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REVIEW

The Role of Piezoelectric Materials in Bone Remodeling and Repair: Mechanisms and Applications

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Abstract: Bones can sense bioelectricity. The process of bone remodeling and repair needs complex physiological signals like bioelectric, biochemical, and biomechanical factors, which work together to promote bone recovery. The formation, healing, and regeneration of natural bones are intricately linked to the influence of electrical signals. Piezoelectric materials have piezoelectric properties similar to bones, making them suitable for bone like repair. This study systematically summarizes the role of piezoelectric materials in bone remodeling and repair, as well as their related preparation techniques. Subsequently, the piezoelectric mechanism of bones is explored in depth, including the study of bone composition, analysis of piezoelectric and osteogenic mechanisms, and research progress on piezoelectric stimulation guided bone regeneration and repair. Through these analyses, the principle of how piezoelectric materials interact with bones to promote bone repair and remodeling has been further understood. Finally, the article analyzes the mechanism of piezoelectric materials on bone remodeling and repair, revealing how piezoelectric stimulation promotes bone regeneration and repair. These findings offer theoretical foundation and practical guidance for the further application of piezoelectric materials in orthopedics.

Keywords: Bioelectricity, Physiological signals, Piezoelectric stimulation, Osteogenic mechanism, Bone remodeling and repair, Piezoelectric material

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Introduction

Natural bones exhibit key piezoelectric, pyroelectric, and ferroelectric properties that is vital in the healing and growth processes of bones. Intelligent biomaterials, also known as functional materials, is utilized in drug delivery and tissue manipulation applications because of their unique biological properties such as cell transport, therapeutic compound delivery, and remoted control capabilities. Currently, research on Piezoelectric Materials (PMs) focuses on enhancing the physical and chemical properties of materials through optimized processing techniques, thereby meeting the needs of bone replacement. The piezoelectric properties of natural bone are mainly due to the non-centrically symmetrical arrangement structure of collagen fibers, which are its organic matrix components. Collagen molecules are displaced under mechanical stress, generating a dipole moment and surface charge.[1,2] Although hydroxyapatite (HA) crystals, which are the main inorganic components of bone, are not generally considered to be significant piezoelectric sources in themselves, their role in the complex hierarchy of bone and possible ion flow contributions still need to be studied. In addition, the interaction between the flow potential of wet bone and piezoelectric effect further promotes bone regeneration and remodeling. Research has shown that applying pressure to PMs to generate an electric potential can enhance bone metabolism activity. Negative polarized PMs are particularly effective in promoting cell growth. Polarized

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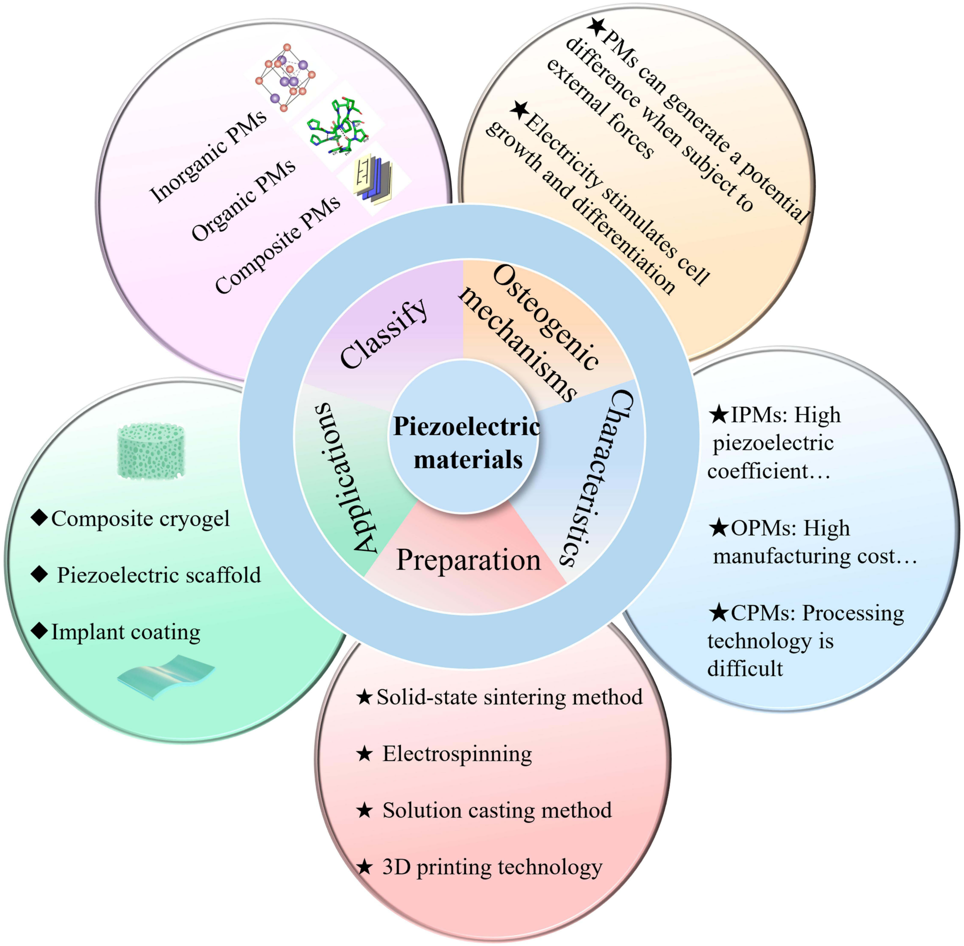
Graphical Abstract



piezoelectric scaffolds can autonomously generate electric potential without external Electric Field Stimulation (EFS), thereby simulating the bioelectric signals of bone behavior under mechanical stimulation.[3] Placing piezoelectric scaffolds at the site of bone defects, combined with electrical stimulation generated by physiological loads, can significantly enhance fracture repair. Piezoelectric ceramics, polymers, and composite materials have shown great potential in promoting osteoblast differentiation, recruiting osteoblasts and stem cells, and promoting bone healing and regeneration due to their significant electromechanical properties.[4] In addition, implanting piezoelectric devices can provide electrical stimulation, further promoting bone regeneration and repair. These scaffolds can enhance cell activity, stimulate bone tissue formation, and are not dependent on drugs or growth factors.[5] Adding stimulating factors to implantable scaffolds can accelerate bone tissue healing, shorten treatment time and cost. This study explores various techniques aimed at addressing the application limitations of materials, such as hydrophobicity, poor biocompatibility, or non-degradability. In summary, PMs occupy a crucial position in bone healing and growth processes. Its unique piezoelectric effect gives a novel approach for bone regeneration and repair. In the future, with the deepening of research and continuous technological progress, PMs are hoped to have a more extensive and in-depth role in orthopedics.

PMs and Bone

Category of PMs and Their Utilization in Bone Remodeling and Repair

PMs are a special kind of crystalline material that can undergo deformation under external forces, resulting in internal polarization and surface charge generation. The phenomenon of converting mechanical energy into electrical energy is called the piezoelectric effect. The piezoelectric effect originated from the discovery of the Curie brothers in 1880. They observed that applying pressure to quartz crystals produces charges that are linearly related to the pressure (positive piezoelectric effect). Subsequently, they confirmed the piezoelectric inverse effect, which refers to the mechanical deformation of crystals in an electric field that is linearly related to the strength of the electric field (indirect piezoelectric effect).[6,7] PMs are primarily segmented into 3 categories: Inorganic PMs (IPMs), Organic PMs (OPMs), and Composite PMs (CPMs), as shown in Figure 1.

Classification and Basic Characteristics Analysis of IPMs

The piezoelectricity of inorganic materials is due to the asymmetry of charge distribution in crystals under mechanical stress, which is mainly caused by the movement of ions in the crystals. The non centrosymmetric atomic structure is the key to forming net polarization, which prevents the dipole moment generated by ion movement from being cancelled out

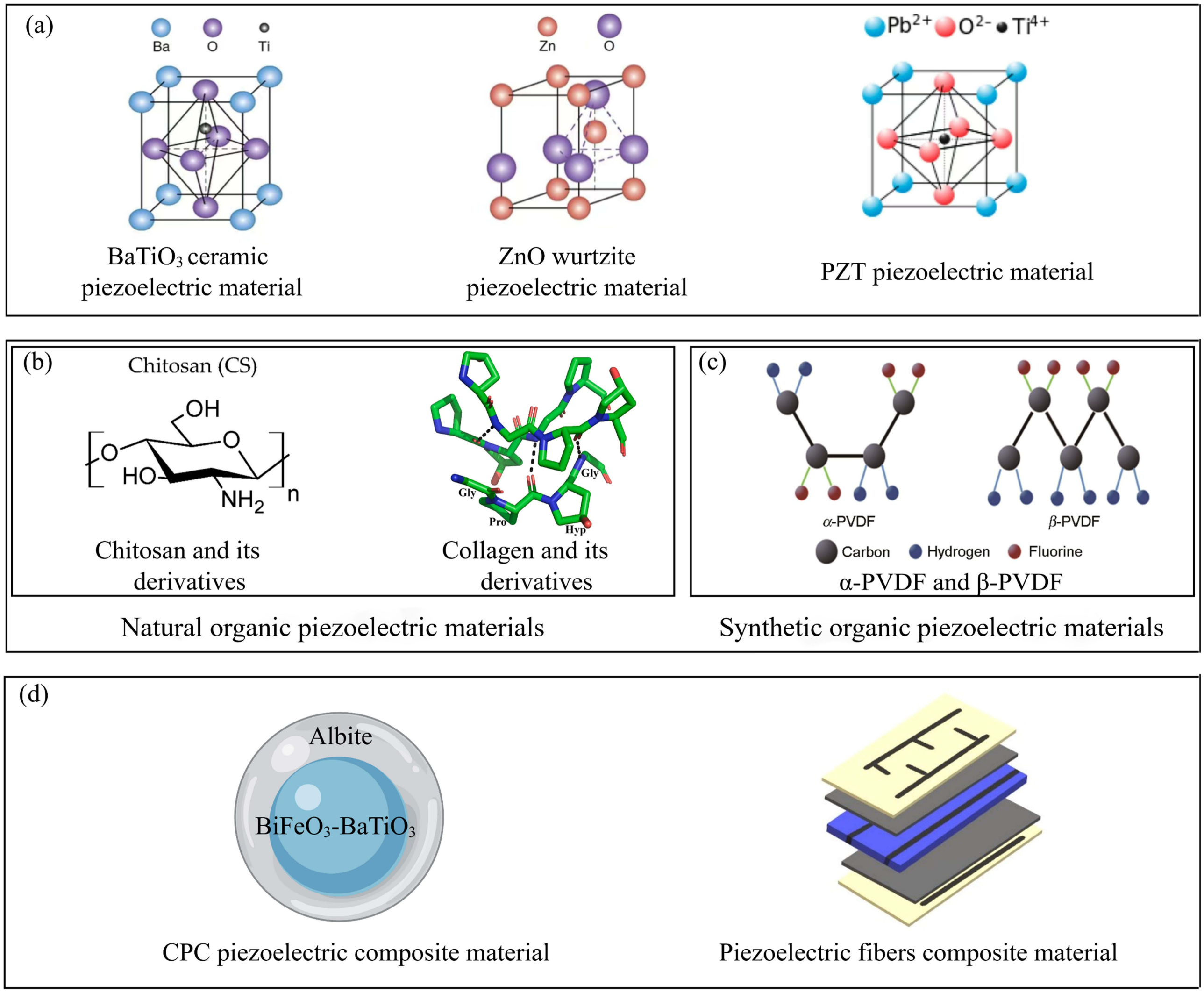


Figure 1 Structure of common piezoelectric materials. (**a**) Crystal structure of IPMs. Reprinted from Ghadarah et al,[8] Cafarelli et al,[9] licensed under CC BY 4.0. (**b–c**) Natural OPMs and Synthetic OPMs.[10–12] Reprinted from Fakhreeva et al,[10] licensed under CC BY 4.0. Reprinted from Tang et al,[11] Copyright 2022, with permission from Elsevier. (**d**) CPMs.

by other dipoles within the single crystal cell.[8,9] Although some centrally symmetric materials do not exhibit piezoelectricity under conventional conditions, they can still exhibit piezoelectric properties at the nanoscale or in non-equilibrium states, such as nano Hydroxyapatite (HAP) crystals.[10,11] IPMs have two categories: piezoelectric crystals and piezoelectric ceramics. The former refers to crystals that grow in a long-range ordered manner according to the crystal spatial lattice, and their structure has no symmetrical center, thus possessing piezoelectricity. When these crystals are subjected to external forces, the ions inside them will undergo displacement, resulting in the generation of electric dipoles and exhibiting piezoelectric effects. Piezoelectric ceramics are made by mixing necessary raw materials such as oxides or carbonates in a specific proportion, and through forming and high-temperature sintering processes, forming irregular collections of fine grains and polycrystals through solid-state reactions between powder particles.[12,13]

$BaTiO_3$ has five kinds of crystal phases. With the decrease in temperature, there is a relative displacement between ions, which leads to spontaneous polarization, and the symmetry of crystal phase is also reduced. $BaTiO_3$ crystal generally refers to $BaTiO_3$ single crystal, while $BaTiO_3$ ceramic generally refers to $BaTiO_3$ polycrystal. Among a series of important parameters of piezoelectric ceramics, the piezoelectric constant dij and the dielectric constant ε are interrelated, and high dielectric constant is usually accompanied by higher piezoelectric coefficient. Generally speaking, the dielectric constant of $BaTiO_3$ increases at first and then decreases with the increase of Tc, that is, the structure and dielectric properties of $BaTiO_3$ ceramics can be regulated by adjusting the sintering temperature.[14] However, $BaTiO_3$ ceramics are difficult to obtain high piezoelectric characteristics using conventional sintering methods, combining $BaTiO_3$ ceramics with other functional or controllable materials is necessary for new material development.

$BaTiO_3$ ceramics are often challenging to achieve high piezoelectric characteristics through traditional sintering methods, necessitating the incorporation of other functional or controllable materials for the development of new materials. Xu et al utilized a solid state reaction sintering method to introduce an appropriate amount of AlN into the $BaTiO_3$ matrix.[15] This addition of AlN enhances the material's mechanical properties while preserving its electrical properties. However, it falls short in replicating the electrophysiological properties of natural bone tissue, which should ideally closely resemble those of natural bone. Natural bone, being a conductive and piezoelectric tissue, benefits from the deposition of calcium salt in damaged bones through streaming-generated potential. $BaTiO_3$ piezoelectric ceramic exhibits a piezoelectric effect similar to that of natural bone, making it a widely studied material due to its ability to convert mechanical energy into electrical energy.

PZT is a solid solution consisting of PbTiO3 (PT) and PbZrO3 (PZ). The term "morphotropic phase boundary" (MPB) refers to the region in PZT materials where both tetragonal and trigonal crystal phases coexist. When PZT approaches the MPB region, it undergoes a transformation leading to the highest values of both piezoelectric and dielectric constants. The formation of the morphotropic phase boundary is crucial for enhancing the piezoelectric properties of PZT.[16] PZT exhibits a significant piezoelectric constant, heightened sensitivity, and quicker response compared to metal oxide-based piezoelectric materials, making it highly esteemed in medical sensor and ultrasonic transducer applications.[17] Doping modification stands out as a commonly used technique to enhance the characteristics of perovskite crystals of the ABO3-type. Through the introduction of various trace elements into PZT, its properties can be modified in distinct ways. For instance, doping PZT with Nb5+ at the A site and B site has been explored.[16] Additionally, PMN-PZT ceramics doped with new rare earth elements La/Sm exhibit higher piezoelectric constants and electromechanical coupling coefficients than pure PMN-PZT or PZT ceramics, despite not being as flexible as organic materials.[18]

A significant challenge for certain high-performance IPMs, particularly lead-based piezoelectric ceramics like PZT, is the potential toxicity associated with heavy metal ion leaching.[19] This poses a critical concern for long-term biocompatibility and biosafety in bone implant applications. Intensive research focuses on developing high-performance lead-free piezoelectrics as safer alternatives. For temporary implants, designing ceramics with controlled biodegradation rates ensures eventual clearance of the material, but requires careful tuning to match degradation with bone healing and manage ion release kinetics.[20] While lead-free materials are safer, they often exhibit lower piezoelectric coefficients compared to PZT. Achieving a balance between sufficient piezoelectric performance for effective electrical stimulation and excellent biocompatibility/long-term biosafety remains an essential goal in material design for orthopedic applications.

The piezoelectric properties of ZnO are attributed to its non-centrosymmetric tetrahedral crystal structure, leading to spontaneous polarization.[21] This effect enhances the influx of calcium ions in ZnO nanowires by activating multiple calcium channels within them.[22] While ZnO toxicity is observed at the nanoscale due to the presence of reactive oxygen species (ROS), it is not apparent at the macroscopic level.[23,24] Lozano et al[25] have also developed BG scaffolds enriched with ZnO, which have been shown to enhance the formation of new bone trabeculae, increase bone density, possess antimicrobial properties, reduce fibrous tissue formation, and ultimately improve the bone healing process compared to scaffolds without ZnO.[25]

The incorporation of ZnO modification in borosilicate bioglass and chitosan (CS) composite scaffolds has been shown to enhance their ability to stimulate bone formation and prevent implant-related bone infections.[26] ZnO exhibits an unpolarized piezoelectric constant (d33) equivalent to that of lead-free materials.[27]

Furthermore, the addition of lithium, a lead-free piezoelectric ceramic, is commonly used to improve the piezoelectric properties of potassium sodium niobate (KNN). The piezoelectric coefficients of KNN and LKNN are reported to be 63pC/N and 98pC/N, respectively.[28,29] Piezoelectric ceramics with different piezoelectric constants display unique surface positive charges. Notably, the sample with the highest positive charge of 80pC/N demonstrates superior antibacterial efficacy, cell proliferation capacity, and biocompatibility compared to the sample with a lower piezoelectric constant.[30] However, the sintering temperature range of KNN is narrow, and there is little room for performance improvement. The microstructure is difficult to control. During the sintering process of KNN ceramics, Na and O are prone to evaporation.[31]

For IPMs, there are many randomly oriented electrical domains in the polycrystalline materials formed by sintering. To obtain macroscopic piezoelectric properties, polarization is necessary. Polarization is usually carried out by strengthening the direct current electric field at high temperature, so that the electric field is oriented in the direction of the electric field as much as possible to retain the remaining polarization after removing the electric field and activate the piezoelectric effect of the material. Polarization conditions (electric field strength, temperature, time) have a decisive influence on key performance parameters such as final piezoelectric constant (d_{33}) and electromechanical coupling coefficient.[32] The piezoelectric properties of unpolarized ceramics are weak or not visible. Table 1 shows the pros and cons of common IPMs properties.

Classification and Basic Characteristics Analysis of OPMs

The piezoelectric effect of OPMs originates from their molecular structure and orientation.[33] Under the action of a strong electric field or tensile tension, molecular dipoles in polymers are redirected to form net polarization, resulting in

Table 1 Summary of Common IPMs Properties

IPMs	Advantages	Disadvantages	Connection With Bone Remodeling and Repair
$BaTiO_3$	High piezoelectric constant, high electromechanical coefficient, strong biocompatibility and osteogenic properties.[14]	Due to its poor biological activity and lack of magnetic properties, it cannot directly generate magneto electric coupling effects.[15]	The piezoelectric effect of $BaTiO_3$ can promote the P&D of bone cells, thereby accelerating the repair and remodeling of bone tissue.
PZT	High sensitivity, small size, excellent piezoelectric coefficient, low dielectric loss, high transition temperature, and excellent heat dissipation performance.[16]	Lead containing. Harmful to the human body.[17]	Due to the toxicity of lead, its application in bone remodeling and repair is currently limited.
ZnO	High piezoelectric coefficient, cyclic nature, strong activity degradation ability, and polarization properties.[21,22]	The properties are not stable enough, with cytotoxicity and relatively poor conductivity.[23,24]	The piezoelectric effect and degradation performance of ZnO can promote the P&D of bone cells.
KNN	KNN have good biocompatibility. The mechanical quality factor is small, the Curie temperature is high, the piezoelectric constant is high, the frequency constant is high, and the dielectric constant is low.[28,29]	The sintering temperature range is narrow, and there is little room for performance improvement. The microstructure is difficult to control. During the sintering process of KNN ceramics, Na and O are prone to evaporation.[30,31]	The piezoelectric effect of KNN can promote the P&D of bone cells, accelerate the regeneration and repair of bone tissue.

piezoelectric effects. This type of organic material has wide applications in the biomedical field.[34] OPMs include two types: natural OPMs and artificially synthesized OPMs.

The β crystal phase of PVDF, characterized by regular molecular chains, parallel dipoles, and significant spontaneous polarization, is frequently used in piezoelectric applications. Research has shown that the non-piezoelectric α phase of PVDF can be converted to the piezoelectric β phase through tension and polarization processes.[35] This conversion involves melting and crystallizing the α phase to form a film, followed by mechanical stretching or polarization transformation to obtain the β phase.[36–38] Piezoelectric devices, researchers can explore more efficient additives, architectures, and their combinations.[39] In the electrospinning process of preparing composite fiber films of PVDF and HAP, heat treatment can induce a transition to the β-phase. Moreover, solutions with lower viscosity experience greater stretching during electrospinning, leading to a higher number of α-β phase transitions.[40]

Poly 3-hydroxybutyrate (PHB) and3-hydroxybutyrate-co-3-hydroxyvaleric acid (PHBV)are types of polyhydroxyalkanoates (PHA) that are biodegradable and possess piezoelectric properties, making them promising for bone tissue applications.[41–43] Doping PHBs with graphene oxide (rGO) or PANI can enhance their piezoelectric response, improving mechanical and electrical energy conversion for better cell stimulation.[44] While polyamide is commonly used for bone regeneration scaffolds, there is no direct evidence that it stimulates bone regeneration. However, Polyamide (PA)/HAP scaffolds produced using selective laser sintering exhibit strong mechanical strength, attract osteoblasts, and stimulate bone growth. Cell activity tests and alkaline phosphatase (ALP) colorimetry showed that PA alone did not stimulate bone regeneration, but PA/HA composite scaffolds significantly enhanced osteoblast proliferation and differentiation.[45]

Polylactic acid (PLLA), a synthetic polymer with piezoelectric properties and biodegradability, exhibits unique characteristics.[46] While flexible and transparent piezoelectric thin films made from PLLA may not possess the same level of piezoelectric constant as inorganic materials and cannot be spontaneously polarized, semi-crystalline PLLA can generate a piezoelectric effect without requiring polarization treatment. PLLA-based high-performance piezoelectric materials show great promise for bone tissue regeneration.[47,48] PLLA improves the mechanical strength and durability of composites, making them more suitable for bone defect areas under significant stress.[49] Combining thermoplastic polyesters such as PLLA and Polycaprolactone (PCL) with polymers derived from bacterial PHBV enhances biocompatibility and encourages cell adhesion.[50] Common concerns in bone regeneration materials include bacterial infections and inadequate bone growth. Studies have indicated that applying bacteriostatic coatings[51] or incorporating ZnO into PLLA[52] can give PLLA antimicrobial properties against Gram-positive bacteria, which may be beneficial in treating bone issues related to infections. This presents an alternative method for developing PLLA materials with both osteogenic and antibacterial characteristics. Table 2 shows the common properties and characteristics of OPMs.

Table 2 Properties of Common OPMs

OPMs	Advantages	Disadvantages	Connection With Bone Remodeling and Repair
Polyvinylidene fluoride (PVDF)	Low density and impedance, high flexibility and piezoelectric voltage constant.[35–38]	High manufacturing cost.	The piezoelectric properties of PVDF enable it to generate charges in response to external stress, which helps promote cell response and proliferation.
Polyhydroxybutyrate (PHB)	Good biocompatibility, biodegradable properties, and certain piezoelectric properties.[41–43]	PHB has high brittleness, is not resistant to impact, is prone to fracture and cracking, and has a narrow hot working window.	PHB, as a biocompatible and biodegradable material, owns potential value in bone regeneration and repair.
Poly (L-lactic acid) (PLLA)	It has certain strength and toughness, can withstand certain external forces, and has good transparency.[46–48]	Poor thermal stability	PLLA can serve as a scaffold material to provide support for cell growth and differentiation.

Classification and Basic Characteristics Analysis of CPMs

CPMs are composed of thermoplastic polymers and IPMs and have the ability to generate current or deform under external force. It mainly includes piezoelectric composite materials composed of sheet, rod, rod or powder PMs embedded in organic polymer substrates.[53]

AlN, known for its excellent piezoelectric and dielectric properties, is classified as an inorganic piezoelectric ceramic.[54] When combined with elastically vibrating polydimethylsiloxane (PDMS) in a film, AlN can generate an electric current when subjected to vibrations from a simple loudspeaker, effectively converting mechanical energy into electrical energy. Results from experiments showed that the continuous alternating current produced by the vibrating film played a crucial role in promoting the growth of MC3T3-E1 cells and the expression of osteogenesis-related genes, such as osteocalcin. Furthermore, the vibrating film exhibited a higher capacity for mineralization compared to both a PDMS film and a non-vibrating PDMS/AlN film. This innovative approach presents a promising solution for the integration of advanced composite piezoelectric materials in the field of bone tissue engineering.[55]

Currently, most composite piezoelectric materials combine inorganic substances with organic substances, resulting in new materials with additional features like antibacterial and anti-inflammatory properties, ease of processing, or biodegradability, in addition to their ability to support bone repair and regeneration. BTO NPs are commonly incorporated into organic polymer matrices as electroactive fillers due to their strong and sustainable electroactivity that mimics physiological and electrical activity.[56] While PCL itself shows minimal piezoelectricity, its excellent biocompatibility and mechanical flexibility make it an ideal polymeric matrix for developing electroactive composites. Ferroni et al demonstrated that incorporating 5 wt% rGO into PCL significantly improved the composite's electrical conductivity and osteoinductive capacity. The rGO-PCL scaffold promoted BMSCs differentiation even without exogenous growth factors, attributed to enhanced charge transfer and surface topography.[57] This synergy highlights PCL's role as a versatile platform for designing multifunctional piezoelectric composites.

Bhaskar et al[58] utilized a combination of BT and PVDF, incorporating high volume BaTiO3 (30 wt%) and multi-walled carbon nanotubes (MWCNT; 3 wt%) as fillers in PVDF. Their cell culture assays revealed that these composites significantly enhanced the proliferation, migratory capacity, and ALP activity of MC3T3-E1 osteoblasts when compared to pure PVDF, thereby promoting the osteogenic process. By integrating electroactive components like ferroelectric ceramic nanoparticles into nanofunctional fibrous scaffolds, the study aimed to mimic the physiological and electrical properties of these scaffolds to enhance bone formation. Results showed that BTO/PLLA fibrous scaffolds with irregular orientation improved osteogenic differentiation, displaying the highest dielectric constants. Conversely, well-arranged fibrous scaffolds had an opposite effect, indicating that random orientation combined with electroactivity contributes to BMSCs' osteogenic differentiation.[59] Table 3 shows the properties of common CPMs.

Table 3 Advantages and Disadvantages of Common CPMs Properties

CPMs	Advantages	Disadvantages	Connection With Bone Remodeling and Repair
Polydimethylsiloxane/ Aluminum nitride (PDMS/AlN)	It has the properties of softness and flexibility and can maintain good deformation ability under force.[54]	The mechanical strength is not as good as IPMs.	Can be used for soft tissue repair.
PVDF/Barium titanate (PVDF/$BaTiO_3$)	Good dielectric properties and corrosion resistance.[56]	The processing technology is difficult, and the toughness of composite materials is low.	It can promote the P&D of bone cells, accelerate the repair of bone tissue.
PCL/rGO	Good biocompatibility, biodegradable properties, and certain piezoelectric properties.[57]	PCL has a high cost and a relatively slow degradation rate.	PCL membrane can serve as a temporary scaffold, providing space for cell P&D.

(*Continued*)

Table 3 (Continued).

CPMs	Advantages	Disadvantages	Connection With Bone Remodeling and Repair
PLLA/BaTiO$_3$	Has certain piezoelectric properties.[58,59]	The PLLA's degradation rate is hard to control.	The biodegradability and biocompatibility of PLLA make it an ideal choice for biomedical implants.
Epoxy resin composite material	Has high strength and hardness. Has excellent wear and corrosion resistance. Can be processed into products of different shapes.	Low toughness and weak resistance to high temperatures.	Can be used to make support structures for biomedical implants, such as bone nails, bone plates, etc.

The Piezoelectric Mechanism of Bones

Composition of Bones

Bone is considered a natural piezoelectric biomaterial, mainly composed of the inorganic phase of crystalline HAP and the organic phase of collagen. The specific structure is shown in Figure 2.

HAP in Figure 2 is one of the most popular biomaterials in Bone Tissue Engineering (BTE). HAP can be obtained naturally or synthesized chemically. The properties, shape, size, crystal structure, and applications of HAP vary depending on the source and extraction method used.[60,61] Barbosa F's research team has developed a piezoelectric nanofiber scaffold containing HAP particles. PMs could generate a potential difference when subjected to external forces,

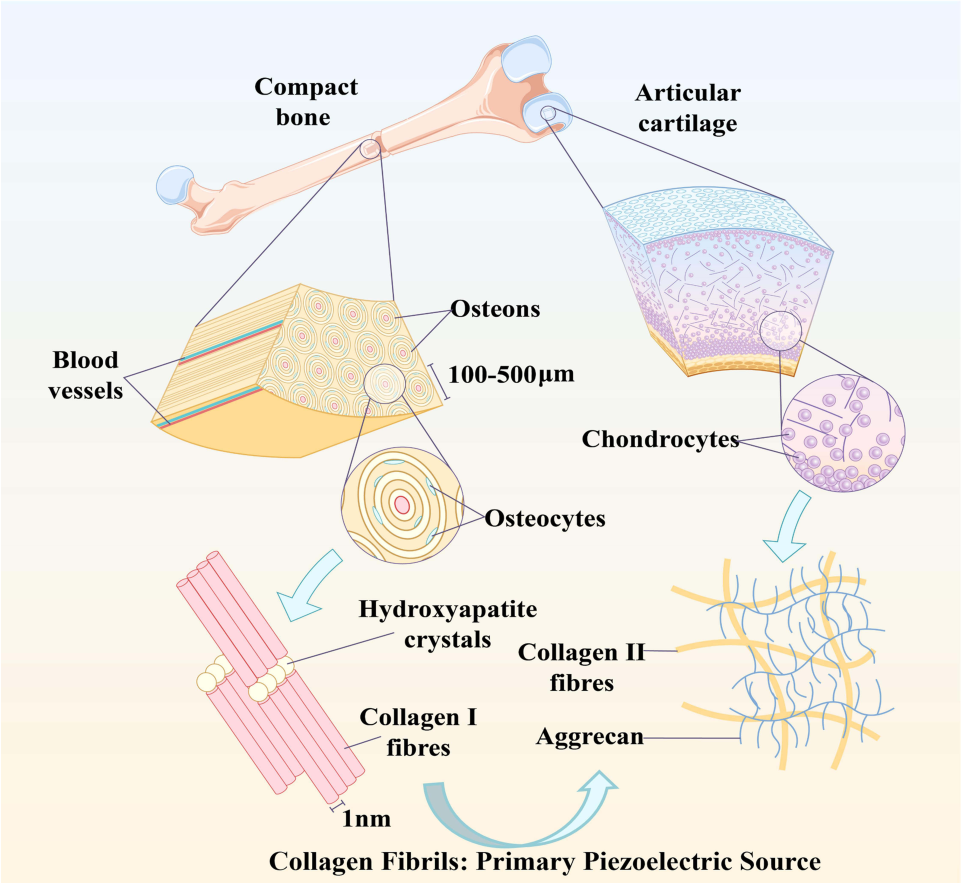


Figure 2 Hierarchical structure of bone highlighting the primary source of piezoelectricity. Piezoelectricity in bones originates predominantly from the aligned collagen fibrils at the nanoscale (indicated by arrows/annotations). Hydroxyapatite (HAP) crystals provide stiffness and mineral reservoir.

which can stimulate the Proliferation and Differentiation (P&D) of bone cells. Therefore, this scaffold could produce electrical signals while receiving mechanical stress, thereby promoting the activity of bone cells and accelerating the repair process of bone tissue.[62] Joo S incorporated HAP into an innovative piezoelectric scaffold design, not only utilizing its potential to promote bone cell growth and differentiation but also combining the advantages of piezoelectric effect and terrain enhancement. This provided a new approach for simulating the complex electromechanical environment and biocompatibility of natural bone tissue, significantly accelerating the process of bone regeneration. This study demonstrated broad utilization prospects in bone regeneration and regenerative medicine.[63] In SwainS et al's study, HA/BT nanocomposites synthesized by solid-state reaction assisted by high-energy ball milling exhibited excellent microstructure and crystal phase characteristics after sintering. With the rise of BT content, the dielectric performance was significantly improved. In addition, these composite materials have shown good blood compatibility and cell compatibility in vitro experiments, especially the composite materials with a 15HA/85BT ratio, which exhibit higher metabolic activity and cell survival rate during cultivation. This indicated that it had great potential as an orthopedic implant in promoting bone regeneration.[64] Collagen is the major organic component of natural bone tissue and is significant in bone structure. It joints in the shape of new bone as a building block and helps maintain the structural integrity of existing bone tissue. The fibrous structure of collagen provides strength and toughness to bones, enabling them to withstand various mechanical loads. Collagen is the most abundant functional protein in mammals, accounting for 25% to 30% of the overall protein content, and in some organisms, it can even reach over 80%.[65,66]

Collagen is structurally composed of three polypeptide chains arranged in a left helix. The 3 independent collagen peptide chains rely on hydrogen bonds formed between glycine to maintain the structure of 3 helices intertwined with each other. Numerous collagen macromolecules can be arranged side by side to form a fibrous cross-linked structure, resulting in a final product with high mechanical strength.[67,68] The normal triple helix conformation of collagen is the basis for its physicochemical properties and biological activity. This gives it high tensile strength, biodegradability, low antigen activity, irritation, and cytotoxicity, as well as promoting cell growth, cell adhesion, and synergistic repair of wounds with new cells and tissues when used as an artificial organ skeleton or wound dressing.

Piezoelectric and Osteogenic Mechanisms in Bones

Regarding the process of bone regeneration and repair, PMs exhibit significant osteogenic effects due to their unique combination of mechanical, electrical, and biological properties. PMs can generate a potential difference when subjected to external forces, thereby stimulating cell growth and differentiation, and promoting bone regeneration. Therefore, in the application of bone reconstruction and regeneration, the materials used not only need to have physical properties similar to natural bones, like strength, toughness, and elastic modulus, to ensure that they can withstand mechanical loads in the body. The material must also possess biological properties compatible with natural bones to pull cell adhesion, proliferation, and differentiation on the material's surface, thereby accelerating the bone regeneration and repair.[69] The hierarchical structure of bone and the stimulating impact of PMs on bone are shown in Figure 3.

In Figure 3(a), the interaction between natural bones and PMs involves complex potential coupling and piezoelectric effects. Applying pressure to bones or PMs will produce a positive piezoelectric effect, creating a potential difference. On the contrary, applying voltage will generate the inverse piezoelectric effect, leading to mechanical stress.[70] In bones, bone piezoelectricity is recognized to be derived from the molecular structure and arrangement of collagen, and HA primarily provides stiffness and an environment for ion storage/release.[1] Collagen molecules move to the surface as charge carriers under force, forming an electric potential and attracting osteoblasts. In addition, Mesenchymal Stem Cells (MSCs) migrate to damaged bones and differentiate into osteoblasts.[71] The accumulation of minerals on the compressed side of the bone and the influence of stress on bone density. The stress generated by physiological load further generates electrical stimulation, triggering voltage-gated calcium channels in the cell membrane, increasing intracellular Ca^{2+}, thereby promoting bone regeneration. The piezoelectric stent implanted in the body generates surface charge stimulation through mechanical vibration, promoting cell proliferation and wound healing. In Figure 3(b), the piezoelectric stent is subjected to mechanical stress, generating an electrical signal that stimulates the opening of voltage-gated Ca^{2+} channels. The increase in intracellular calcium ion concentration activates calcium regulated phosphatase, leading to the dephosphorylation of NF-AT. Then, NF-AT is transferred from the cytoplasm to the nucleus for gene transcription, promoting

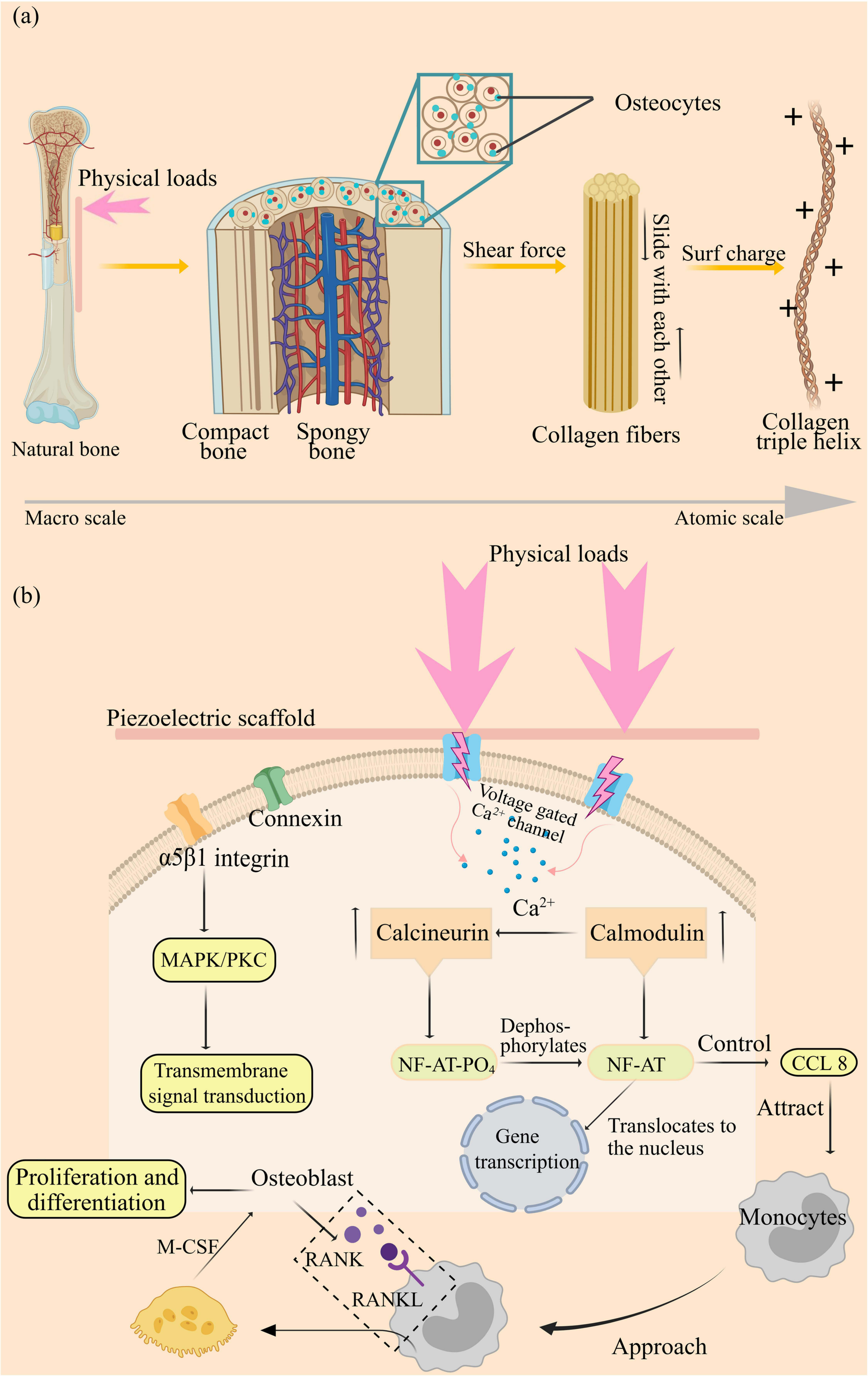


Figure 3 (**a**) The hierarchical structure of bones. (**b**) The stimulating effect of PMs on bone.

the synthesis of growth factors and ECM, ultimately facilitating the synthesis and repair of soft and hard tissues. Mechanical stimulation can also directly activate junction protein half channels and mechanical receptors, such as integrins. Integrins bind to ECM to transmit mechanical forces into cells, activating mitogen activated protein kinase (MAPK) and MAPK-C signaling pathways, connecting signal transduction between bone cells.[72,73] Calcium regulated

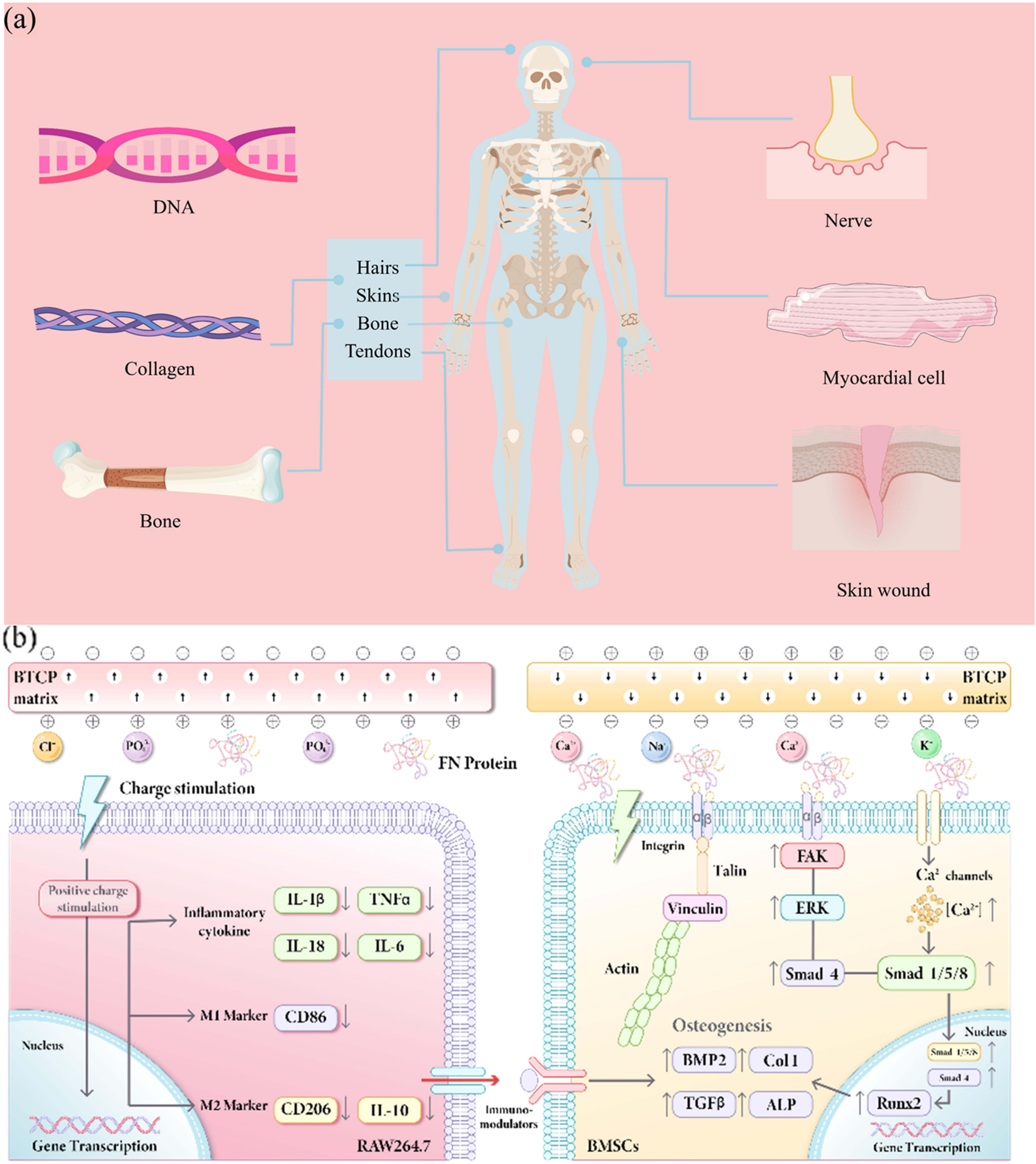


Figure 4 (**a**) Endogenous bioelectricity (right) and piezoelectricity (left). (**b**) Surface potential and charge of piezoelectric biomaterials.

phosphatase/NF-AT signaling also plays an important regulatory role in regulating bone mass. NF-AT can control the chemokine CCL8, attracting monocytes towards osteoblasts. Osteoblasts secrete RANK, which binds RANKL on monocytes to regulate the differentiation of monocytes into osteoblasts. Osteoclasts can produce cytokines such as M-CSF, which promote the P&D of osteoblasts. Electrical signals are meaningful throughout the entire bone repair process. Endogenous potential spontaneously forms at the defect site, guiding cellular behavior and mediating bone healing during fracture occurrence. The specific distribution and charge mechanism of endogenous bioelectricity and piezoelectricity are shown in Figure 4.

Liu et al found that during natural tissue regeneration, the tissue microenvironment and stem cell niche provide a series of biochemical signals for regulating cell behavior and tissue function. Electrical stimulation can regulate a series of biological processes from migration, cell cycle, and differentiation to nerve conduction, embryonic development, and tissue regeneration. In Figure 4(a), Liu et al elaborated on the concepts and distributions of endogenous bioelectricity and piezoelectricity, which serve as important foundations for the design and application of electroactive biomaterials.[74] Piezoelectric scaffolds, due to their inherent piezoelectricity, can simulate natural processes in the extracellular matrix. This characteristic makes piezoelectric scaffolds significant in the biomedical field, especially in tissue engineering and regenerative medicine. Das K et al performed an in-depth analysis of the synergistic effect between Surface Charge Polarization (SCP) or EFS and the functional properties of piezoelectric biomaterials. It was found that when the piezoelectric bracket is subjected to external forces (such as mechanical stress), its surface will generate charge polarization. This polarization phenomenon not only changes the charge distribution on the scaffold surface, but also affects the electrophysiological state of surrounding cells.[75] Cells are sensitive to electric fields, so SCP can regulate cell function by affecting the membrane potential of cells. In addition to SCP, piezoelectric scaffolds can also regulate their functional properties through external EFS. External electric fields can act on piezoelectric scaffolds to generate internal electric fields, which in turn affect the electrophysiological environment of surrounding cells. EFS has been shown to affect processes like cell migration and P&D. In vitro experiments, SCP or EFS of piezoelectric scaffolds can promote cell adhesion and spreading, increase cell proliferation rate, and induce cell migration or differentiation in specific directions. In in-vivo experiments, the electrical activity of piezoelectric scaffolds can promote the regeneration and repair of damaged tissues, accelerating the healing process of wounds. In vivo experiments, the electrical activity of piezoelectric scaffolds can promote the regeneration and repair of damaged tissues, accelerating the healing process of wounds. The results in vivo bone restoration are shown in Figure 5, and $BaTiO_3$ composite hydrogel and PLLA nanofiber membrane were used to repair mandibular bone defects in rats. According to micro-CT and histological analysis, it could be seen that both treatment methods had better repair effects than the control group.[76,77] In addition, piezoelectric scaffolds can also influence the fate selection of stem cells by regulating the local microenvironment, thereby guiding tissue regeneration in specific directions. In Figure 4b, Mao et al prepared piezoelectric $BaTiO_3$/β-TCP (BTCP) ceramics using a 2-step sintering method and established different surface charges through polarization. Experiments have shown that the d33 of BTCP can be controlled by changing the sintering rate and temperature. Moreover, BTCP with negative surface charge promotes protein adsorption and extracellular Ca^{2+} influx of Bone Marrow MSCs (BMSCs), enhancing their attachment, spreading, migration, and Osteogenic Differentiation (OsD). BTCP with positive surface charge significantly inhibited M1 polarization of macrophages, altered the secretion of pro-inflammatory cytokines, and thereby enhanced OsD of BMSCs. This indicates that positive surface charges can regulate the immune regulatory properties of bone, which is conducive to the formation of an immune microenvironment for osteogenesis.[78]

Piezoelectric Stimulation Guiding Bone Regeneration and Repair

Based on the above research, piezoelectric stimulation, as an innovative biophysical regulation method, has shown significant potential in guiding bone regeneration. By precisely regulating the surface charge distribution of piezoelectric scaffolds or applying external electric fields, the electrophysiological environment of cells can be optimized, promoting the proliferation, migration, and OsD of BMSCs. It can also regulate the activity of immune cells and create an immune microenvironment conducive to bone regeneration. Electrical stimulation not only important in the migration, adhesion, P&D of stem cells, but has also enhances the osteogenic value of diverse MSCs and osteoblast-like cells in vitro. In addition, electrical stimulation can also guide cell migration and orientation through chemotaxis and cathodic response. This mechanism of action enables osteoblasts to proliferate and differentiate more effectively, thereby accelerating the regeneration and repair of bone tissue. Meanwhile, electrical stimulation can also promote collagen and calcium deposition around bone marrow stem cells, increase the expression levels of Runx2 and calmodulin, thereby facilitating the formation and repair of bone tissue.

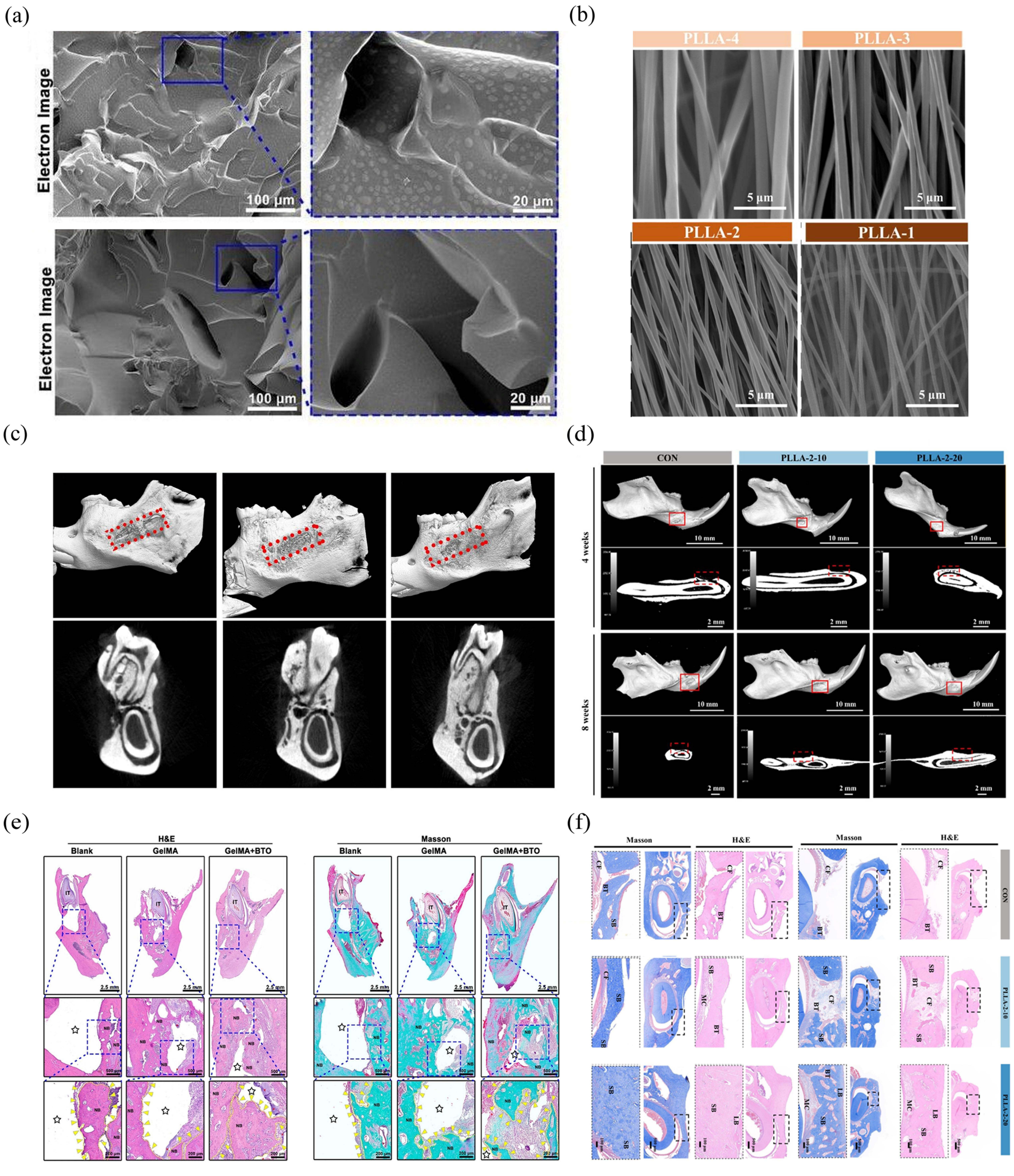


Figure 5 (**a**) Hydrogels (above) and hydrogels doped with BaTiO3 nanoparticles (below). (**b**) SEM images of nanofibers prepared with different concentrations of PLLA spinning solution. (**c**) Micro-CT images of blank group, GelMA group and GelMA +BTO group from left to right. The changes in the rat mandibular alveolar bone defect model in the three groups after 8 weeks can be clearly seen, among which the GelMA +BTO group shows effective bone regeneration ability. (**d**) After 4 and 8 weeks of treatment, micro-CT images of piezoelectric nanofiber membrane treatment defects with a mass concentration of 2wt.% in the control group and both groups. Under the treatment of piezoelectric film, obvious new bone appeared in the mandibular defect of the rats, and basically recovered completely at the 8th week. (**e**) Histological sections of mandibular alveolar bone in rats in this study. (**f**) Histological evaluation of the bone repair ability of PLLA nanofiber membranes. (**a,c,e**) Reprinted from Sui B, Ding T, Wan X, et al. Piezoelectric stimulation enhances bone regeneration in alveolar bone defects through metabolic reprogramming of macrophages. Exploration. 2024;4 (6):20230149.[76] licensed under CC BY 4.0. https://creativecommons.org/licenses/by/4.0/. (**b,d,f**) Reprinted from Chen S, Wang X, Zhang D, et al. Tunable piezoelectric PLLA nanofiber membranes for enhanced mandibular repair with optimal self-powering stimulation. Regen Biomater. 2024:12:rbae150.[77] licensed under CC BY 4.0. https://creativecommons.org/licenses/by/4.0/.

Zhang X et al developed a flexible nanocomposite membrane that simulates endogenous potential.[56] The nanocomposite film achieved a surface potential of −76.8 mV by lifting the composition ratio and corona polarization treatment, which is in line with the endogenous biological potential level and exhibits high stability under bone defect conditions. It promotes the activity and OsD of BMSCs, continuously maintain the electrical microenvironment in the body and provide innovative and suitable strategies for bone regeneration therapy. Huang X et al achieved electro-mechanical triggering of bone integration at the bone/implant interface by in situ constructing titanium dioxide (TiO_2) nano cones/bismuth trioxide (Bi_2O_3) nanodots heterojunction on the surface of bone implants.[79] This heterojunction exhibits an intrinsic electric field at the nanoscale interface, and its elastic modulus is comparable to that of bone tissue, significantly promoting the attachment, spreading of BMSCs, and the in-vivo osteogenic process. Its mechanism of action involves intracellular enrichment mediated by Yes-related protein biomechanical signaling pathways and phosphatidylinositol 3-kinase signaling pathways. This study confirms that the coupling of biomaterial morphology and electrical parameters can regulate cell behavior. Zhang et al optimized the osteogenic properties of PVDF trifluoroethylene (PVDF-TrFE) flexible piezoelectric films with different surface potentials by regulating the beta content.[80] A membrane with a surface potential of −53 mV (piezoelectric coefficient d33=10 pC N^{-1}) was observed to significantly promote OsD of BMSCs. In-vivo experiments have also shown that under this potential, the membrane can promote bone regeneration, while BMSCs own the lowest levels of reactive O_2 species and the highest mitochondrial membrane potential. This indicates that the membrane provides the optimal amount of electrical stimulation for the energy metabolism of BMSCs. An effective method was built for controlling the surface potential of PVDF-TrFE membrane and emphasizes the significance of optimizing electrical stimulation. Zhang Y et al designed a biomechanical driven shape memory piezoelectric nanogenerator (sm-TENG) combined with a fixed splint for promoting OsD.[81] The Pulse Direct Current (PDC) generated by the generator can promote proliferation, directional arrangement, and increase intracellular calcium ions of MC3T3-E1 pre-osteoblasts. Meanwhile, under long-term cultivation, the ALP activity of cells can be increased, ultimately leading to increased calcium deposition and osteogenesis. This study validates the value of sm-TENG as a power source for PDC stimulation of bone repair.

Application Analysis of PMs in Bone Remodeling and Repair

The above research demonstrates various methods that utilize electrical principles to promote bone repair. Nanocomposite membranes provide favorable growth environments for cells by simulating endogenous bioelectric potentials; Mechatronics coupling clues utilize built-in electric fields and similar elastic moduli to promote cell adhesion and OsD; Regulating the surface potential of materials to stimulate cell P&D, optimizing energy metabolism of BMSCs; Shape memory piezoelectric nanogenerators convert biomechanical energy into electrical energy, providing continuous electrical stimulation to cells and accelerating bone repair. These principles are similar to using PMs to stimulate bone repair. PMs generate charges when subjected to external forces, which can simulate the bioelectric microenvironment of bone tissue.[2] Bone tissue itself has a piezoelectric effect, which can convert the stress it receives into bioelectric signals, thereby regulating bone growth, structural remodeling, and repair.[82,83] Therefore, when PMs are used as bone implants or scaffolds, they can produce charges on the surface under stress, restore the potential of damaged bone tissue, and thus promote bone healing. The existing PMs often act in bone regeneration and repair in the form of coatings, gelatin, piezoelectric scaffolds, piezoelectric periosteum, etc., as shown in Figure 6.

Figure 6(a) shows the effect of zinc oxide coating on bones in metal implants. Li et al successfully deposited nanoscale zinc oxide films on the surface of 3D porous iron scaffolds using atomic layer deposition technology, achieving precise control of film thickness. This method significantly reduced the degradation rate of the scaffold, enhanced cell adhesion ability, and endowed the scaffold with strong antibacterial capacity against Gram negative and Gram-positive bacteria. At the same time, good biocompatibility has been maintained, providing new potential candidate materials for the field of bone repair materials.[84] In Wang N et al's research, metal and metal oxide nanoparticles could solve many problems in orthopedics through their unique physical, chemical, and mechanical properties in orthopedic implants and BTE. These include enhancing antibacterial ability, promoting the transfer of bioactive molecules, improving mechanical strength, promoting bone integration, and cell labeling and imaging. However, there was also a risk of toxicity to surrounding cells and tissues.[85] In Figure 6(b), the composite low-temperature gel provides the active microenvironment

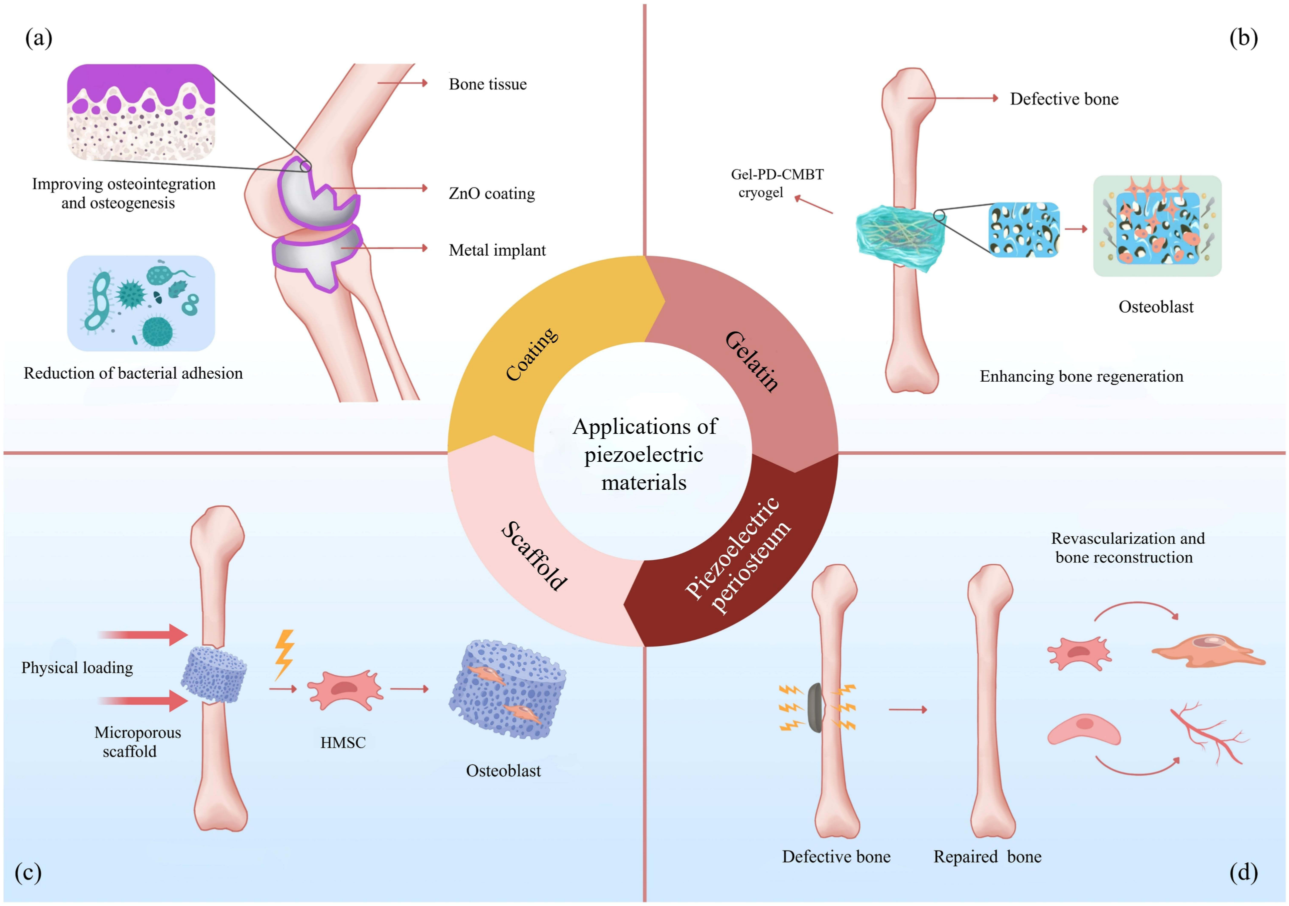


Figure 6 (**a**) The effect of the zinc oxide coating on bone in a metal implant. (**b**) The composite cryogel provides an electroactive microenvironment for the defective bone to promote osteogenesis. (**c**) The piezoelectric scaffold produces electrical stimulation and promotes the differentiation of human BMSCs into osteoblasts. (**d**) The piezoelectric periosteal promotes angiogenesis and BMSCs differentiation in the bone defect area, resulting in the formation of repaired bones.

for the defective bone to promote osteogenesis. Chang S et al used responsive hydrogels as new smart biomaterials to sense a variety of external stimuli and display special properties. They prepared it as a scaffold material in tissue engineering to promote cell adhesion, P&D, which can complete precise bone defect repair.[86] Li X et al found that various natural or synthetic biomaterials currently used in clinical practice cannot fully replicate the structure and properties of the original bone. Therefore, they focused on the research of biocompatible hydrogel materials, and composited hydrogels with nanoparticles of different dimensions. The hydrogel compounded with nanoparticles of various dimensions could better fill the bone defect area and had higher adaptability.[87] The electrical signal provided by the hydrogel could regulate the polarization of macrophages to M2-type, promote the secretion of anti-inflammatory and healing promoting cell growth factors, and regulate the polarization of macrophages by regulating the PI3K/Akt signal axis. At the same time, the hydrogel could spontaneously generate alternating current under pressure. This alternating current stimulation could effectively promote the expression of Vascular Endothelial Growth Factor (VEGF) and fibroblast growth factor (bFGF) in macrophages and tissue defect sites, thereby promoting the generation of novel blood vessels to damaged tissues. In addition, the study also showed that the hydrogel had the ability to promote M2 macrophage phenotype polarization, OsD and angiogenesis, and could accelerate bone regeneration and remodeling. Therefore, as a potential bioactive scaffold biomaterial, the piezoelectric hydrogel implant had the special ability to generate piezoelectric microenvironment, providing a new solution for clinical repair of critical bone defects. Figure 6(c) shows the piezoelectric scaffold generating electrical stimulation to promote the differentiation of human BMSCs into osteoblasts. Chen P et al used electrospinning technology to combine biodegradable high-performance PM potassium sodium niobate ($K_{0.5}Na_{0.5}NbO_3$, KNN) nanowires with polylactic acid (PLA) nanofibers to prepare a 3D multi-channel piezoelectric scaffold. By using programmed ultrasound irradiation as remote mechanical stimulation, this 3D piezoelectric stent could provide in vivo electrical stimulation with adjustable timelines, durations, and intensities as needed. Under appropriate ultrasound stimulation, 3D tissue scaffolds made of piezoelectric composite nanofibers could accelerate the recovery of motor function and promote the repair of spinal cord injuries.[88] Qi F synthesized $BaTiO_3$-GO nanoparticles by in-situ growth of $BaTiO_3$ on Graphene Oxide (GO) and introduced them into PLLA powder to prepare PLLA/$BaTiO_3$-GO scaffolds using laser additive manufacturing technology. The oxygen peak of O at the specific electron binding energy of 1s in $BaTiO_3$-GO decreased from 54.4% to 14.6%, and the Ti^{3+} peak positively correlated with oxygen vacancies significantly weakened. This indicates that the introduced GO significantly reduces oxygen vacancies. Therefore, compared with PLLA/$BaTiO_3$, the piezoelectric current of PLLA/$BaTiO_3$-GO increased from 80 nA to 147.3 nA. The enhanced piezoelectric current effectively accelerated cell differentiation by upregulating alkaline phosphatase expression, calcium deposition, and calcium influx.[89] Figure 6(d) shows that piezoelectric periosteum promotes angiogenesis and differentiation of BMSCs in the bone defect area, forming repaired bone. Liu H proposed a novel biomimetic periosteum preparation strategy that utilizes functionalized PMs to comprehensively enhance bone regeneration effects. Biocompatibility and biodegradability of PHBV, antioxidant polydopamine modified hydroxyapatite (PHA), and barium titanate (PBT) were adopted. By a simple 1-step spin coating method, it was further incorporated into the polymer matrix to prepare biomimetic periosteum with excellent piezoelectric effect and improved physicochemical properties.[90] Although bioactive glass (BG) is not a piezoelectric material, its excellent bioactivity, bone conduction/induction, and ion release ability make it often used as a functional additive in piezoelectric composites (eg compounding with ZnO and $BaTiO_3$) to synergistically promote bone regeneration.BG has been shown to promote angiogenesis,[91,92] possess antibacterial and anti-inflammatory properties,[93–96] and stimulate osteogenesis.[97,98]

The addition of PHA and PBT can significantly enhance the physicochemical properties and biological functions of piezoelectric periosteum, including improving surface hydrophilicity and roughness, enhancing mechanical properties, adjustable degradation behavior, and stable and required endogenous electrical stimulation. All of these are beneficial for accelerating bone regeneration. The prepared biomimetic periosteum exhibits good biocompatibility, osteogenic activity, and immune regulatory function in vitro. It not only promotes the adhesion, proliferation, spreading, and osteogenesis of MSCs, but also effectively induces polarization of M2 macrophages, thereby inhibiting the inflammatory response induced by Reactive Oxygen Species (ROS). Through in-vivo experiments, biomimetic periosteum with endogenous piezoelectric stimulation synergistically accelerated the formation of new bone in a rat model of large-sized skull defects. After 8 weeks of treatment, the entire defect was almost completely covered by new bone, and the thickness was close to that of the host bone.[90]

Preparation and Analysis of PMs for Bone Regeneration and Repair

Preparation of IPMs

IPMs are mainly obtained by mainstream technologies such as high-temperature solid-state reaction. For perovskite type (ABO_3-type) lead-free piezoelectric ceramic materials, the key process of obtaining dense ceramics by sintering oxide precursors at high temperatures involves the following steps: Powder synthesis begins with oxide mixing and primary and secondary ball milling. After pretreatment, a uniform flow of ceramic samples is formed. Next, it is extruded by high temperature. Finally, sintering and silver treatment are carried out to obtain ceramic sheets with piezoelectric properties.[99,100] A similar method is used for the preparation of PZT multilayer ceramics, including ball milling, forming, high-temperature sintering (1200–1500°C), and polarization (activating piezoelectricity).[101–103] The dielectric constant of the material remains at a high level near room temperature, and a slightly protruding peak appears at room temperature, corresponding to the R-T phase transition of the ceramic at room temperature. The dielectric loss of ceramics at room temperature is also relatively low, maintained at around 5%. The dielectric constant describes the physical quantity of a material's response to an electric field. For organic ceramic materials, a high dielectric constant means that they are more sensitive to the response of electric field lines. These properties will further affect the behavior of cells, such as cell adhesion and P&D. These properties is vital in bone regeneration and repair.[104,105]

Preparation of OPMs

The core process of OPMs preparation is the solution processing method based on the "polymer dissolution-molding-phase conversion" process. The method of solution blowing spinning (SBS) and cold pressing process for preparing PVDF film adopts a simple, efficient, and low-cost approach that combines SBS, cold pressing, and low-temperature thermal annealing to obtain highly polar phases. PVDF films are prepared under different pressure conditions and compared to the direct hot-pressing method of PVDF powder, this method is more optimized.[106–108] Similarly, the preparation process of PVDF/MWCNT composite nanofiber films is also to prepare spinning solutions from PVDF powder and MWCNT as raw materials.

After that, the solution is injected into a syringe for electrospinning, and the resulting film is dried in a 60-degree oven for 10 hours.[109] The advantages of organic piezoelectric materials prepared by solution processing method in bone repair are tunable biodegradability and defect conformability, and it also brings the challenges of moderate piezoelectric output and rapid property decay in vivo. To address these problems, SBS cold pressing to enhance the PVDF β crystal phase[106] or blended piezoelectric ceramic nanowires (such as KNN/PLLA) may be an innovative solution.[88] Recent advancements in electrohydrodynamic atomization techniques, particularly electrospinning and electrospraying, continue to expand the possibilities for fabricating piezoelectric biomaterials. Innovations focus on achieving complex architectures (eg, core-shell fibers for drug delivery,[110] gradient structures mimicking natural tissue interfaces), precise control over fiber alignment and piezoelectric phase content, and incorporation of diverse functional nanoparticles. Coaxial electrospinning allows for sophisticated drug loading strategies within piezoelectric polymer fibers.[111] Electrospraying facilitates the creation of micro/nano-particle coatings or composite microspheres with piezoelectric properties. These developments offer exciting avenues for creating multifunctional scaffolds that precisely control the spatiotemporal delivery of electrical, mechanical, and biochemical cues for enhanced bone regeneration.[112]

Preparation of CPMs

Piezoelectric composite materials, also known as composite polymer PMs, combine the high-voltage electrical characteristics of traditional IPMs with the flexibility of polymer PMs. This solves the problem of high rigidity of inorganic materials and low electrical coefficient of organic materials. These composite materials can achieve piezoelectric properties without the need for additional processes such as stretching.

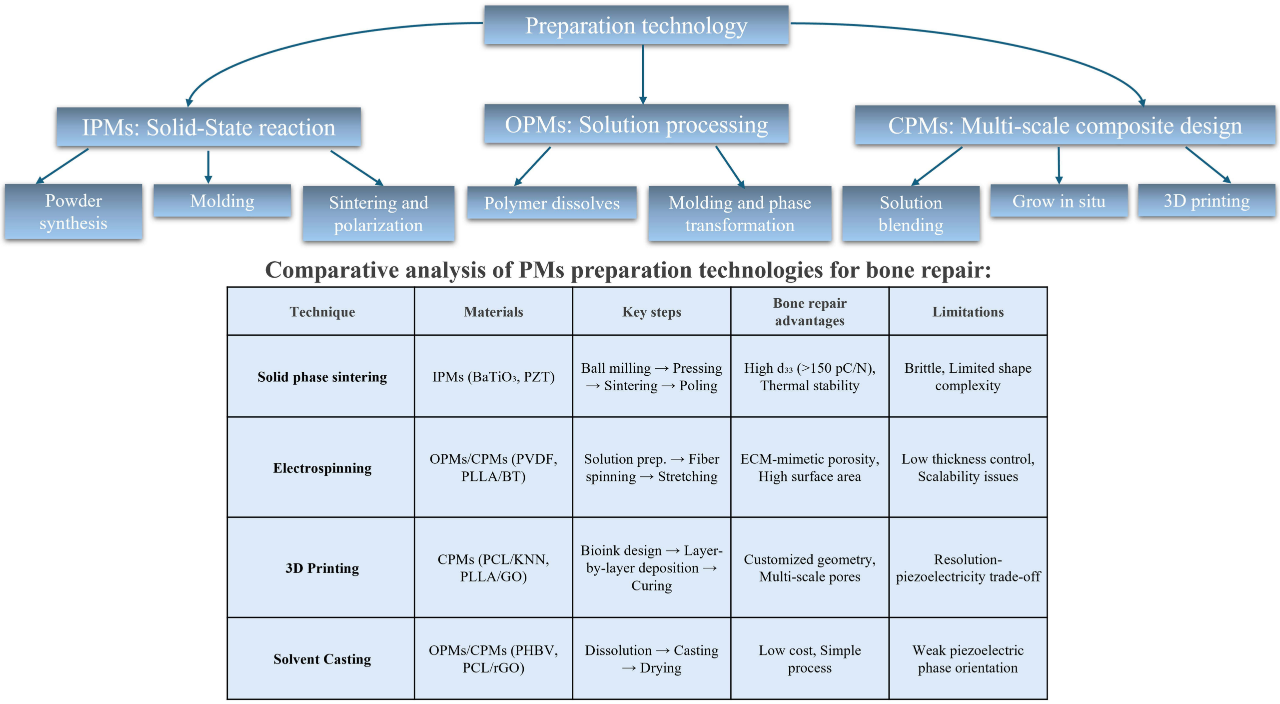
The hybridization strategy prepared by CPMs combines the advantages of combined IPM/OPM. Piezoelectric fillers ($BaTiO_3$, ZnO) are dispersed in a polymer solution (PVDF, PCL), which can then be molded by casting or electrospinning. The growth of active phases within polymers (eg, $BaTiO_3$/GO)[89] is a method of in-situ synthesis. In addition to, 3D printing technology for light curing or fused deposition can be used to create multi-layer structures. When using CPMs to repair bone, the key is filler dispersion homogeneity (affects conductivity) and interfacial bonding (affects stress transfer). For example, antibacterial ZnO-PLLA electrospun mats[52] and drug-eluting coaxial fibers (AVT@PVDF)[111] are the embodiment of the multifunctional advantages of CPMs.The preparation processes for several common IPM, OPM, CPM are shown in Figure 7.

Mechanism Analysis of PMs on Osteogenic Remodeling and Repair

PMs promote bone regeneration through dynamic processes from electromechanical reaction to biocoupling. The mechanisms are systematically categorized into four interrelated pathways:

Piezoelectric Stimulation Triggers Intracellular Signaling Pathways

Compared with polarized BTCP ceramics with a positive surface charge (BTCP+) and raw BTCP powder, the polarized BTCP with a negative surface charge (BTCP-) increased the adsorption of cellular matrix protein fibronectin and the cytosolic Ca^{2+} of BMSCs increased by nearly 3 times. After 6 hours of incubation of BMSCs on BTCP, the expression of integrin p-ERK of the polarized BTCP with a negative surface charge was almost 2–3 times higher than that of the other two groups by Western blot and grayscale analysis. Expression of enhanced integrins and activated voltage-gated Ca^{2+} channels ultimately promote mineral deposition (osteogenic differentiation) through FAK/ERK and BMP/Smad signaling pathways.[78] Chen J et al found in piezoelectric dynamic therapy that the $BaTiO_3$ coated Ti6Al4V scaffold produced sustained electrical signals under the action of LIPUS. These signals could stimulate cells, regulate their behavior, including proliferation, differentiation, and arrangement of



Comparative analysis of PMs preparation technologies for bone repair:

Technique	Materials	Key steps	Bone repair advantages	Limitations
Solid phase sintering	IPMs ($BaTiO_3$, PZT)	Ball milling → Pressing → Sintering → Poling	High d_{33} (>150 pC/N), Thermal stability	Brittle, Limited shape complexity
Electrospinning	OPMs/CPMs (PVDF, PLLA/BT)	Solution prep. → Fiber spinning → Stretching	ECM-mimetic porosity, High surface area	Low thickness control, Scalability issues
3D Printing	CPMs (PCL/KNN, PLLA/GO)	Bioink design → Layer-by-layer deposition → Curing	Customized geometry, Multi-scale pores	Resolution-piezoelectricity trade-off
Solvent Casting	OPMs/CPMs (PHBV, PCL/rGO)	Dissolution → Casting → Drying	Low cost, Simple process	Weak piezoelectric phase orientation

Figure 7 Summary of mainstream techniques and key steps for the preparation of IPMs, OPMs, and CPMs.

the cytoskeleton. The results showed that cells treated with piezoelectric dynamic therapy had higher survival rates, better pseudopodia adhesion, and more actin bundles. This indicated that the piezoelectric effect of $BaTiO_3$ contributed to cell growth.[113] In Saos-2 cells grown on piezoelectric nanogenerators, the duration and amplitude of calcium peaks can vary over time. Voltages capable of locally altering membrane potential allow extracellular Ca^{2+} influx, producing high-amplitude Ca^{2+} transients. On the other hand, electrical stimulation can reorganize plasma membrane proteins, inducing the release of intracellular Ca^{2+} stores, resulting in low-amplitude Ca^{2+} transients.[22] The Calcium signal presented in BMSCs attached to random annealed PVDF membranes is transient but energetic.[114]

Regulation of Cellular Behaviors by Piezoelectric Cues

$BaTiO_3$ plays a positive role in the morphological, functional and biological behavior of BMSCs, which are associated with osteogenic differentiation and bone regeneration. It is reported that $BaTiO_3$-incorporated materials[78] or composite fiber scaffolds[59] that can make BMSCs cultured on them have a large cell spreading area and polygonal cell shape, and these are closely related to the osteogenic activity of BMSCs, which is conducive to bone regeneration. The mechanisms involved include the electrotaxis effects of the dielectric properties of $BaTiO_3$ nanoparticles and the important role of cell shape in regulating stem cell differentiation into specific tissues.[59]

Immunomodulation of Bone Microenvironment

The regulation of immune cells such as macrophage polarization, T cell regulation, and ROS clearance by piezoelectric stimulation can lead to a better bone microenvironment for regeneration. Proinflammatory cytokine genes CD86, IL-18, and IL-6 were significantly downregulated on BTCP+, and the expression of IL-10 and M2 marker CD206 were significantly upregulated on BTCP+, indicating that polarized positive charges were more effective in alleviating the inflammatory response.[78] A nanocomposite piezoelectric periosteum with PDA-modified HA (PHA) and BaTiO3 (PBT) generators was also reported to reduce the inflammatory score of rat cranial defects by 75%. Piezoelectric periosteum promotes the temporal transition from M1 phenotype to M2 phenotype in macrophages and is expected to promote the secretion of osteogenesis-related cytokines by M2 macrophages.[90] Moreover, PDA coating could reduce the inflammatory responses of biomaterials both in vitro and in vivo. They found that the degradation products of PDA reduce nuclear factor κB (NF-kB) signaling and LPS-induced ROS activation in macrophages.[90] Jc-1 detected mitochondrial membrane potential, and the results showed that the mitochondria of cells on the d33 = 10 pC/N P(VDF-TrFE) membrane had a high membrane potential, suggesting that the membrane could improve the mitochondrial function of BMSCs, and that correct electrical stimulation would reduce ROS in BMSCs, thereby improving osteogenesis.[80]

Piezoelectricity-Driven Vascularization

There have been many studies that demonstrate that piezoelectric periosteum at the site of the defect significantly promotes vascularization and leads to microangiogenesis. Piezoelectric periosteum stimulates endogenous cells to produce and secrete endogenous VEGF, while the expression of CD31 and α-SMA increase, inducing regeneration of vascular networks in defective areas.[90] It has also been reported that ZnO-modified scaffolds can increase the density of neovascularization in rabbit femur by 2.8-fold.[25] Chen J et al loaded atorvastatin (AVT) into the shell of the material. Through coaxial electrospinning technology, AVT was uniformly wrapped within the fiber shell and gradually released over a certain period of time. The released AVT could act on vascular endothelial cells (such as human umbilical vein endothelial cells, HUVECs), promoting their proliferation, migration, and formation of vascular networks. Blood vessels provided necessary nutrition and oxygen to bone tissue. In this material, piezoelectric stimulation promoted the P&D of osteoblasts, while AVT promoted the proliferation and angiogenesis of vascular endothelial cells. These two effects complemented each other and jointly promoted the regeneration of bone tissue.[111]

Future Perspectives and Emerging Strategies

Beyond traditional compositional tuning and doping, novel strategies are emerging to design next-generation piezoelectric ceramics for bone repair. These include exploiting piezocatalysis,[115] where the piezoelectric effect is harnessed to drive catalytic reactions (eg ROS generation for antibacterial activity or enhanced ion release for bioactivity) under mechanical stimulation. Computational materials design (eg, machine learning) also holds promise to accelerate the discovery of lead-free piezoelectrics with optimized biocompatibility and electromechanical properties.

For material design, future efforts should focus on designing next-generation smart PMs with combined functionalities: enhanced piezoelectricity and biocompatibility (especially for lead-free ceramics), tailored biodegradability matching bone healing kinetics, intrinsic antibacterial/anti-inflammatory properties, and stimuli-responsiveness. The integration of piezocatalytic activity offers a promising route for on-demand therapeutic effects.

Bone is a highly metabolically active, multifunctional, and complex organ characterized by unique regenerative and repair properties.[116] In the practical application of clinical translation, we believe that accelerating the translation of promising PMs from bench to bedside requires robust long-term in vivo studies in large animal models, comprehensive biosafety assessments, and standardized evaluation protocols for piezoelectric biomaterials in orthopedic applications. And as for the development of interdisciplinary integration, convergence with fields like computational materials science (for accelerated discovery), advanced microscopy, and electrophysiology will be key to unlocking the full potential of piezoelectric therapy for bone repair.

Conclusion

PMs have shown great potential and application prospects in bone regeneration and repair. Through in-depth analysis of PMs, it is found that IPMs, OPMs, and CPMs each have unique properties and advantages, providing diverse choices for bone regeneration and repair. The piezoelectric mechanism of bones is an important foundation for the application of PMs in bone repair. The study of the composition of bones reveals their complex structure and composition, while the analysis of piezoelectric and osteogenic mechanisms further elucidates how bones promote cell proliferation, differentiation, and mineralization through piezoelectric effects. In addition, studies on piezoelectric stimulation guiding bone regeneration and repair have also shown that appropriate piezoelectric stimulation can significantly accelerate the healing process of bones. In terms of the application of PMs, various PMs are promising candidate materials that have shown great potential for applications in bone regeneration and repair. These materials provide necessary electrical stimulation to damaged bones by simulating their piezoelectric properties, thereby promoting bone regeneration and repair. Meanwhile, the preparation technology of PMs for bone regeneration and repair is constantly advancing, providing strong support for the preparation of PMs with excellent performance. In summary, PMs play an important role in bone regeneration and repair, and their unique piezoelectric effect provides new pathways and methods for bone regeneration and repair. In the future, with the continuous advancement of PM preparation technology and the deepening of application research, PMs will play a more extensive and in-depth role in the field of orthopedics.

Abbreviations

AlN, Aluminum Nitride; ALP, Alkaline Phosphatase; AVT, Atorvastatin; bFGF, Fibroblast Growth Factor; BG, Bioactive Glass; BMSCs, Bone Marrow MSCs; BTE, Bone Tissue Engineering; CPMs, Composite PMs; CS, Chitosan; DMF, Dimethylformamide; EFS, Electric Field Stimulation; HAP, Hydroxyapatite; HUVECs, Human Umbilical Vein Endothelial Cells; IPMs, Inorganic PMs; KNN, Potassium Sodium Niobate; LIPUS, Low-Intensity Pulsed Ultrasound; MAPK, Mitogen Activated Protein Kinase; MPB, Morphotropic Phase Boundary; MWCNT, Multi-walled Carbon Nanotubes; OPMs, Organic PMs; OsD, Osteogenic Differentiation; PA, Polyamide; PCL, Polycaprolactone; PDC, Pulse Direct Current; PDMS, Polydimethylsiloxane; PHA, Polyhydroxyalkanoates; PHB, Poly 3-hydroxybutyrate; PLLA, Poly(L-lactic Acid); PMs, Piezoelectric Materials; PVDF, Polyvinylidene Fluoride; PZT, Lead Zirconate Titanate; rGO, Graphene Oxide; ROS, Reactive Oxygen Species; SCP, Surface Charge Polarization; TiO_2, Titanium Dioxide; VEGF, Vascular Endothelial Growth Factor.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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