SRY-box transcription factor 9 acts as the master regulator of cartilage formation, inducing collagen type II and aggrecan production. These findings suggest that piezoelectric modulation acts upstream of canonical osteogenic and chondrogenic transcriptional programs, providing a unifying regulatory mechanism.

The electric polarization generated by piezoelectric surfaces also modulates cell–matrix interactions through integrin clustering and focal adhesion kinase activation. This process triggers Ras–Raf–MEK–ERK and PI3K–Akt signaling cascades, which promote cytoskeletal organization, cell viability, and metabolic activity. Mitochondrial function is subsequently enhanced, leading to increased adenosine triphosphate generation and moderate production of reactive oxygen species. At physiological levels, reactive oxygen species act as secondary messengers, fine-tuning MAPK and Wnt/β-catenin signaling to promote osteogenesis and angiogenesis. However, excessive reactive oxygen species disrupts mitochondrial membrane potential and impairs regenerative outcomes, underscoring the need for balanced piezoelectric stimulation.

Ultimately, these interconnected biochemical and biophysical processes converge to determine cellular lineage commitment. Runx2-centered transcriptional programs orchestrate bone matrix mineralization, while SRY-box transcription factor 9-directed signaling regulates cartilage extracellular matrix synthesis. Through the synchronized modulation of Ca^{2+} dynamics, redox homeostasis, and mechanotransductive signaling, piezoelectric biomaterials can successfully reconstruct a bioelectric microenvironment favorable for both bone and cartilage regeneration.

5.5. Potential side effects of piezoelectric biomaterials

Despite their therapeutic promise, piezoelectric biomaterials present several potential risks that warrant careful evaluation. Excessive electrical stimulation, particularly under high-intensity mechanical loading or ultrasound activation, may overstimulate Ca^{2+} channels, leading to abnormal mineralization in bone or fibrocartilage formation in cartilage. Similarly, materials that generate reactive species under stimulation may induce mitochondrial depolarization or oxidative stress if the reactive oxygen species production exceeds physiological thresholds.

Material-dependent risks also exist. Non-degradable polymers such as PVDF and PVDF-TrFE may cause chronic inflammation, fibrotic encapsulation, or difficulty in removal during revision procedures. In contrast, brittle ceramics or nanoparticles (BT, KNN, ZnO) may release ions at uncontrolled rates or accumulate in tissues, raising long-term toxicity concerns. Mechanical mismatch between stiff piezoelectric fillers and compliant cartilage or soft tissues can cause stress concentrations, local microtrauma, or impaired integration.

Given these risks, piezoelectric scaffolds must be evaluated using dose–response relationships that define safe electrical outputs, controlled degradation kinetics, and acceptable ion-release profiles. Incorporating safety thresholds into scaffold design and activation protocols will be essential for minimizing adverse events while preserving therapeutic efficacy.

5.6. Biological implications and translational potential

Piezoelectric scaffolds offer profound biological implications by providing a direct interface between mechanical forces and cellular signaling networks. Their ability to modulate Ca^{2+} dynamics, mitochondrial activity, redox balance, and mechanosensitive transcription suggests that piezoelectric regulation acts upstream of many canonical regenerative pathways. This positions piezoelectric biomaterials not only as structural scaffolds but also as dynamic regulators of the tissue microenvironment.

From a translational perspective, several hurdles remain. Long-term stability and reproducibility of piezoelectric performance must be ensured under physiological loading cycles. The safe degradation of polymers and controlled clearance of ceramic components require further investigation. Manufacturing consistency, sterilization protocols, and regulatory compliance will need to be established before clinical implementation. Imaging-guided activation strategies, including ultrasound- or magnetic-responsive piezoelectric scaffolds, may improve clinical safety by allowing non-invasive modulation of bioelectric cues. Personalized scaffold fabrication using patient-specific imaging combined with advanced 3D printing could enable anatomically accurate constructs with tailored electrical and mechanical gradients.

Overall, the convergence of piezoelectric biomaterials with advanced manufacturing technologies provides a compelling roadmap for next-generation regenerative therapies. Continued interdisciplinary research is essential to fully harness their potential while addressing the biological and translational challenges that remain.

6. Conclusion

Piezoelectric scaffolds offer a compelling strategy for regenerating bone and cartilage by converting mechanical forces into instructive electrical stimuli. The rapid development of 3D printing technologies has further expanded their application by enabling precise control over scaffold architecture, gradient design, and functional customization. This review synthesizes recent advances in piezoelectric materials and fabrication strategies, and outlines the biological mechanisms that underpin their therapeutic potential in bone and cartilage regeneration.

Despite encouraging progress, several challenges still hinder the clinical translation of these systems. One of the most persistent difficulties is the need to simultaneously achieve biodegradability, mechanical robustness, and stable electrical output within a single scaffold. This challenge is particularly evident in load-bearing bones and at the osteochondral interface, where mechanical and bioelectrical gradients play critical roles. Future research should, therefore, draw inspiration from the graded and anisotropic features of native osteochondral tissues to create coordinated mechanical–electrochemical hierarchies.

Another key limitation concerns the inability to monitor healing in real time and dynamically adjust stimulation, particularly in complex or severe defects where complications may hinder regeneration. Most existing studies rely on fixed material properties that cannot respond to changes in the defect environment. The incorporation of ultrasound-responsive piezoelectric scaffolds with integrated sensing systems could yield "visualizable" platforms capable of quantifying local charge parameters, tracking healing progression, and enabling personalized adjustments to the regenerative microenvironment.

The path toward clinical translation also requires more comprehensive *in vivo* evidence. Many studies are still confined to *in vitro* experiments or small-animal models, which do not fully capture the complexity of human osteochondral defects. Long-term evaluations in large-animal models are needed, particularly to assess immune responses, the stability of electroactivity under repeated mechanical loading, degradation behavior, and fatigue resistance. In addition, progress toward standardized fabrication protocols, reproducible piezoelectric outputs, and regulatory compliance will be essential for ensuring reliability and scalability.

Overall, piezoelectric biomaterials, when combined with the precision of advanced 3D printing, represent a promising direction for next-generation osteochondral regeneration. Continued collaboration among materials scientists, engineers, biologists, and clinicians will be crucial for addressing current limitations and transforming laboratory discoveries into clinically meaningful therapies.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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