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Review Article

Piezoelectric biomaterials for providing electrical stimulation in bone tissue engineering: Barium titanate

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ABSTRACT

With the increasing clinical demand for orthopedic implants, bone tissue engineering based on a variety of bioactive materials has shown promising applications in bone repair. And various physiological cues, such as mechanical, electrical, and magnetic stimulation, can influence cell fate and participate in bone regeneration. Natural bone has a piezoelectric effect due to the non-centrosymmetric nature of collagen, which can aid in cell adhesion, proliferation and differentiation, and bone growth by converting mechanical stimuli into electrical stimuli. Piezoelectric materials have the same piezoelectric effect as human bone, and they are able to deform in response to physiological movement, thus providing electrical stimulation to cells or damaged tissue without the need for an external power source. Among them, Barium titanate ($BaTiO_3$) is widely used in tumor therapy, tissue engineering, health detection and drug delivery because of its good biocompatibility, low cytotoxicity and good piezoelectric properties. This review describes the piezoelectric effect of natural bone and the characteristics of various types of piezoelectric materials, from the synthesis and physicochemical characteristics of $BaTiO_3$ and its application in biomedicine. And it highlights the great potential of $BaTiO_3$ as piezoelectric biomaterials in the field of bone tissue engineering in anticipation of providing new ideas and opportunities for researchers.

The translational potential of this article: This review systematically discusses barium titanate, a bioactive material that can mimic the piezoelectric effect of natural bone tissue, which can intervene in the regenerative repair of bone by providing a sustained electrical microenvironment for bone repair scaffolds. This may help to solve the current problem of poor osteogenic properties of bioactive materials by utilizing barium titanate.

1. Introduction

Bone plays a variety of important roles in the human body, and it can repair smaller injuries through self-repair and regeneration. However, a large number of bone defects due to severe trauma, infection, and tumor resection may exceed the ability to self-repair [1]. This makes orthopedic grafts the second most popular grafts in the world besides blood [2]. For large bone defects, tissue engineering techniques based on bioactive materials with good biocompatibility, degradability, osteoconductivity and osteogenic properties show good promise [3]. However, single biomaterials have limited promotion of cell adhesion, proliferation and new bone formation. Therefore, various bioactive substances have been used by researchers to modify bone graft materials by chemical bonding, coating and blending to enhance the physicochemical and biological properties of scaffolds used in bone tissue engineering.

In recent years, emerging research is gradually shifting the research focus to endow bone tissue engineering scaffolds with various types of biological cues, such as mechanical stimulation, electrical stimulation and magnetic stimulation [4]. Various reports have shown that

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bioelectrical cues such as piezoelectricity, pyroelectricity, and ferroelectricity are present in natural living bone [5–7], and these electrical stimuli play an important role in regulating activities such as cell proliferation, differentiation, and motility [8]. Among the many electrical stimuli, the piezoelectricity effect in natural living bone is due to the non-central symmetry of the piezoelectric collagen in the bone, which when acted upon by an external mechanical stimulus thus generates electrical stimulation. This electrical stimulation promotes proliferative adhesion of osteoblasts [9] and Ca^{2+} and PO_4^{2-} present in body fluids can be attracted to oppositely charged dipoles, thereby promoting bone mineralization [10]. Although the piezoelectric effect can play an obvious role in promoting osteogenesis, there is still a lack of research related to the potential mechanisms that may underlie this phenomenon. Currently, the most recognized possible cause is related to voltage-gated calcium channels in osteogenesis-related cells. The electrical effect results in an increase in intracellular Ca^{2+} concentration and accelerates osteogenesis by upregulating the calmodulin signaling pathway [11].

Piezoelectric materials can mimic the piezoelectric properties of natural living bone to generate a continuous and stable charge supply in vivo through mechanical stimulation. Currently, a variety of high-performance piezoelectric materials have been used for bone defect repair. These piezoelectric materials are numerous and can be broadly categorized into piezoelectric ceramics and piezoelectric polymers, which differ markedly in the mechanism of piezoelectric generation. For piezoelectric polymers, electrode polarization is induced by reorientation of molecular dipoles upon induction of mechanical stress. The piezoelectric effect in piezoelectric ceramics evolves mainly due to the rearrangement of ions in dielectric materials, which lack inversion symmetry in their crystal structures [12,13]. Among them, as the first lead-free piezoelectric ceramic reported for bone regeneration studies, Barium titanate ($BaTiO_3$) has a high dielectric constant and excellent ferroelectric properties [14]. In addition, this amazing material has good biocompatibility, piezoelectric properties and nonlinear optical properties. Currently, $BaTiO_3$ has been widely used in various fields of biomedicine. Among them, the research related to its use as a novel bone repair material is the most extensive. In addition, it also has good application prospects in areas such as nonlinear imaging purposes [15], drug delivery [16], tumor therapy [17], antimicrobial materials [18], electrical repair of nerves [19] and intelligent sensing devices [20].

Several reviews have emphasized the importance of various types of piezoelectric materials in bone repair, but have been too concise about the fascinating material $BaTiO_3$. As researchers' interest in applying $BaTiO_3$ to the field of bone tissue engineering increases, more comprehensive reviews are needed to help inform researchers.This review provides a systematic overview of the piezoelectric effect from natural bone and various types of piezoelectric materials. The physicochemical properties, synthesis methods, and existing application scenarios of $BaTiO_3$ are presented for introduction, with special emphasis on its promising applications in bone repair.

2. Piezoelectricity in human bone

A variety of bioelectric effects exist in living organisms, among which the piezoelectric effect was first observed from a bundle of wool [21]. In 1982, researchers discovered that the shape and density of bone changes according to the force applied to the bone, and that bone growth and atrophy can be regulated by altering the motion of the bone [22]. The main reason for this phenomenon is that piezoelectric effects play an important role in the development of bone structure and mechanical delivery of bone at the cellular level. The piezoelectric effect of bone converts mechanical energy into electrical energy, a process that generates an electrical charge that attracts osteoblasts and aids in calcium attachment, with the polarity of the charge depending on the direction of mechanical stress or bone deformation [10,23]. By studying the quantitative piezoelectric properties of bone, Fukada found that its piezoelectric constant is about one-tenth that of quartz [24]. And the piezoelectric coefficient value of human tibia varies in the range of about 7.7–8.7 pC/N [25].

Bone tissue consists of approximately 22 wt% asymmetric collagen and approximately 69 wt% hydroxyapatite (HA) [26]. The piezoelectric effect of bone disappears after removal of collagen, but bone treated only by demineralization remains piezoelectric [27]. Thus, early researchers suggested that collagen with its asymmetric structure was the primary source of piezoelectricity rather than HA. However, as research progressed, some scholars gradually proved that HA may also have piezoelectric properties. Biomolecules have high structural order with inherent helical or chiral asymmetry, leading to inherent polarization and piezoelectric low symmetry. Typically, natural biomolecules have relatively low piezoelectric coefficients, usually in the range of 0.1–10 pm/V [28]. At the earliest, researchers analyzed the piezoelectric properties of amino acid crystals with different structures by nuclear quadrupole resonance spectroscopy to preliminarily verify that the amino acid crystallographic class matches the theoretical properties, and that amino acids can exhibit a wide range of piezoelectricity from 0.5 pC/N to 178 pC/N [29]. In addition, Kholkin et al. [30] found that peptides detected a strong shear piezoelectric response d15 (35 pm/V at a diameter of 100 nm and 60 pm/V at a diameter of 200 nm) under piezoresponsive force microscopy. Different piezoelectric coefficient test methods often produce different results when used on the same material. The transverse mode PFM method of testing a single type I collagen protofiber isolated from bovine Achilles tendon with a diameter of 100 nm was found to have a unipolar axial polarization and to act primarily as a shear piezoelectric material, with a piezoelectric constant d15 of 1.01 pm/V [31]. In contrast, the piezoelectric charge coefficient d14 was 0.096 Pc/N as measured by resonance measurements [32]. Nevertheless, each test method has its own unique advantages, and it is of great significance to choose the appropriate test method reasonably. However, Collagen consists of three twisted polypeptides due to its unique helical structure [33], and the helically arranged peptide bonds on the polypeptide chains and the presence of hydroxyl groups on the hydroxyproline side chains, which gives it a longitudinal, static polarization [34]. When a physical force of compression/stretch is applied, the polarization strength in the longitudinal direction changes due to the winding/rewinding motion of the structure, which is the piezoelectric effect. In addition to bone, this electrical effect is widespread in other organs, such as bone, tendons, ligaments, cartilage, skin, dentin, cornea and sclera, which are composed of collagen or keratin [35–38]. The function of natural piezoelectricity remains elusive, but it is generally believed to be closely related to many physiological processes, tissue growth and remodeling.

3. Piezoelectric materials for bone repair

In the past decade, research on the combination of piezoelectricity and bone has attracted more and more attention from researchers, with China and the United States not only having the largest number of publications, but also actively participating in collaborations with other countries [39]. Fig. 1 lists the top 10 countries that have made the greatest contributions to this field, as well as statistics on the number of articles related to piezoelectric materials used in bone repair in the last 10 years. Piezoelectric materials are piezoelectric due to their non-central symmetry and can be classified by type into piezoelectric ceramics and piezoelectric polymers. The piezoelectric effect is a molecular phenomenon that induces a macroscopic potential, i.e., a piezoelectric potential, through the successive superposition of dipole polarizations [40]. The piezoelectricity of piezoelectric ceramics arises from the non-centrosymmetry of the crystal structure. When mechanical stress is applied to the crystal, the displacement of positive and negative ions within the crystal creates a dipole moment and cannot be canceled by other dipoles [41]. In addition, chalcogenide-structured ferroelectric ceramics have a non-zero net charge even when no mechanical stress is applied. When external stress is applied, it can further change the

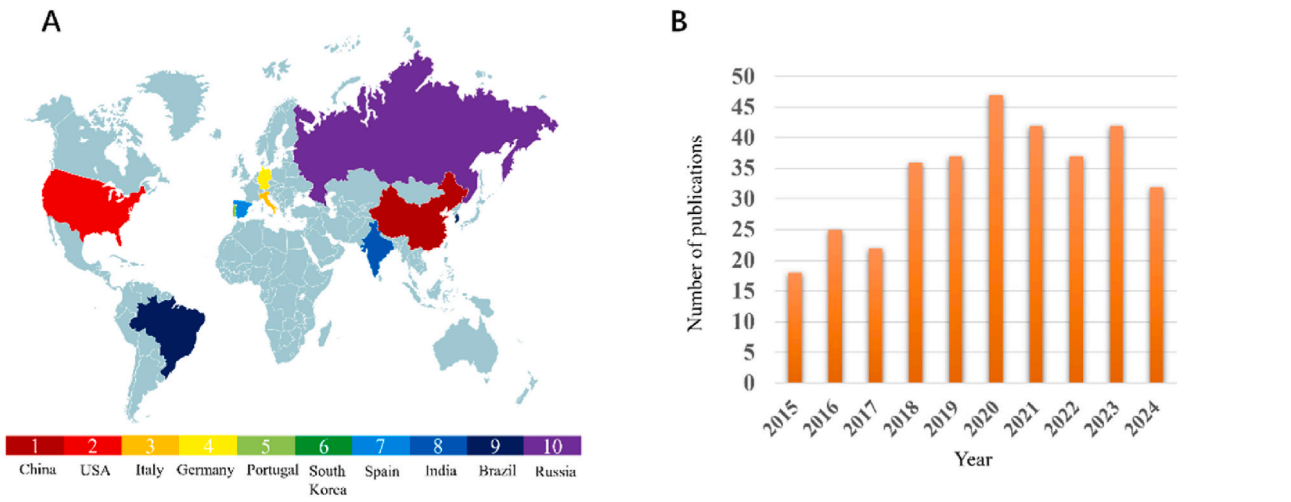

Fig. 1. (A) The 10 countries with the most piezoelectric materials-related research at present; (B) The publication of piezoelectric materials-related articles in the last decade.

position of the relevant sites in the crystal cell and alter its electrode properties [42]. As for piezoelectric polymers, the orientation and alignment of molecular dipoles are the main reason for their piezoelectricity [43]. In living organisms, the polarization of biomolecules is clearly defined by structure and is limited in being controlled by external electric fields. As a result, various biological materials exhibit piezoelectricity, but generally do not exhibit ferroelectricity. In contrast, for conventional piezoelectric materials, the direction of polarization can be easily aligned by applying an external electric field to exhibit ferroelectric behavior. This makes $BaTiO_3$ simultaneously piezoelectric and ferroelectric.

Piezoelectric ceramics possess higher piezoelectric coefficients compared to piezoelectric polymers. Common piezoelectric ceramics include lead zirconate titanate (PZT), $BaTiO_3$, potassium sodium niobate (KNN), magnesium silicate, and potassium lithium sodium niobate [44]. However, although the piezoelectric constants of lead-containing materials such as PZT are significantly higher than those of other materials, the elemental lead released from them is highly cytotoxic, which is the main reason for limiting their clinical applications [45]. Although some of the studies this explored a variety of methods to slow down the release of elemental lead, they still could not completely stop the leakage of lead [46]. Lead-free ceramics, such as $BaTiO_3$ and KNN have also been reported to exhibit low cytotoxicity at higher concentrations. $BaTiO_3$--based lead-free piezoelectric ceramics with high dielectric constants and excellent ferroelectric properties are probably one of the most studied compounds in the perovskite family, and were the first piezoelectric ceramics to be discovered and cited in the medical field. It is characterized by good biocompatibility, and its piezoelectricity is the main reason for its use in tissue engineering [47].

NKN-based ceramics, on the other hand, are considered as one of the best candidates due to their equally excellent performance in terms of piezoelectric coefficient, mechanical quality, Curie temperature and density [48]. In addition, materials such as zinc oxide and boron nitride have both semiconductor properties and piezoelectric effect, although their piezoelectric coefficients are lower than those of the commonly used piezoelectric ceramics mentioned above, they can still generate piezoelectric potentials comparable to the cell membrane potential [49,50]. Moreover, zinc oxide and magnesium silicate release Zn^{2+} and Mg^{2+} in vivo, which will further aid in bone repair. Piezoelectric polymers have a different mechanism in generating piezoelectricity compared to piezoelectric ceramics and exhibit a relatively low piezoelectric coefficient. However, the superior biocompatibility and high processability make them more widely used in tissue engineering [51]. The polymers can be categorized into natural and synthetic piezoelectric polymers according to their source. Synthetic piezoelectric biopolymers mainly include polyvinylidene fluoride (PVDF) and its copolymers, poly (l-lactic acid) (PLLA), polyhydroxybutyrate (PHB), and peptides [52–55]. Natural piezoelectric polymers, on the other hand, mainly include some biocompatible polysaccharides such as cellulose, chitosan, starch and proteins such as collagen, silk and keratin [29]. The most widely used synthetic piezoelectric polymers are PVDF and its copolymers, which have excellent piezoelectricity and good biocompatibility, making them ideal for the fabrication of functional scaffolds for bone and neural tissue engineering applications [56]. And its biggest advantage is that it can be used in a variety of processing methods, and electrostatic spinning is the most commonly used method to prepare piezoelectric PVDF. Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) and PHB are derived from the large family of polyhydroxyalanoates, which is a biodegradable and biocompatible biodegradable polymer with good biodegradable and biocompatible biodegradable piezoelectric polymers, which are becoming increasingly popular in the biomedical field [57]. Compared to PHB, the mechanical strength of PHBV is significantly enhanced due to the incorporation of hydroxyvalerate monomers [58]. The piezoelectric coefficient of PHBV (1.6–2.0 pC/N) is similar to that of human bone, and its use in bone over cartilage tissue engineering demonstrated good osteogenic properties [59]. In contrast, PLLA, which is also a degradable piezoelectric polymer, can be hydrolyzed to produce non-toxic products. In addition to these synthetic polymers, natural polymerization possesses higher biocompatibility, but its poor mechanical properties limit its application in tissue engineering. The polysaccharides cellulose and chitosan are significantly lower than piezoelectric ceramics and synthetic piezoelectric polymers in terms of piezoelectric coefficient, but their excellent biocompatibility and degradation properties well make up for their shortcomings [60,61]. Collagen, on the other hand, is the main reason for the piezoelectric effect of natural bone, and the structure and function of natural bone can be well simulated by doping HA into collagen. The advantages, disadvantages and piezoelectric properties of different piezoelectric materials are compared in Table 1 column.

4. Piezoelectric material $BaTiO_3$

4.1. Structure and properties

As early as in the 1990s, $BaTiO_3$ was used in capacitors due to its excellent ferroelectric properties [62]. With further studies on the physical properties and crystal structure of $BaTiO_3$, the polarized $BaTiO_3$ produces certain piezoelectricity due to the change of its crystal

Table 1
Piezoelectric materials, their piezoelectric coefficients and advantages and disadvantages.

Types of piezoelectric materials	Advantages	Disadvantages	Piezoelectric Material	Piezoelectric Coefficient (pC/N) (d33)	Ref
Ceramics	Mechanical properties compatible with natural bone, higher brittleness	Higher brittleness, more toxic, unable to degrade	Barium titanate (BT)	190	[159]
			Lithium sodium potassium niobate (LNKN)	98	[160]
			Lead zirconate titanate (PZT)	225–590	[161]
			Potassium sodium niobate (KNN)	93	[160]
Polymers	Better biocompatibility, biodegradable	Poor mechanical properties and low piezoelectric coefficient	Poly(L-lactide) (PLLA)	9.82(d14)	[54]
			Poly (vinylidene fluoride) (PVDF)	32	[52]
			Poly hydroxy butyrate (PHB)	1-2(d14)	[53]
Natural materials	Major causes of piezoelectricity in bone	Weak electricity production capacity	Diphenylalanine (FF)	18	[30]
			Collagen*	0.2–2 (d14)	[162]
			Bone	7.66-8.72	[25]

structure [63]. The crystal structure of $BaTiO_3$ undergoes a variety of phase transitions with temperature. Above the Curie temperature (120 °C) it exhibits a classical cubic perovskite structure with a highly symmetric structure, where Ba^{2+} and O^{2-} together form the FCC lattice and the smaller Ti^{4+} cations are located in the octahedral interstitial sites. The centers of cations and anions coincide with each other resulting in no polarization in the crystal structure and hence no ferroelectricity [64]. Whereas, when the temperature is between 5 and 120 °C, the cubic symmetric structure transforms into an asymmetric structure and as the cation center deviates from the anion center resulting in the transition of the crystal to spontaneous polarization and cis-phase to ferroelectric phase. While between −90 and 5 °C it exhibits a rhombic structure [65]. The ferroelectric nature in $BaTiO_3$ is due to the fact that the dipole has a length scale of only a few angstroms (i.e., the separation distance between the positive and negative charges of the elementary dipole), which can be influenced by varying the microstructure, composition, concentration of stress defects, and surface composition of the ferroelectric dipole in terms of its type and strength [66].

$BaTiO_3$ particles of various structures and sizes have been prepared by a range of synthetic methods, and their dielectric, ferroelectric, and mechanical properties can be altered by controlling their size and shape [67]. For example, when the particle size is reduced in the micrometer range, the dielectric constant increases significantly. However, the dielectric constant gradually decreases when the size goes below the micrometer range [68]. This size effect stems not only from the intrinsic atomic scale polarization, but also depends on the extrinsic nature of the material which is closely related to the processing history and crystallinity [69]. In addition, the surface effect of $BaTiO_3$ particles is one of the main reasons affecting its performance. Particles that have been modified by introducing functional groups or by incorporating other substances through modification by means of surface ligands, chemical bonding or coating can be more homogeneously dispersed in the polymer as well as have better properties [70]. Lei et al. [71] modified selenium nanoparticles on the surface of barium titanate nanoparticles to form heterostructures, which promoted a second distribution of piezoelectric-induced carriers under ultrasound irradiation and improved electron–hole pair separation. The ultrasound-responsive selenium-modified barium titanate nanoparticles exhibited more significant antimicrobial efficiency providing a new idea for the treatment of infected bone defects.

Different synthesis methods and synthesis temperatures affect the nucleation rate, crystal growth rate and crystal aggregation during the synthesis process to produce particles with different size distributions and crystal structures, which affects the material's ability to produce electricity. In addition, the morphology of piezoelectric materials is important for their piezoelectricity, as demonstrated by electric response force microscopy and finite element simulations that the piezoelectric response of $BaTiO_3$ nanowires is much higher than that of their nanoparticles [72]. This change in shape facilitates the piezoelectric catalytic activity and thus improves the biological activity.

4.2. Synthesis and applications in biomedicine

Factors such as nucleation rate, crystal growth rate and aggregation of crystals during the synthesis of $BaTiO_3$ particles affect the size distribution and crystal structure of the particles [73]. A variety of controlled syntheses are currently used to prepare $BaTiO_3$ particles of different sizes with excellent properties. Compared with the traditional $BaTiO_3$ particles synthesized by solid–state reaction of $BaCO_3$ and TiO_2 at high temperature, $BaTiO_3$ particles synthesized by controlled synthesis have monodisperse size distribution and highly regular crystal structure, which can better utilize their electrical and mechanical properties in different applications [74]. Co-precipitation is the simplest method to prepare nanoparticles by dissolving cations in water and then doping them with alkali leading to nucleation and growth of nanoparticles [75]. However, the size dispersion of nanoparticles obtained by this simple method is large. The solvothermal/hydrothermal method, on the other hand, is currently the most popular synthesis method, in which different morphologies of nanoparticles can be prepared by adjusting the parameters of the synthesis process by sealing the organic or aqueous solution in an autoclave and raising the temperature of the solvent to the desired reaction temperature higher than the normal boiling point of the solvent [76]. The sol–gel method utilizes the hydrolysis and polymerization of the metal-alcohol salts to convert the monomers into a colloidal particle solution, and then $BaTiO_3$ crystals are obtained by drying and removing the "sol" from the solution. It is characterized by the simplicity of the process and the possibility of producing powders on a large scale [77]. The outputs of BaTiO3 from the sol–gel and sol-precipitation methods were obtained by mixing tetraisopropyl orthotitanate with 2-propanol, acetic acid, and barium acetate, as well as by mixing tetraisopropyl orthotitanate with acetic acid and deionized water, and precipitating it by adding concentrated KOH solution, respectively. By comparison it was found that the powders obtained by the sol–gel method showed large agglomerates and/or aggregates with dense appearance and irregular dimensions, while the powders obtained by the sol-precipitation method had a less dense appearance and regular dimensions. Moreover, the dielectric constant of the materials increased with increasing temperature, the crystalline phase and band gap of the materials, and higher results were obtained for tetragonal samples calcined at 1000 °C. The organometallic method uses organometallic precursors with fixed stoichiometric ratios of metal cations dissolved in certain organic solvents and is widely regarded as the best method to control the size and morphology of the resulting crystals [78]. The moisture-sensitive diol salt was injected into a mixed solvent of diphenyl ether and oleic acid under argon or nitrogen atmosphere at 140 °C. When the Ba and Ti ions reached the exact stoichiometry, the injection of hydrogen peroxide into the system triggered the hydrolysis of the

precursor and the formation of homogeneous $BaTiO_3$ nanoparticles of 8 nm in diameter; the resulting nanorods had a cubic phase, and each of the nanorods was a single crystal. In addition, template-assisted methods can be used to enable $BaTiO_3$ crystals to undergo directional crystallization as characterized [79]. The molten salt method uses molten salt as a solvent to grow crystals and does not involve toxic and unstable precursors [80]. Through the flexible use of different synthesis methods, it can basically meet the different application scenarios of $BaTiO_3$ at present.

$BaTiO_3$ has been developed for a variety of biomedical applications due to its excellent properties. $BaTiO_3$ is biocompatible and produces piezoelectric effects that have been shown to improve cell proliferation, migration and tissue repair. This ability to better mimic natural tissues has led to the use of $BaTiO_3$ in the repair of different tissues. For example, Fouad et al. [81] prepared novel biocomposite nanofibers composed of poly (ethylene oxide)/silk proteins/$BaTiO_3$, which were used in the tissue engineering of the heart and showed good repair performance. Tissue-engineered blood vessels made of $BaTiO_3$ also showed better stability and excellent biocompatibility in vivo [82]. ROS-induced apoptosis in tumor cells is emerging as a promising approach in tumor therapy. Currently, activated oxygen (ROS)-generating systems, such as photodynamic and acoustic treatments, are highly dependent on the level of oxygen in the tumor microenvironment. However, the level of oxygen is too low in the tumor microenvironment to generate sufficient ROS, whereas $BaTiO_3$ can generate an unbalanced charge on the surface under ultrasonic irradiation, which induces a series of redox reaction processes to increase the production of ROS and oxygen [83]. In addition, ROS and oxygen can modulate the dense fibrotic stroma in the tumor microenvironment to enhance drug penetration by further oxidizing surface arginine and thus generating nitric oxide [84]. This manner of tumor eradication by $BaTiO_3$ has been referred to as piezocatalytic therapy [85]. In addition, the generated ROS have an inhibitory effect on the growth of bacteria [86]. Based on this, researchers have developed a variety of $BaTiO_3$-doped nanocomposites with excellent antibacterial activity and tissue repair [9]. $BaTiO_3$ converts mechanical signals into electrical signals and self-powered sensors based on piezoelectric materials are widely used in various forms of wearable sensors. $BaTiO_3$-based piezoelectric nanogenerators show great potential and ability to respond to tactile stimuli with high mechanical-to-electrical conversion efficiency due to their stable responsiveness [20].

In addition, magnetoelectric nanorobots for the purpose of performing cell targeting, penetration and transport were prepared by coating $BaTiO_3$ crystals in the form of ferroelectric thin film shells on a single-crystal ferromagnetic core. Under AC magnetic field excitation, controlled transportation of drugs to the targeted location is possible [15]. On the other hand, tumor therapeutic drugs encapsulated by $BaTiO_3$ nanoparticles significantly promote drug accumulation in tumors due to ROS that can overcome the immunosuppressive microenvironment of tumors [87]. Functionalized $BaTiO_3$ nanoparticles with hydrophobic capping ligands and used them as novel nanoprobes as substrates for PLS analysis and as hydrophobic affinity probes for extracting hydrophobic proteins from *Escherichia coli* prior to MALDI-MS analysis [88]. The one-dimensional structure of magnetoelectric Fe3O4@BaTiO3 nano-chains enables localized electrical stimulation of the brain, thus demonstrating excellent therapeutic effects similar to those of conventional wired deep brain electrical stimulation [89]. Fig. 2 summarizes the synthesis of $BaTiO_3$ and its current major applications in the biomedical field.

5. Application of $BaTiO_3$-based composites in bone tissue engineering

$BaTiO_3$ piezoelectric ceramics are too brittle and have poor properties in terms of bioactivity and osteoconductivity, which limit their application in tissue engineering. Composites prepared by compositing $BaTiO_3$ with other bone repair materials in various ways, such as by blending or coating, have shown promising applications. However, the current study found large inconsistencies in the piezoelectric coefficients of existing bone due to differences in bone symmetry, the underlying physics of the strain-induced potentials generated, and the values of the piezoelectric coefficients measured, which differed by three orders of magnitude. Halperin et al. [25] further investigated the piezoelectric effect in wet and dry bone using piezoresponse force microscopy. It allowed measuring the piezoresponse with nanometer resolution directly in the collagen matrix and obtaining piezoresponse images in

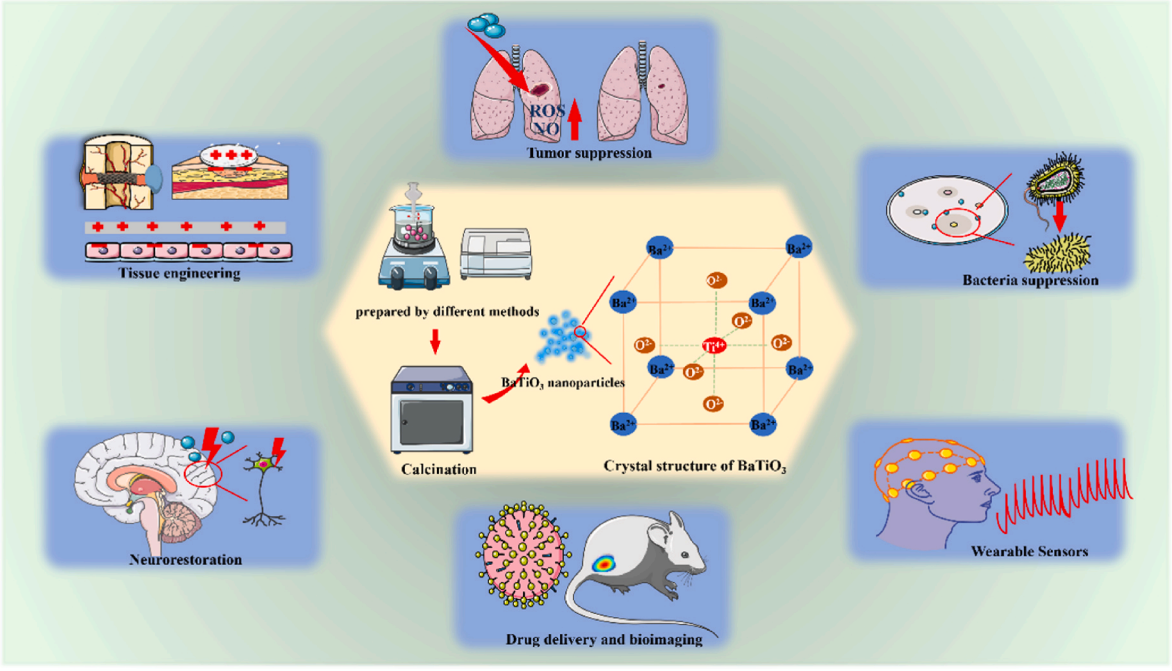

Fig. 2. Synthesis of barium titanate and current major directions in biomedical applications.

the vicinity of the Haver channel. The piezoelectric coefficients of bone were derived to be around 7.66–8.72 pC/N after multi-site testing. For unpolarized barium titanate composites, the piezoelectric constant is much lower than that of the bone, while the piezoelectric coefficient of the composites through the polarization treatment can reach 9.21 pC/N similar to that of the human bone [90,91].

Mechanoresponsive and voltage-gated ion channels exist on the cell surface in response to mechanical or electrical stimuli, and they are important in regulating cellular metabolism and various physiological processes. Among them, the calmodulin-calmodulin-NFAT signaling cascade and the extracellular signal-related protein kinase (ERK) signaling pathway play important roles, and they are highly sensitive to changes in intracellular Ca^{2+} levels [92,93]. When electrical stimulation generated by piezoelectric materials acts on voltage-sensitive calcium channels, Ca^{2+} levels are altered, leading to cellular regulation. Vascular regeneration plays an important role in the repair and reconstruction of bone, however, there is no direct proof that electroactive materials can promote blood vessels by. However, electrical stimulation can promote vascular regeneration by increasing VEGF release [94]. In addition, electrical stimulation has also been shown to significantly promote phagocytic uptake by macrophages, selectively modulate cytokine production, and promote the transition of macrophages from a pro-inflammatory M1 phenotype to a pro-healing M2 phenotype while attenuating the release of inflammatory factors [95].Currently, its possible potential mechanism of action for promoting osteogenesis is summarized in Fig. 3.

7.1. $BaTiO_3$-ceramics composites

HA is currently the most widely used ceramic material, and the composite bioceramics prepared by blending of HA with $BaTiO_3$ have good piezoelectric constants, cytocompatibility, and cell adhesion [96]. So far, however, for bioceramics used for in vivo and in vitro experiments are in the form of dense blocks [97]. However, scaffolds with excellent osteogenic properties often need to have excellent interlinked pores, a porous structure that facilitates inward growth and osseointegration of nascent bone. In order to prepare porous piezoelectric composite HA-$BaTiO_3$ composite scaffolds with neatly aligned pores, Zhang et al. [98] prepared composite scaffolds with different HA-$BaTiO_3$ contents by freeze casting using suspension, respectively. The content of $BaTiO_3$ in the composite scaffolds was directly proportional to the compressive strength and piezoelectric coefficient with and inversely proportional to the porosity. Meanwhile, dual templates led to the coexistence of lamellar pores and aligned macropores, exhibiting the ability to generate directed long-range ordered structures. After in vitro experiments on freeze-cast HA-$BaTiO_3$ composite scaffolds with different porosities of 40 %, 50 %, and 60 %, respectively, it was found that the cell density and the activities of alkaline phosphatase (ALP) and bone collagen (BGP) were significantly higher in the porous group than in the dense group. Osteoblasts adhered and stretched better on porous HA-$BaTiO_3$ than on dense HA-$BaTiO_3$, especially HA-$BaTiO_3$ with 50 % and 60 % porosity. However, there was no significant difference in cell morphology, cell density, and activities of ALP and BGP between the polarized group and the nonpolarized group ($P > 0.05$). This may be related to the absence of mechanical loading of the polarized samples [99]. On the other hand, in the HA-$BaTiO_3$ composite scaffolds prepared by spark plasma sintering, the stability between the two phases would not be high temperature would not be broken. The grain and grain boundary activation energy values (~1–1.5 eV) are almost similar for all samples. And the porous monolithic HA samples and composite samples have the same conduction mechanism [100]. However, HA-$BaTiO_3$ ceramics are known to release toxic particles when used in vivo for a long period of time, which can lead to inflammatory reactions and ultimately make the implantation of biomaterials fail. For this reason, Ashutosh et al. [101] injected different concentrations of HA-$BaTiO_3$ composites into the knee joints of mice, and observed that there were no traces of injected particles or inflammatory reactions in the vital organs, except for a slight localized reaction at the delivery site. And serum biochemical analysis using pro-inflammatory cytokines (TNF-α and IL-1β) also complemented the non-immunogenic response to the injected particles.

A series of auxiliary methods have been used to enhance $BaTiO_3$ to exert osteogenic effects in vitro and in vivo, and these methods mainly include polarization and loading loads. Polarization of bioceramics such as HA can affect their biocompatibility, but there is still a relative lack of investigations on in vitro polarization of HA-$BaTiO_3$ composites. Frances et al. [102] co-cultured osteoblasts in vitro under static no-loading

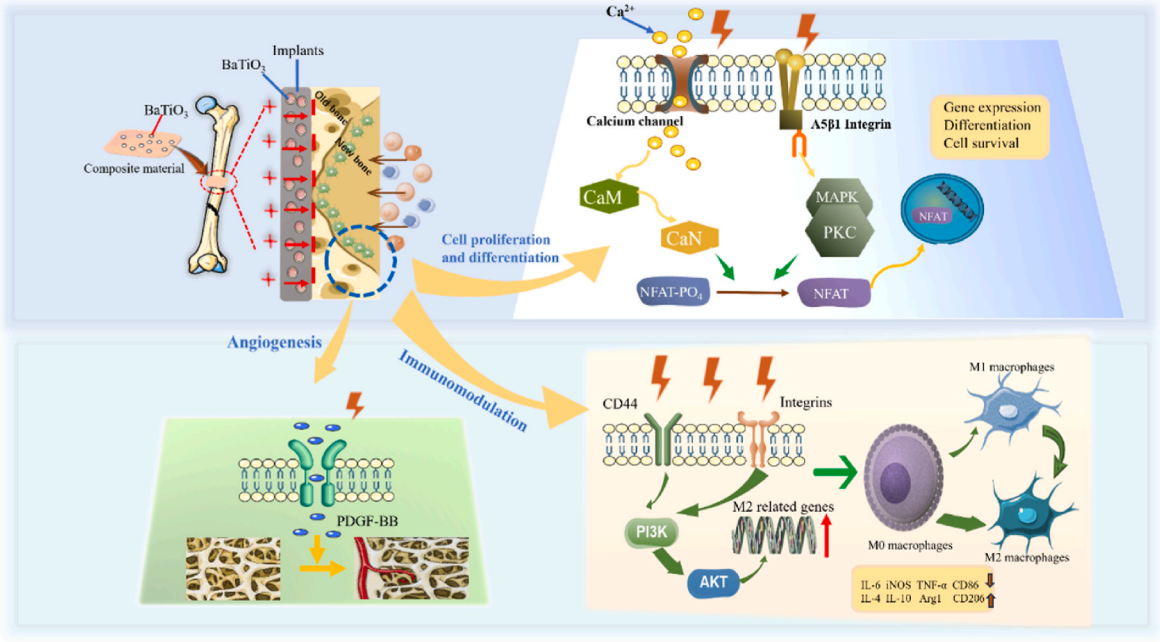

Fig. 3. The electrical signal generated by barium titanate composites can promote the proliferation and differentiation of osteoblasts by increasing the intracellular calcium ion concentration, promote the differentiation of macrophages to M2 to regulate the immune response and can promote the vascular growth of bone tissue.

conditions with commercially available HA and commercially available HA-$BaTiO_3$ composite discs containing 90 % $BaTiO_3$ after polarization. The results showed that there was no difference between unpolarized HA-$BaTiO_3$ and pure HA in terms of cell attachment, proliferation, viability, morphology and metabolic activities. In contrast, the polarized HA-$BaTiO_3$ ceramics showed better cell proliferation than the unpolarized group in a short period of time, while the long-term effects were similar. In addition, it has been reported that HA-$BaTiO_3$ composites substituted by partially strontium after polarization minimized bacterial adhesion and growth [103]. Besides strontium, collagen has also been used to enhance the osteogenic properties of $BaTiO_3$ composites. And the interaction between doped collagen and the mineral phase was significantly enhanced, and the mineralization of collagen fibers was increased [104]. The electrical stimulation of natural bone relies on the movement of the human body, and this pattern can be well simulated by the implantation of piezoelectric bone scaffolds in vivo. In contrast, in vitro experiments are usually performed without dynamic compression, which can limit the generation of electrical stimulation to the detriment of the experiment. For this reason, Schädli et al. [105] and Tang et al. [106] designed a dynamic loading device with mechanical size and controllable frequency, respectively, to promote bone marrow mesenchymal stromal cells by comparing the same HA-$BaTiO_3$ under cyclic loading and static conditions. When cyclic loading affected the HA-$BaTiO_3$ piezoelectric bioceramics, the piezoelectric effect of $BaTiO_3$ promoted the growth of osteoblasts and the interaction with HA in a way that was superior to the effect of HA alone. This in vitro bioreactor strategy may accelerate the development of engineered bone scaffolds and reduce the use of animals in experiments. The above experiments confirmed the excellent cytocompatibility and osteogenic ability of HA-$BaTiO_3$. In addition, the porous piezoelectric hydrogel bone scaffolds prepared by incorporating HA and $BaTiO_3$ modified with polydopamine nanoparticles into chitosan/gelatin matrix had certain promotional effects in immunomodulation and angiogenesis. The composites not only effectively induced macrophage polarization to M2 phenotype, but also promoted migration, tube formation and vascular differentiation of human umbilical vein endothelial cells, and migration, bone differentiation and extracellular matrix mineralization of MC3T3-E1 cells. In particular, the PI3K/Akt signaling axis plays an important role in regulating macrophage M2 polarization [107].

In addition to HA, the researchers used binder jetting to fabricate macroporous biomaterial scaffolds made of bioactive ceramic crystalline glass composites made of $BaTiO_3$ and 45S5 bioactive glass. The composite scaffolds can achieve bone that mimics or even exceeds piezoelectric constants ranging from 1 to 21 pC/N, and calcium phosphate can accumulate on the surface as expected [108]. In addition, Koju et al. [109] reported for the first time the combination of $BaTiO_3$ with smart injected calcium phosphate bone cement for the preparation of specific bioceramics. The compressive strength, injectability, bioactivity, biocompatibility, and even scouring resistance of this new ceramic with piezoelectric osteogenic capability were enhanced. $BaTiO_3$ does not affect the self-characterization of the bone cement and the impermeable linearity of $BaTiO_3$ will help to easily detect the presence of bone cement at the fracture site during surgery. In addition, a bacterial cellulose was used as a polymer template, calcium phosphate and $BaTiO_3$ were deposited on the bacterial cellulose membrane under ultrasonic irradiation, and the resulting system was heat-treated under optimized conditions to remove the polymer template and achieve a 3D porous structure. Complex characterization of intermediate and final samples demonstrated increased grain size within this composite ceramic and densification by enhanced diffusion. Both the prepared and heat-treated samples were biocompatible and well accepted by mesenchymal stem cells (MSCs) cultures [110]. A series of related studies are given in Table 2, where $BaTiO_3$-ceramic composites show promising applications in bone tissue engineering.

7.2. $BaTiO_3$-polymer composites

Polymers have been widely used for bone defect repair due to their excellent physicochemical and biological properties, and the use of piezoelectric nanoparticles as fillers to develop novel composites is essential. It has been demonstrated that by doping calcium titanate, strontium titanate and $BaTiO_3$ into piezoelectric polymers (polycaprolactone) (PCL), the nanomaterials can be dispersed homogeneously, and the composites' dielectric constants, mechanical properties, and osteogenic gene expression have been enhanced compared to pure PCL [111].

Among many polymers, PVDF and its derivatives have excellent dielectric properties, which were enriched by reinforcing $BaTiO_3$ ceramic materials into the polymer matrix using various composite methods. Researchers prepared poly(vinylidene fluoride-trifluoroethylene) (P(VDF-TrFE))-$BaTiO_3$ composite membranes and demonstrated in in vitro experiments that they facilitated the adhesion,

Table 2
$BaTiO_3$-ceramics composites for bone tissue engineering.

Material	Processing method	*In vitro*/in vivo study	Key assessments	Ref
HA (18 wt %)-$BaTiO_3$	Polymer bonding	Mouse calvaria pre-osteoblast MC3T3-E1 cells	The cells showed extensive attachment to the surface of the material.	[96]
HA (10,30,50 wt %)-$BaTiO_3$	Frozen Suspension Casting	Murine fibroblast cells	The scaffold has no cytotoxic effect on cells.	[98]
HA (10 wt %)-$BaTiO_3$	Ice template method	MG63 cells	Cell density, cell adhesion capacity and activities of ALP and BGP were significantly higher in the porous group than in the dense group.	[99]
HA (40 wt%)-$BaTiO_3$	Physical mixing	Human osteosarcoma cell line (Saos-2)	Polarization increases cell attachment, proliferation, viability, morphology and metabolic activity in the short term.	[102]
HA (30 wt%)-$BaTiO_3$	Sol–gel and solid state	MG63 human osteoblast-like cells	The polarized composite minimizes bacterial adhesion and growth.	[103]
Coll–HA-$BaTiO_3$	Sol–gel-hydrothermal method	The amniotic fluid cell cultures	Significantly enhanced interaction between collagen and mineral phases and increased mineralization of collagen fibers.	[104]
HA (30 wt%) -$BaTiO_3$	Solvent casting particulate leaching method	Human marrow stromal cells	The cyclic loading treated group showed better osteogenic capacity.	[105]
HA (0–10 wt %)-$BaTiO_3$	Slip casting	Osteoblasts	The cyclic loading treated group showed better osteogenic capacity.	[106]
Chitosan/gelatin-HA (10 wt %)-$BaTiO_3$(0,5,10 wt %)	Physical mixing	The RAW 264.7 cells	Piezoelectric hydrogels promote endothelial cell migration and activate the PI3K/Akt signaling axis to regulate macrophage M2 polarization.	[107]
45S5 bioactive glass-$BaTiO_3$	Binder jetting	Mouse calvaria pre-osteoblast cells MC3T3-E1	Scaffolds show high cytocompatibility as well as cell attachment and proliferation.	[108]
Calcium phosphate bone cement-$BaTiO_3$	Physical mixing	OB-6 pre-osteoblast cell line	Increased compressive strength, injectability, bioactivity, biocompatibility, and even scouring resistance.	[109]
Calcium phosphate-$BaTiO_3$	Bacterial cellulose template method	MSCs	Improved biocompatibility and increased adhesion of MSCs.	[110]

ALP, Alkaline phosphatase; BGP, Bone collagen protein; HA, Hydroxyapatite; MSCs, Mesenchymal stem cell.

spreading, proliferation, and typical mRNA expression of fibroblasts [112] and osteoblasts obtained from human alveolar bone fragments [113]. Freitas et al. [114] further explored the effects of different tissue sources on the adhesion, spreading, proliferation, and typical mRNA expression of cells in P(VDF-TrFE)-$BaTiO_3$ composite membranes, and they implanted bone marrow or adipose tissue-derived MSCs together with the composite membranes into rat tibial defects. Luciferase-expressing osteoblasts from bone marrow and adipose tissue were detected at the bone defect after 25 days, and there was no difference in the luciferin signal between the two sources of cells. Binding of osteoblasts from bone marrow to the P(VDF-TrFE)-$BaTiO_3$ composite membrane increased bone formation, whereas osteoblasts from adipose tissue did not enhance bone repair induced by the membrane itself. This effect of the composite membrane to promote stem cell differentiation without the help of external biochemical differentiation inducers may be related to the different waveforms of electrical stimulation generated by the membrane. By analyzing the effect of electrical stimulation on human MSCs using monophasic DC, square wave and biphasic waveforms, it was found that DC stimulation led to an increase in the intracellular level of reactive oxygen species thus promoting early osteogenesis in MSCs, while square wave stimulation guided late osteogenesis with lower ROS regeneration [115]. Moreover, osteoblasts inoculated with P(VDF-TrFE)-$BaTiO_3$ composite membrane osteoblasts expressed higher levels of osteogenic genes and apoptotic markers [116]. Lopes et al. [117] performed a large-scale microarray analysis of miRs on membrane-grown bone tissues and verified that the higher rate of PVDF-induced bone formation was, at least in part, caused by an increase in miR-34a and a decrease in RANKL which may inhibit osteoclast differentiation and activity as well as bone resorption.

Nano-$BaTiO_3$ can act as a nucleating agent to induce the formation of β-phase in PVDF, while the piezoelectric properties of PVDF increase with the increase of β-phase and further enhance the composite piezoelectric properties due to its high piezoelectricity coefficient [118]. The surface potential of P(VDF-TrFE)-$BaTiO_3$ composite membranes can be regulated up to −76.8 mV, which conforms to the endogenous biological potential level. The surface potential of the polarized nanocomposite membranes showed remarkable stability, with more than half of the original surface potential remaining for up to 12 weeks under bone-deficient conditions [119]. However, it has also been reported that doped $BaTiO_3$ nanoparticles are more inclined to aggregate in the polymer, which can weaken the nucleation ability of the β-phase in PVDF and thus affect its piezoelectric effect. For this reason, researchers have functionalized $BaTiO_3$ with polydopamine after hydroxylation. Through chemical bonding interactions, the $BaTiO_3$ nanoparticles can be uniformly distributed in the PVDF matrix, thus significantly increasing the β-phase fraction from 46 % to 59 % and increasing the output voltage by 356 % [120]. Liu et al. [121] prepared polarized $CoFe_2O_4$/$BaTiO_3$/P(VDF-TrFE) core–shell particle-encapsulated composite membranes to increase the charge density on the $BaTiO_3$ shell and enhance the β-phase transition in the P(VDF-TrFE) matrix by utilizing the external magnetic field force conducted on the $CoFe_2O_4$ inner core. And in vivo experiments confirmed that repeated application of magnetic field on the membrane promoted the repair of bone defects even in the presence of osteogenic inhibition due to dexamethasone- or lipopolysaccharide-induced inflammation. In addition, by doping the PVDF-$BaTiO_3$ composite films with conductive materials such as carbon nanotubes [122] and Graphene quantum dot [123] can also improve the dielectric properties, electrical conductivity, and surface roughness, as well as promote cell proliferation, migration, and osteogenesis. In addition to the addition of functional conductive materials, ultrasonic energy with several desirable properties, such as low energy attenuation and strong penetration ability, can be used to simulate in vitro exercise loads and promote electrical stimulation of composite membranes. The PVDF-$BaTiO_3$ composite film stimulated by ultrasound showed excellent power generation capability to be used as a sustainable power source and was able to generate a high voltage of 4.5 V even when the composite film was implanted at a depth of 8.22 cm subcutaneously [124].

In recent years, guided bone regeneration has been used for bone repair as a surgical technique, which utilizes a barrier membrane to establish a protected area and help osteoblasts colonize this enhanced area without competition from overlying soft tissue cells [125]. Whereas PVDF films are promising in guiding bone regeneration, doping $BaTiO_3$ into PVDF would further enhance the increased gene expression of osteoblasts RUNX9, BSP, OPN, OPG, CALCR, and MMP9 in an animal model of osteoporosis [126]. However, lacking the defective site of MSCs induction toward osteoporosis, only a small amount of bone formation was observed in the PVDF-$BaTiO_3$ composite films. For this reason, Almeida et al. [127] further localized bone marrow-derived MSCs after implantation in order to help bone regeneration with modifications against classical guided bone regeneration methods. In addition, Bai et al. [91] found that PVDF-$BaTiO_3$ composite films exhibited higher bone inductance compared to polytetrafluoroethylene membranes and earlier neovascularization as well as more intact bone structure in rabbit mandibular bone defects of critical size after doping with deproteinized bovine bone. PVDF and P (VDF-TrFE) and $BaTiO_3$ composite films have been extensively studied for their potential as internal generators to accelerate bone growth. However, such materials are difficult to degrade in vivo, which can lead to some potential problems. In contrast, the degradable polymer PHBV, which has excellent biocompatibility and piezoelectricity, shows promising applications. PHBV-$BaTiO_3$ composite polarized scaffolds exhibit good degradability and pro-mineralization effects, and highly promote cell attachment, proliferation and collagen II gene expression [128,129]. The PHBV-$BaTiO_3$ composite piezoelectric periosteum after polydopamine encapsulation also acts as an immunomodulator, which inhibits the secretion of inflammatory factors in the defective area and improves the production of anti-inflammatory cytokines and osteogenic factors by promoting the conversion of macrophage M1-M2 phenotype. This immunomodulatory effect promotes MSCs recruitment and synergistically promotes bone regeneration and vascular network reconstruction by providing electrical stimulation [130]. Polylactic acid (PLA), which is also a piezoelectric polymer, also has excellent degradability, and the PLA-BaTiO3 composite membrane also shows good osteogenic ability and has the best performance at 20 % $BaTiO_3$ content [131]. In addition to artificial polymers, chitosan [132,133], alginate [134,135] and gelatin [136] inside natural polymers can also be used as carriers of $BaTiO_3$.

Polymer-$BaTiO_3$composites are necessary for the preparation of three-dimensional porous composite scaffolds using 3D printing technology, in addition to the common use of thin films for bone repair. Polycaprolactone (PCL) in polymers was selected and used as the dispersed phase due to its low melting point, ease of processing and wide application in bone tissue engineering. The composite scaffolds were prepared by homogeneous co-mixing of PCL with $BaTiO_3$ using melt printing. The higher mechanical properties, dielectric constant and better cell growth promoting ability make it show great potential for the application in tissue engineering of load bearing bone [137]. And the composite scaffolds stimulated by in vitro ultrasound are more conducive to cell proliferation and differentiation, and the responsiveness of different cell species to ultrasound at different frequencies varies [138]. To further not improve the performance of the composite scaffolds, the researchers synthesized highly conductive binary doped polyaniline nanoparticles by oxidative polymerization into the scaffolds, which resulted in the composite material generating an unprecedented voltage of 9.288 V and a water contact angle of $7 \pm 11^{\circ}$ [139], which made it an ideal scaffold for cell attachment and protein interaction. Wang et al. [93] prepared microspheres with negative surface potential by combining strontium-doped $BaTiO_3$ nanoparticles with poly (lactic co-glycolic acid) and a high electrostatic voltage field. This negative surface potential caused by the addition of strontium modulates cell membrane potential and leads to an increase in intracellular Ca^{2+}

concentration, which activates the calmodulin phosphatase (CaN)/nuclear factor (NFAT) signaling pathway in activated T cells and promotes osteogenic differentiation. In addition to the direct blending of this polymer with piezoelectric ceramics, Tang et al. [140] prepared layered porous ceramics from $BaTiO_3$ by directional freeze casting, and then infiltrated the pore channels with polymethylmethacrylate bone cement under negative pressure to finally obtain a layered composite structure. This structure is similar to the structure of Haversian bone units of natural bone and allows directed growth of osteoblasts with polarity [141].

In contrast, Kemppi et al. [142] used respiratory mapping in composites to show the formation of cellular structures favorable for cell growth and that uncoated $BaTiO_3$ allows water to condense into larger droplets during the production process as compared to silica-coated $BaTiO_3$ and alumina-coated $BaTiO_3$, resulting in larger pores than cells in the scaffolds. However, for polymer-$BaTiO_3$ composite scaffolds, the fiber orientation of the polymer has been shown to be a major influence on their osteogenic properties [143,144]. PLLA-$BaTiO_3$ composite

Table 3
BaTiO3-Polymer composites for bone tissue engineering.

Material	Processing method	*In vitro*/in vivo study	Key assessments	Ref
PCL-$BaTiO_3$	Electrospinning	MC3T3-E1 subclone 4 mouse pre-osteoblasts	Increased expression of osteogenic genes.	[111]
P(VDF-TrFE)-$BaTiO_3$	Physical mixing	Human alveolar bone fragments	Demonstrated better in vitro biocompatibility and allowed bone-like nodule formation.	[113]
P(VDF-TrFE)-$BaTiO_3$	Physical mixing	BMMSCs/ADMSCs + Rat cranial model	The osteogenic capacity of BMMSCs was greater than that of ADMSCs on the composite membrane.	[114]
PVDF-$BaTiO_3$(10,20,30,40 wt %)	Melt blending	Human MSCs	Electrical stimulation with different waveforms promotes differentiation of MSCs.	[115]
P(VDF-TrFE)-$BaTiO_3$	Physical mixing	Human alveolar bone fragments	Supports the acquisition of an osteoblast phenotype in vitro while upregulating the expression of apoptotic markers.	[116]
PVDF-$BaTiO_3$	Melt blending	A model of fibular defects in Wistar rats.	Increase in miR-34a and decrease in RANKL caused higher bone formation rate.	[117]
P(VDF-TrFE) (35 wt%)-$BaTiO_3$ (65 wt%)	Physical mixing	BMMSCs + A model of cranial defects in SD rats	Increased cellular activity and osteogenic differentiation, rapid bone regeneration.	[119]
PVDF-$BaTiO_3$	Selective Laser Sintering	MG-63 cells	Enhanced surface electrical signals significantly promoted cell adhesion, proliferation and differentiation.	[120]
P(VDF-TrFE)-$BaTiO_3$	Physical mixing	Rat BMMSCs + A model of cranial defects in SD rats	It also promotes repair of bone defects in the presence of osteogenic inhibition.	[121]
PVDF-$BaTiO_3$(30 wt %)-MWCNT (3 wt %)	Melt mixing	Murine calvarial preosteoblasts (MC3T3-E1)	Enhancement of proliferation, migration and osteogenesis of preosteoblastic cells.	[122]
P(VDF-TrFE)-$BaTiO_3$	Physical mixing	Bilateral ovariectomy in Wistar rats	Expression of genes related to bone resorption was significantly higher.	[126]
P(VDF-TrFE)-$BaTiO_3$	Physical mixing	Bilateral ovariectomy in Wistar rats	More bone formation was observed after injection of BMMSCs.	[127]
P(VDF-TrFE)-$BaTiO_3$-DBB	Physical mixing	Rat BMMSCs + Rabbit mandibular defect model	Earlier appearance of neovascularization as well as more complete bone structure.	[91]
PHBV-$BaTiO_3$	Electrostatic spinning	MSCs	Highly promotes cell attachment, proliferation and collagen II gene expression.	[128]
PHBV-$BaTiO_3$	Electrostatic spinning	—	Good degradation and mineralization properties.	[129]
PHBV-$BaTiO_3$-PDA	Vacuum Spin Coating	BMMSCs from SD rats	Good immunomodulatory and osteogenic properties.	[130]
PLA-$BaTiO_3$(0,5,10,20,30,40 wt %)	Solution casting method	The mouse embryonic bone marrow MSCs MC3T3-E1 cell line + SD rat cranial model	Increased cell adhesion and proliferation and new bone formation.	[131]
PLLA- $BaTiO_3$	Physical co-mingling	BMMSCs + SD rats	Electroactive, biodegradable, antibacterial and anti-inflammatory activity	[146]
Chitosan-$BaTiO_3$(1,5,10,20,30,35 wt%)	Solvent casting	Human fibroblast	The cytotoxicity of hydroxylated BaTiO3 was significantly reduced.	[132]
Chitosan-$BaTiO_3$	Encapsulated microspheres	MSCs in rats	MSCs achieved differentiation to adipocytes and osteoblasts at high doses	[133]
Alginate-$BaTiO_3$	Bioink	—	Excellent cytocompatibility; enhanced cell aggregation.	[134]
Alginate-$BaTiO_3$	Physical mixing	Human MSCs	Increased osteogenic differentiation.	[135]
Gelatine-PD-$BaTiO_3$	Freeze drying	BMMSCs from SD rats	Higher capacity for cellular osteogenic differentiation and new bone formation.	[136]
PCL-$BaTiO_3$(40 wt %)	Mechanical compounding, melt printing	Human bone osteosarcoma Saos-2 cell line	Higher mineralization and deposition of bone-like extracellular matrix.	[137]
PCL-$BaTiO_3$(25,45,65 wt %)	Mechanical compounding, melt printing	Preosteoblast MC3T3 mouse cells	In vitro ultrasound-stimulated composite scaffolds are more favorable for cell proliferation and differentiation	[138]
PCL-$BaTiO_3$(20, 30, and 40 wt %)-PANI (5 wt%)	Electrostatic spinning	MG-63 cells	Increased cell adhesion	[139]
PLGA-$BaTiO_3$(40 wt%)	High-voltage electrostatic technology	Mouse embryo osteoblast precursor cells (MC3T3-E1) cells + SD rat cranial model	Increased cell proliferation and differentiation; activation of the calcium-regulated phosphatase/nuclear factor signaling pathway in T cells.	[93]
PMMA-$BaTiO_3$	Cryocasting Pressure Suction	SD rat osteoblasts	Osteoblasts undergo directed growth.	[140]
PLDLA-$BaTiO_3$	Body map method	BMMSCs in sheep	Excellent biocompatibility.	[142]
PLLA-$BaTiO_3$(1,3,5,7,10 wt%)	Electrostatic spinning	BMMSCs in rats	Randomly oriented composite fiber scaffolds significantly promote polygonal spreading and facilitate early osteogenic differentiation of cells.	[145]

BMMSCs, Bone marrow mesenchymal stem cells; ADMSCs, Adipose mesenchymal stem cells; MWCNT, Multiwalled carbon nanotubes; DBB, Deproteinized bovine bone; PANI, Polyaniline nanoparticles; PDA, polydopamine; PLGA, Poly (lactic co-glycolic acid); PMMA, Polymethyl methacrylate; PLDLA, Poly-L/D-lactide copolymer; PLA, Polylactic acid; PD, Poly (ethylene dioxythiophene)/polystyrene sulfonate matrix; P(VDF-TrFE), polyvinylidene fluoride-trifluoroethylene.

scaffolds with randomly oriented composite fiber scaffolds significantly promoted polygonal spreading and facilitated early osteogenic differentiation of MSCs, whereas aligned composite fiber scaffolds promoted cell elongation and prevented osteogenic differentiation [145]. Ca/Mn co-doped $BaTiO_3$ nanofibers exhibit additional osteogenic activity by the incorporation of bioactive Ca/Mn elements in addition to excellent piezoelectric properties. The piezoelectric nanofibers could form a fibrous network within the polarized PLLA. The composites exhibit strong antimicrobial and anti-inflammatory properties, providing additional benefits for bone repair [146]. The applications of $BaTiO_3$-polymer composites in bone tissue engineering are listed in Table 3.

7.3. BaTiO3-metal composites

Among many metallic materials, most of the existing studies have chosen titanium (Ti) and its alloys [147], which have excellent biocompatibility, excellent corrosion resistance and good mechanical properties, to be combined with $BaTiO_3$, in anticipation of overcoming the biological inertness of Ti and its alloys as well as restoring the impaired electrical microenvironment due to large bone defects. Currently, $BaTiO_3$ piezoelectric ceramics can be attached to metal surfaces as coatings by hydrothermal synthesis and wet chemistry, etc. Ti-$BaTiO_3$ composite scaffolds can effectively promote the osteogenic differentiation of MSCs in vitro as well as the bone formation and growth of implants in vivo [148]. However, for larger segmental bone defects, there is a lack of effective mechanical stimulation at the defect site during the early stages of fracture healing, which can seriously affect the function of the piezoelectric ceramic coating and, consequently, the healing of bone tissue. Low-intensity pulsed ultrasound (LIPUS) can be used as a mechanical wave to enhance additional mechanical stimulation of the composite material in vitro. LIPUS-treated composite scaffolds showed more significant osteogenic capacity in a rabbit radius large segmental bone defect model [149]. Cai et al. [150] found that piezoelectric stimulation generated by LIPUS and $BaTiO_3$ significantly increased intracellular Ca^{2+} concentration, and blockade of L-type calcium channels using verapamil eliminated the differences in Ca^{2+} concentration between groups. And the increased intracellular Ca^{2+} concentration had a significant promotion effect on osteogenesis. Wu et al. [90] demonstrated that LIPUS-activated Ti-$BaTiO_3$ composite scaffolds could help bone repair by inhibiting the inflammatory MAPK/JNK signaling cascade and activating oxidative phosphorylation (OXPHOS) and ATP synthesis in macrophages, which promoted M2 polarization and modulated inflammatory responses. In addition, there are in vitro experiments generating endogenous electric fields that effectively promote the proliferation of human umbilical vein endothelial cells as well as the secretion of PDGF-BB and VEGF [94]. Although the construction of $BaTiO_3$ coatings on titanium porous scaffolds has been shown to promote bone regeneration, however, the phase transition of $BaTiO_3$ has been insufficiently investigated, and the effective piezoelectric coefficient (<1 pm/V) of its coatings is low. In contrast, tetragonal $BaTiO_3$ nanoparticle coatings with effective piezoelectric coefficients of 10–180 pm/V were prepared by anodic oxidation combined with two hydrothermal processes. And compared with the functional coatings with effective piezoelectric coefficient (<10 pm/V), the new nanostructured tetragonal $BaTiO_3$ coatings could better help human jaw bone MSCs elongation and reorientation, extensive lamellar elongation, stronger intercellular junctions and osteogenic differentiation [151]. The applications of $BaTiO_3$-metal composites in bone tissue engineering are listed in Table 4.

In addition, Chernozem et al. [152]endowed $BaTiO_3$ as a shell to the surface of a material with magnetostrictive capability by means of hydrothermal method only. The constructed core–shell structure of the magnetoelectric mini-robotic device is stimulated by an external magnetic field to generate a certain strain, which is subsequently converted by the $BaTiO_3$ into a certain electric charge. And in the piezoelectric effect of electrical stimulation can be used to inhibit or kill cancer cells, as well as to help tissue regeneration. Kozielski et al. [153] prepared injectable magneto-electric nanoelectrodes by strain-coupling $BaTiO_3$ by sol–gel growth on magnetic CoFe2O4 nanoparticles, which wirelessly transmit electrical signals to the brain in response to an external magnetic field. This design of piezoelectric $BaTiO_3$ core-shells provides a new idea for the development of multifunctional piezoelectric materials.

Despite the fact that $BaTiO_3$ and its composites have demonstrated good osteogenesis-promoting, inflammation-resistant, and tissue-vascularization-promoting characteristics in bone repair, researchers should still be concerned about the potential toxic effects present in $BaTiO_3$. Although $BaTiO_3$ shows promising applications, its inherent cytotoxicity remains a concern. The induction of intracellular pro-oxidants (reactive oxygen species and hydrogen peroxide) and the reduction of antioxidants (glutathione and several antioxidant enzymes) are the main ways in which $BaTiO_3$ nanoparticles induce oxidative stress and thus cytotoxicity in vivo. After interaction with human lung cancer (A549) cells, depletion of mitochondrial membrane potential and induction of caspase-3 and -9 enzyme activities were observed. Addition of N-acetylcysteine, a ROS scavenger, effectively abolished this effect [154]. How to specifically modulate ROS release is key to addressing the poor therapeutic efficacy and minimizing biosafety concerns [155]. In addition, the cytotoxicity of BaTiO3 nanoparticles was significantly

Table 4
BaTiO3-Metal composites for bone tissue engineering.

Material	Processing method	*In vitro*/in vivo study	Key assessments	Ref
Ti6Al4V-$BaTiO_3$	Hydrothermal preparation of coatings	MC3T3 osteoblasts + RAW264.7 macrophage	Promoted M2 polarization of macrophages and modulated the inflammatory response.	[90]
Ti6Al4V-$BaTiO_3$	Wet chemical preparation of coatings	BMMSC + femoral defect model in rabbits	Significantly enhanced osteogenesis and osseointegration.	[148]
Ti6Al4V-$BaTiO_3$	Coating	BMMSCs in SD rats + femoral defect model in sheep	Promoting cellular osteogenic differentiation in vitro and bone formation and growth in implants in vivo.	[149]
Ti6Al4V-$BaTiO_3$	Hydrothermal synthesis	The mouse pre-osteoblast cell line MC3T3-E1	Increased intracellular calcium ion concentration promotes in osteogenesis.	[150]
Ti6Al4V-$BaTiO_3$	Wet chemical preparation of coatings	BMMSCs + sheep spinal fusion model in SD rats	Increased cell proliferation, migration, and osteogenic differentiation; increased proliferation and migration of human umbilical vein endothelial cells and on secretion of VEGF and PDGF-BB.	[94]
Ti-$BaTiO_3$	Anodizing combined with two hydrothermal processes	hJBMSCs	Tetragonal $BaTiO_3$ coating aids cell elongation and reorientation, extensive lamellar extension, strong intercellular junctions and osteogenic differentiation.	[151]

BMMSCs, bone marrow mesenchymal stem cells; hJBMSCs, human jaw bone mesenchymal stem cells.

correlated with the type and dose of cells. After co-culturing $BaTiO_3$ nanoparticles (50 μg mL^{-1}) with A549 cells exposed for 24, 48, and 74 h, the cell survival was 91 %, 84 %, and 81 %, respectively, and $BaTiO_3$ nanoparticles did not show significant cytotoxicity. However, adenosquamous carcinoma cells showed lower survival at the same dose [156].

Since $BaTiO_3$ is non-degradable in vivo, composites with friction/wear/corrosion/in vivo degradation occur, $BaTiO_3$ particles released from within the composite can cause acute or chronic inflammation. The severity depends on the physicochemical properties of the particles and the immune response of the host cells. Moreover, most of the $BaTiO_3$ in common use today are nanosized particles, and the fine abraded particles can be transferred to other organs through the body circulation, thus penetrating the plasma membrane and causing cytotoxicity. For example, after intra-articular injection of 2 and 20 mg/ml of TiO_2 nanoparticles into the knee joints of rats, toxic reactions were observed in the joints and nanoparticles were found in organs such as the heart, liver, and lungs [157]. Comparison of phagocytosis of particles of different sizes (40 nm, 420 nm, and 1 μm) by macrophages revealed that uptake increased with time and particle concentration. They were mainly located inside phagosomes, heterophagosomes, and in the case of nanoparticles also in the nearby cytoplasmic lysate. No particles were found in the nucleus. Although nanoparticles did not adversely affect macrophages, the experiment did not further verify whether an inflammatory response occurred [158]. Although most researchers have demonstrated the safety of $BaTiO_3$ composites in vitro, there is still a lack of validation of their long-term safety in vivo. In addition, there is still a lack of uniformity regarding the optimal frequency, intensity, and duration of electrical stimulation for bone regenerative repair, limited by a number of variables such as the type of composite, barium titanate content, and polarization strength. This also limits its further clinical translation.

6. Summary and prospects

Since the piezoelectric effect has been gradually demonstrated to play an important role in a series of physiological activities in bone, the development of novel bone tissue engineering scaffolds with piezoelectric effect through the addition of piezoelectric materials has gradually begun to attract the attention of researchers. This review highlights the great potential of $BaTiO_3$ as a piezoelectric biomaterial in the field of bone tissue engineering. $BaTiO_3$ is characterized by easy synthesis, good biocompatibility, low cytotoxicity, and excellent piezoelectricity, make it an ideal candidate for the development of advanced scaffolds that mimic the natural electrical environment of bone tissue. Currently, composite scaffolds prepared from $BaTiO_3$ with other biomaterials such as bioceramics, polymers, and metals have shown potential in enhancing osteogenic differentiation, promoting cell adhesion and proliferation, immunomodulation, angiogenesis, and ultimately facilitating effective bone repair and regeneration.

However, despite the encouraging results, the long-term stability, potential toxicity, and integration with existing tissue engineering technologies remain challenges to be addressed, as $BaTiO_3$ is not degradable in vivo. In addition, there is a lack of unified physical and chemical characterization methods for this novel material, and the effects of different experimental conditions such as temperature, humidity, and polarization time on the piezoelectric properties of the material still need to be further investigated. Future research should focus on optimizing the synthesis and fabrication of $BaTiO_3$-based materials to improve their properties and biocompatibility. The clinical application of $BaTiO_3$ is still an area to be explored. Clinical trials and long-term studies are essential to evaluate the efficacy and safety of $BaTiO_3$-based biomaterials in human patients. Advances in this field are expected to revolutionize bone tissue engineering and bring new hope to patients with bone-related diseases.

7. Authorship

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Each author certifies that this material or part thereof has not been published in another journal, that it is not currently submitted elsewhere, and that it will not be submitted elsewhere until a final decision regarding publication of the manuscript in Journal of Orthopaedic Translation has been made.

Indicate the specific contributions made by each author (list the authors' initials followed by their surnames, e.g., Y.L. Cheung). The name of each author must appear at least once in each of the three categories below.

CRediT authorship contribution statement

All authors have read and approved the article. Concept and design: S.C, X.C. and X.Y.L. Drafting of the manuscript: H.G.H., K.Z.W., X.L. Revision of the manuscript for important intellectual content: H.W., J.Z.W., M.R.S. Supervision: Z.H.L., X.C.

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Declaration of competing interest

A conflict of interest occurs when an individual's objectivity is potentially compromised by a desire for financial gain, prominence, professional advancement or a successful outcome. The Editors of the *Journal of Orthopaedic Translation* strive to ensure that what is published in the Journal is as balanced, objective and evidence-based as possible. Since it can be difficult to distinguish between an actual conflict of interest and a perceived conflict of interest, the Journal requires authors to disclose all and any potential conflicts of interest.

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