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Review

Electroactive ceramic biomaterials on the principle of bone piezoelectricity towards advanced bone engineering

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ABSTRACT

This review concentrates on the electroactive ceramic biointerfaces inspired by bone piezoelectricity for advanced ceramic biomaterials. Bone generates electrical potentials through the piezoelectric properties of collagen fibrils and apatite minerals under mechanical loading. These electrical signals influence osteoconductivity and regenerative capacity by osteogenic cells. Synthetic ceramic biomaterials can be electrically polarized to mimic bone's natural electroactivity. Polarization improves surface wettability of biomaterial surfaces by increasing surface free energy, promoting serum protein adsorption and osteoblast adhesion while also influencing osteoclast differentiation. These surface modifications by polarization can be achieved without changing surface morphology or crystallinity and offer stable and long-lasting bioactivity at biointerface. This review details the physicochemical mechanisms underlying polarization, protein interaction, and cellular responses at biointerface. Understanding these interactions enables the rational design of electroactive ceramics that effectively guide bone regeneration. Polarized ceramics demonstrate potential as electroactive and long lifetime biomaterials in orthopedic, dental, and soft-tissue applications, suggesting a broad translational scope for regenerative medicine.

1. Introduction

A biointerface is defined as the contacting region between a biomaterial and the surrounding tissues, including cells, bodily fluids, blood, inorganic ions, proteins, and lipids. The interactions of biomaterials implanted into soft/hard tissues with biomolecules impacting on the healing and regeneration of tissues. A large number of studies on the biointerfaces have aimed to regulate cells for tissue regeneration. As introduced below (Section 2), a number of review reports currently focus on the use of bone piezoelectricity principle or physical methods of electrical or ultra-sound stimulation for cell or tissue regulation [1–6].

In the vicinity of an interface of implanted biomaterial with bone tissue, osteoconduction proceeds along the following stages: (1) serum protein adsorption, (2) recruitment of cells, (3) cell adhesion and proliferation, (4) osteoblast differentiation and osteoid production, (5) matrix calcification, and (6) bone remodeling [7,8] (Fig. 1). Blood components exuding from the encompassing tissue are the first substances to interact with implanted biomaterials and play important roles in fibrosis [9], inflammation [10], thrombosis [11], and complement activation [12]. These components also trigger subsequent cell responses related to osteoconduction.

Cell behavior is largely regulated by extracellular ions, proteins, and lipids, and when a cell contacts with other cells, antigens, and the extracellular matrix work as the regulatory factors. These effects can be observed in various circulating hormones, cytokines, chemokines, and growth factors. These signaling molecules reach the nuclei through channels, receptors, and integrins of the cell membrane.

The importance of physicochemical features in cell responses has been recognized since the 1980s with the discovery that fibroblast-like cells suspended in agar rarely proliferated (8 %), whereas adherence allowed proliferation of 30 % and 90 % on small and large adhesive patches, respectively [13]. The morphology of fibroblasts is reportedly influenced by the stiffness of the gels [14]. Engler et al. demonstrated that cell differentiation is affected by the substrate rigidity of

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polyacrylamide hydrogels. Moreover, mesenchymal stem cells exhibited neurogenic, myogenic, and osteogenic commitment on soft, stiff, and stiffer gels, mimicking the rigidity of brain, muscle, and bone tissues, respectively [15].

The underlying concept of bone tissue engineering stands on the utilization of the inherent biological responses of the host. To address the mechanism of osteoconduction, this review concentrates on the influences of the physical properties and stimulative effects of bone on the bone regeneration capacity of osteogenic cells in skeletal tissues. Ceramic biomaterials are widely applied in the orthopedic and dental fields for regeneration of skeletal tissues by the compatibility for controlling osteogenic behaviors. Understanding of the mechanisms underlying the interactions at the interface between cells and ceramic biomaterials is strongly anticipated to contribute to the design of new biomaterials to induce tissue regeneration via regulation of hydrated bodily fluids, proteins, and cells.

2. Piezoelectricity of bone tissue

Bone is a vital tissue that constantly repeats reconstruction by osteoblasts and resorption by osteoclasts. The bone remodeling cycle can be affected by various factors such as mechanical stimulation, metabolic causes, endocrine changes in addition to medical drugs. Mechanical loading on bone metabolism is widely known to impact on the phenomenological effects such as the healing of fractures [16] and bone absorption in the microgravity environment of space [17].

Wolff's Law states that the functional adaptation of bone causes the trabeculae to reorient with principle stress trajectories in response to changes in environmental loads due to trauma or life-pattern changes [18] (Fig. 2 ①). In 1957, Fukada et al. first reported the piezoelectricity in bone (Fig. 2 ②) [19]. Basset et al. showed that mechanical loading on bone minerals introduces an electrical potential produced due to collagen piezoelectricity [20]. Bone exposed to compression develop negative potentials but develop positive potentials under tension [20]. Frost et al. demonstrated that bone remodeling is influenced by both negative and positive potentials [21]. Living bones grow thicker on the compressed concave side and thinner on the tensed convex side.

The shear forces among collagen fibrils creates piezoelectric energy. Collagen fibrils in compact bone execute a piezoelectric process, providing collective and cohesive responses to mechanical loading underlying physiological effects [20,22]. The piezoelectric properties of a single collagen type I fibril in the fascia [23], tendon [24], and cornea [25] were recently examined using high-resolution piezoresponse force microscopy (PFM). Precise analyses revealed that the deformation was maintained along the entire fibril length and independent of the fibril conformation [23]. Mascarenhas measured the piezoelectricity of collagen fibrils in decalcified bone by the method of the thermally stimulated depolarization current (TSDC) [26]. The TSDC profiles provided the activation energy and half period at body temperature, which were calculated as 1.0–1.5 eV and 2–13 h, respectively [27]. In vivo experiments of recording human tibia on walking demonstrated piezoelectricity as strong as 300 mV, whereas collagen fibrils can only store small surface charges. Remarkably, a current of 100 nA was detected in bone collagen fibrils by external application of 10 $kV{\cdot}cm^{-1}$ and bone formation increased progressively at currents of 5–20 μA [28]. However, the electric potential created by the collagen fibrils alone was insufficient. Although it is relatively easy to generate piezoelectric energy in collagen fibrils, the energy disappears after several hours. The generation of piezoelectric potentials in bone by the displacement of collagen fibrils diminishes after recover to its original position. Such rapid disappearance of piezoelectricity is inefficient and ineffective for bone remodeling as well as fracture healing, because bone formation requires several weeks for complete achievement [29].

The bone matrix is mainly composed of apatite minerals, collagen fibrils, and non-collagenous proteins [30,31]. TSDC measurements have shown that the collagen fibrils and apatite minerals of bone store piezoelectric energy [27] (Fig. 3). The mechanisms underlying the generation of electric current differ between the collagen fibrils and mineral components of bone tissue. Displacement of collagen fibrils produces an electrical potential with a half period because their replacement causes a loss in potential [23]. At the interfaces among the collagen fibrils and mineral crystals, apatitic minerals function as transducers of semiconductors, since a large parts of free electrons localize at the collagen fibril side and relatively few at the mineral side [20,22]. Resultantly, free electrons are forced to migrate to the insulator mineral side induces current in the bone structure. In bone tissue,

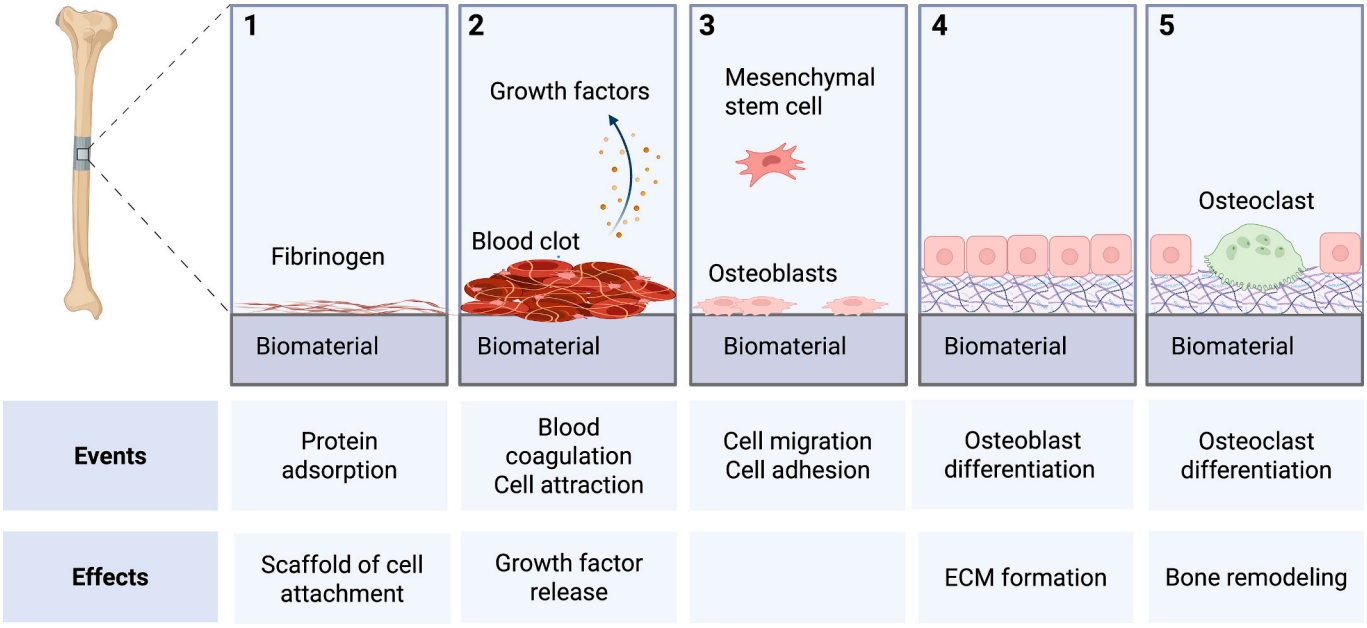


Fig. 1. Biological mechanism of osteoconduction at an interface between the implanted biomaterial and bone tissue: (1) serum protein adsorption, (2) recruitment of cells, (3) cell adhesion and proliferation, (4) osteoblast differentiation and osteoid production, (5) matrix calcification, and (6) bone remodeling. Reproduced with permission [135]. Copyright 2006, Wiley-VCH.

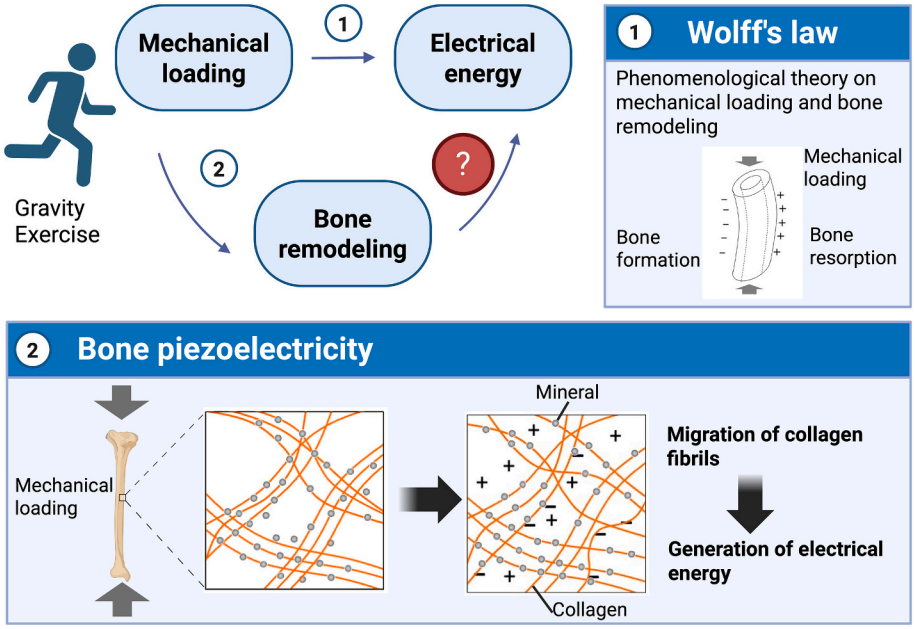
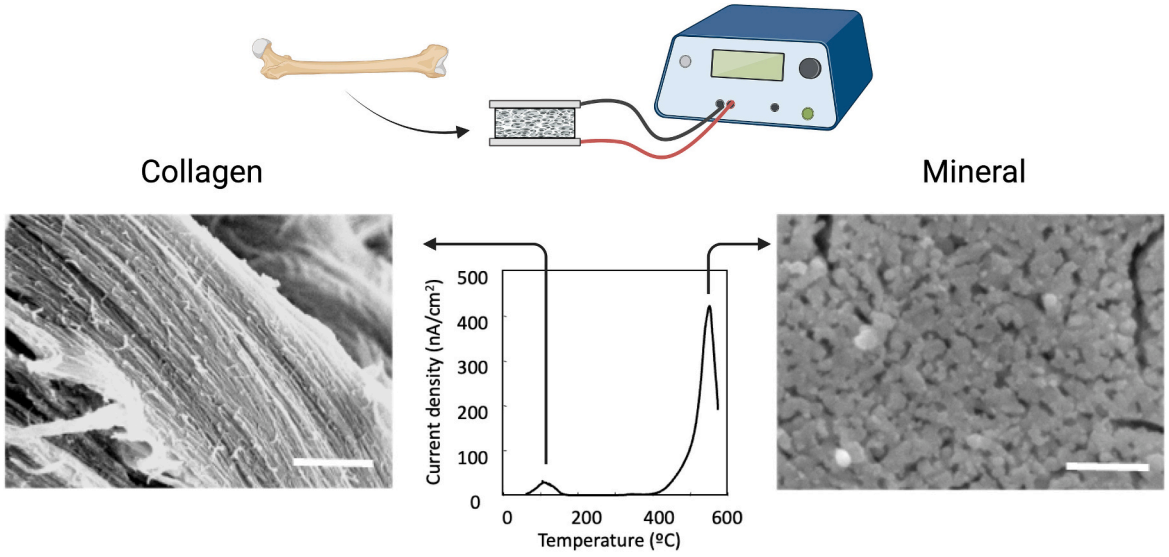


Fig. 2. Wolff's law, in addition to bone piezoelectricity, is key to understanding the connection between mechanical loading and bone remodeling. Mechanical loading generates electrical potential in the collagen fibrils of bone. These discoveries suggest that mechanical loading, such as gravity and exercise, generates piezoelectricity in the bone matrix. However, the connection between bone remodeling and electrical energy remains unclear.



20 μC/cm²	**Electrical energy**	600 μC/cm²
7 hours	**Half life time**	30,000 years
Generation of electrical potentials	**Role**	Electrical reservoir

Fig. 3. Two electrical signals were detected from thermally stimulated depolarization current measurement of bone slices, which confirmed the electrical potential of collagen fibrils and minerals. The electrical energy of bone minerals is reportedly larger and more stable than that of collagen fibers, which can generate electrical potentials, but disappeared after several hours. On the other hand, minerals can store electrical energy for long periods. Reproduced with permission [27]. Copyright 2012, Wiley-VCH.

minerals store greater amounts of piezoelectric energy (~10-fold) than collagen fibrils. The half period of energy of bone minerals at body temperature is 10^7–10^{11} years. Both negativity and positivity of piezoelectric potentials impact on the behaviors of osteogenic cells in bone remodeling. Those stable potentials throughout minerals are sufficient for stimulation of osteogenic cells during bone remodeling.

The activation energy required for depolarization of bone minerals estimated from TSDC curves (1.2–1.5 eV) is analogous to that of

synthesized carbonate apatite (CA) (1.2 eV). As the inorganic components of bone tissue contain various kinds of partially substituted ions, such as 2–8 wt% CO_3^{2-} and a small amount of Na^+, K^+, Mg^{2+}, and Cl^- in crystalline lattices [32], the similarity in activation energy values can be possibly explained with a consideration that the charge-carrying ions participating in piezoelectricity are the same or similar. Synthesized CA can store higher electrical energy (4.3×10^3 μC·cm^{-2}) than stoichiometric hydroxyapatite (HA) (1.6 μC·cm^{-2}) because of distortions in the crystal lattices of apatite minerals [27]. Therefore, the electrical property of bones strongly demonstrates the determinate importance of carbonates in bone minerals for bone piezoelectricity.

3. Piezoelectric and polarized scaffolds

Electrical stimulation with medical devices via direct current, capacitive coupling (CC), and inductive coupling (IC) is reported to accelerate fracture healing [33]. The most commonly used approaches of DC [34], CC [35], and IC [28] involve implanting an electrode into the fracture site, placing skin electrodes on opposite faces of the bone to be stimulated, and creating an electrical field by changing the external magnetic field. Numerous clinical studies have reported the advantages of electrical stimulation via DC, CC, and IC in bone healing and piezoelectric scaffolds [36].

Materials that exhibit piezoelectricity include lead collagen, DNA, zirconate titanate, sodium potassium niobate, poly(vinylidene fluoride) (PVDF), and poly(l-lactic acid) (PLLA) [37,1,38–42]. Piezoelectricity is tied to the symmetry of the crystal structure of piezoelectric materials, which require a lack of a center of symmetry. Under applied stress, the centers of the positive and negative ions of piezoelectric materials migrate from each other depending on the direction of the stress. Once such polarization is realized, a voltage difference is formed between the two surfaces of the crystal. HA, a main inorganic component of bone, is theoretically not piezoelectric materials due to the crystallographic symmetry. However, electrical polarization induced by external voltage induces positive or negative charges on the solid surfaces of HA. The application of an external voltage can polarize the bone tissue as well as synthetic inorganic biomaterials, such as HA [43–48], HA coated on Ti [49], CA [50], β-tricalcium phosphate (β-TCP) [51,52], biphasic calcium phosphates of HA [53], titania (TiO_2) [52], bioactive glass [54,55], and yttria partially stabilized zirconia (PSZ) [56].

The polarization of HA results from the transition of protons via the lattice hydroxide ions in HA structure [57,58], which forms stable polarization charges on the HA surface [59]. Negative surface charges form due to accumulation of migrated protons along applied electrical fields. The increased surface negativity lowers the average zeta potential of polarized surfaces, strengthening the electrical double layer between solidus and liquidus interfaces. As a result, the surface free energy (SFE) can dominate wettability of long distant solid surfaces, consequently manipulate behavior of proteins and cells. The surface force of polarized HA extends to several μm or even millimeters, influencing H_2O molecules as well as proteins and cells.

4. Surface characterization of piezoelectric and polarized scaffolds

Polarization brings no change on constituent elements, crystallinity, or surface roughness at the detectable levels of confocal laser scanning microscopy (CLSM), X-ray diffraction (XRD), and X-ray photoelectron spectroscopy (XPS), as the polarization mechanism depends upon the diffusion of charge-carrying ions in the crystalline structure. Carrier ions are reportedly protons in HA, oxygen in CA and β-TCP, and oxide ions in TiO_2 and PSZ. Because of the mechanism of carrier ion migration in the crystalline structure, the electrical potentials by polarization does not disappear in short period. The half periods for the electrical potentials stored in HA were calculated as 10^7–10^{11} years at body temperature [27]. A recent study experimentally proved over-a-decade-life time of polarized HA ceramics [60]. The electrical potentials after 60 days [57] and cell culture for 7 days [59] were almost at the same level as that before the experiments.

A sintering ambience rules the surface properties of polarized HA, as determined by comparison of HA sintered in an atmosphere of saturated water vapor (wHA) vs. air (aHA); aHA has much larger average grain-size than wHA. The grain-size difference in HA ceramics prepared by microwaves under the various conditions of sintering temperature and time were reported to affect the SFE as well as cell viability and differentiation [61]. These findings are consistent with the comparison of wHA with aHA; aHA with a larger grain-size showed a smaller SFE, regardless of the sintering method.

Both wHA and aHA can be polarized, however, the electrical charge stored by aHA is approximately 10-fold greater because of the differences in grain size and OH^--content. The previous work demonstrated that these two factors predominate the characteristics of polarized HA [58]. The polarization properties of HA depend on two kinds of proton conduction effects: trans-granular dipole polarization and space-charge polarization along the grain boundaries. Despite the high polarization charges, aHA exhibited no significant change in the SFE or wettability. Such surface characteristics of polarized aHA can be attributed to the lower content of hydroxide ions as charge carriers in polarization, in comparison with wHA. The grain size can give another explanation to impart thermodynamic stability, although further study is required to fully understand.

Several physicochemical parameters determine the surface characteristics, which include topography, roughness, stiffness, crystallinity, substituted ions, zeta potential, surface wettability, SFE, and the composition of constituent elements and functional groups. These parameters have the potential to affect water, proteins, and cells at the biointerfaces between biomaterials and cells. Electrical polarization improves surface wettability by increasing the SFE or surface tension [62].

There are several methods to evaluate the SFE (γ: mJ•m^{-2}) of solid materials by measurements of the contact angles (θ: °) of liquid drops on a surface. For example, the two-liquid-phase method is used to calculate the SFE of solid materials [63] (Fig. 4a). The contact angles of water are measured in hydrocarbon oils with different polarities, such as hexane, heptane, octane, decane, and hexadecane (Fig. 4a). Jouany's equation is used to calculate SFE, as follows:

$$\gamma_W - \gamma_H + \gamma_{HW}\cos\theta = 2\sqrt{\gamma_S^d}\left(\sqrt{\gamma_W^d} - \sqrt{\gamma_H}\right) + I_{SW}^p, \quad (1)$$

$$I_{sw}^p = 2\sqrt{\gamma_s^p \times \gamma_w^p}. \quad (2)$$

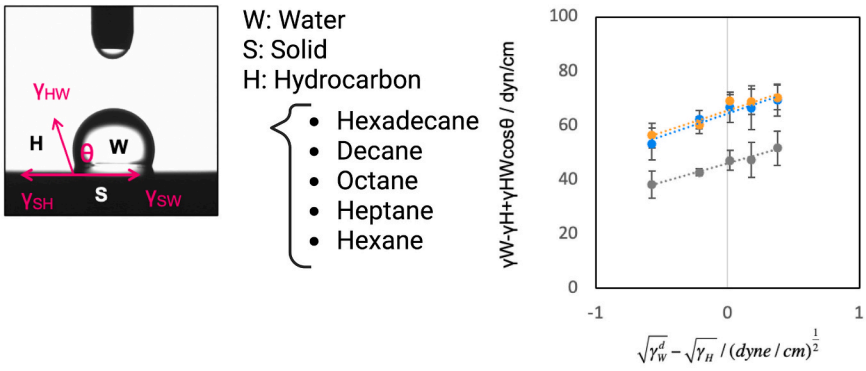
where the subscripts W, H, and S designate water, hydrocarbon, and solid, respectively, the parameters γ_S^d and γ_W^d and I_{SW}^p correspond to the dispersion components and the nondispersive interaction between the solid and water, respectively, and the indices γ_s^p and γ_w^p express the nondispersive polar factors. The work of adhesion denoted with W between the solid and water comprises of the dispersive and nondispersive interactions [64].

$$W_{sw} = I_{sw}^d + I_{sw}^p \quad (3)$$

$$W_{sw} = 2\sqrt{\gamma_s^d \times \gamma_w^d} + 2\sqrt{\gamma_s^p \times \gamma_w^p}. \quad (4)$$

The dispersive (γ_w^d) and polar (γ_w^p) components of water are calculated as 21.8 and 51.0 mJ•m^{-2}, respectively [64].

The SFE of polarized wHA is approximately 1.6-fold greater than that of conventional wHA (Fig. 4b), while the dispersion and polar components of the solid SFE are approximately 1.4- and 1.9- fold greater, respectively. In the calculation of the work of adhesion, the contribution ratio of γ_w^p to γ_w^d is 8.4/6.4 in the total W_{sw}, indicating the predominance



	Dispersion components γ_s^d (mJ/m²)	Polar components γ_s^p (mJ/m²)	Surface fee energy (mJ/m²)
wHA (conventional)	10	34	45
wHA (negative)	42	77	119
wHA (positive)	49	78	127

Fig. 4. A two-liquid-phase method to calculate the SFE. (a) The contact angles of water are measured in hydrocarbon oils, such as hexane (18.4 mJ·m^{-2}), heptane (20.1 mJ·m^{-2}), octane (21.7 mJ·m^{-2}), decane (23.8 mJ·m^{-2}), and hexadecane (27.5 mJ·m^{-2}). (b) SFE of wHA with or without polarization treatment calculated using Jouany's equation and dispersion and polar components of the SFE calculated based on the slope and *y*-intercept of the plots of the contact angles in the hydrocarbon oils. The SFE of polarized wHA was approximately 1.6-fold greater than that of conventional wHA. Reproduced with permission [62]. Copyright 2016, Elsevier.

of the polar over dispersive interaction. Thus, the polar component contributes more largely to the adhesion work of water to the solid than the dispersive component. Changes in the SFE therefore have greater effects on polar molecules of water and proteins. Actually, the contact angles of water are considerably decreased on polarized wHA. These changes in the contact angles of water and SFE of the surfaces of polarized wHA indicate that increasing the SFE improves the wettability of the polarized wHA specimens. Both the polarized and conventional HA specimens showed almost equal surface roughness, crystallinity, and crystal phase to each other under the same sintering atmosphere. Resultantly, the wettability of wHA given by polarization was much improved from the changes in SFE [62].

Surface analysis of polarized wHA showed no influence of electric polarization on the surface roughness, crystallinity, crystal phase, or morphology of microstructure. Significant differences in the SFE were experimentally demonstrated between electrically polarized and untreated wHA, whichever the polarity is charged. The SFE of the polarized wHA increased by approximately three-fold of conventional wHA. The SFE is determined by polar and dispersive components, suggesting that the increased SFE of polarized HA is predominantly attributed to the polar component.

The surface wettability was improved on wHA [47,59], HA coated on Ti [49], CA [65], β-TCP [65], biphasic calcium phosphates of HA [53], TiO_2 [52], and PSZ [65]. The contact angles of the wHA surface decreased with increasing polarization temperature (200 °C–600 °C), indicating improved wettability of the wHA surfaces in accordance with changes to the polarization conditions [62]. This response has close correlation to the increase in stored charges with the increasing polarization temperature.

5. Protein adsorption at the biointerface

The immediate reaction after biomaterial implantation takes place as the interaction of proteins in blood with tissue fluids [7,8]. Blood components that leak from the surrounding tissue are the first substances that interact with an implanted biomaterial and trigger subsequent responses, including acute and chronic inflammation, thrombosis, complement activation, infection, foreign body reaction, granulation tissue- and fibrosis capsule-development, and provisional matrix formation.

Host reactions at an early stage after implantation of a biomaterial include injury, blood-biomaterial interactions, acute/chronic inflammation, foreign body reaction, and granulation tissue- and fibrous capsule-development. Fibrin is an important blood protein in the biointerfacial layer. Fibrin polymers are formed by the adsorption of fibrinogen by the implanted biomaterial, which is then catalyzed by a thrombin or fibrin monomer in plasma and adsorbed onto the implanted biomaterial. The adsorption of proteins on solid surfaces in vitro is caused by the large number of links. For example, noncovalent binding of proteins to the HA surface is caused by acid-based formation of hydrogen bonds. Protein adsorption is affected by both ionic change due to dissolution of the HA surface and pH changes arising from HA surface contacting with an aqueous environment [66]. Near the polarized HA surfaces, the ion concentrations differ from those of conventional HA [67]. Indeed, polarized HA accelerates the adsorption of fibrin [68]. These differences can be attributed the attraction of Ca^{2+} to the polarized HA surface.

Acidic and basic proteins obey their respective different mechanisms of adsorption. Acidic proteins adsorb through electrostatic interactions of the COOH groups with Ca^{2+} on the HA surface or through PO_4^{3-} ion exchange. The positive and non-charged parts of the protein weakly bind to HA surface. Basic proteins predominantly bind through amino groups to the HA surface. The protein residues favorable for adsorption enumerate phosphoserine, γ-carboxyglutamic acid, aspartic acid, and glutamic acid [69]. Structural changes to protein molecules that occur during both adsorption and desorption on biomaterials can be attributed to a decrease in the α-helix content [70]. In each case, transition enthalpy of fibrinogen showed an increase with adsorption to the HA surface. Electrostatic interactions are proposed as the main mechanism controlling the adsorption of fibrinogen onto the HA surface [70]. The

consideration supports the speculation that the polarity of the surface charges modified fibrin adsorption onto the polarized HA surface in vivo. Fibrin reportedly plays an effective role for osteoconduction in biomaterial applications. Orthopedic operation employs a fibrin sealant for promotion of healing of surgical wounds and improvement of the osteogenic capabilities of poor angiogenic materials [71].

The changes of SFE considerably affect such polar molecules of water and proteins. The contact angle of water diminishes with the increasing SFE of polarized HA, giving rise to improved wettability of polarized HA [59]. In addition, the SFE and wettability of polarized ceramic surfaces also affect biomaterials containing carbonate apatite and β-tricalcium phosphate. The improvement of surface wettability promoted protein adsorption onto polarized HA at an early stage after implantation [68]. Adsorption of fibrin was therefore accelerated onto polarized HA immediately after implantation into the tibiae of rats in comparison with usual untreated HA.

In a biomedical context, the piezoelectric effect plays a multifaceted role in protein adsorption by generating surface charges under mechanical deformation, which in turn modulates the local electrostatic environment and surface energy—key factors influencing the amount, orientation, and conformation of adsorbed proteins at the biomaterial interface. This modulation can enhance or selectively regulate adsorption of blood proteins (e.g., fibrinogen), extracellular matrix proteins (e.g., osteopontin) and growth factors, thereby directing downstream cell adhesion, proliferation, and differentiation. For example, piezoelectric scaffolds composed of natural polymers such as collagen, cellulose, chitosan, or synthetic polymers like PLLA not only exploit mechano-electrical coupling to promote osteogenic protein adsorption and bone repair, but also support broader tissue-specific functions including cartilage regeneration and wound healing [37,72]. Furthermore, engineered piezoelectric hydrogels and composites (e.g., PVDF-based or ZnO-enhanced constructs) have demonstrated enhanced wound healing, immune modulation, and potential for self-powered biosensing, owing in part to their ability to recruit and organize proteins crucial for signaling and tissue regeneration [73,74]. Taken together, these findings highlight the promise of piezoelectric biomaterials not only as active interfaces for controlled protein presentation but also as dynamic, self-responsive systems for advancing regenerative medicine and implant design.

6. Cell behaviors at the biointerface

At a biointerface, cell adhesion plays a predominant regulatory role in the differentiation and formation of the extracellular matrix (ECM). Adhesion occurs between adjacent cells (cell-to-cell adhesion) as well as between cells and the ECM/substrate (cell-to-ECM/substrate adhesion). Cells adhere to biomaterials through a focal adhesion complex, including integrins, between cells and the substrate. The information from biomaterials enters the cell directly or indirectly (Fig. 5). Direct stimulations from the biomaterial surface enters the cells through integrins at the cell membrane and then reach the nuclei via signal transduction. The surface characteristics are among the most important factors in direct stimulation. Indirect stimulations are mediated by various molecules, such as growth factors, cytokines, chemokines, and exosomes secreted by the other cells, which may act on the same cells that produce them via autocrine signaling. In addition, cells adhered to the biomaterial can affect neighboring cells through cell-to-cell adhesions, such as gap junctions (Fig. 5).

Surface polarization enhanced both osteoblast adhesion and migration on HA in vitro [75]. Cell adhesion process strongly depends on the characteristics of the biomaterials surfaces with extracellular stimulation. The surface characteristics of biomaterials, including the topography, roughness, crystallinity [76,77], wettability, constituent elements, functional groups, substituted ions [78,79], and SFE, affect cell attachment and adhesion [76,80,77,7] (Fig. 5). The surface characteristics are reportedly affected by surface roughness, crystallinity, the

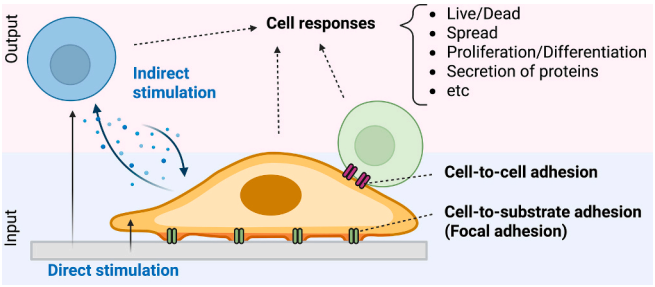


Fig. 5. Cell-to-cell and cell-to-ECM/substrate adhesions. Cells adhere to a biomaterial substrate through a focal adhesion complex, including integrins. Direct stimulation originates from biomaterial surfaces, enters the cell through integrins at the cell membrane, and then reaches the nuclei via signal transduction. Surface characteristics are among the most important factors influencing direct stimulation. Indirect stimulation is mediated by various molecules, including growth factors, cytokines, chemokines, and exosomes secreted by the other cells, which may act on act on the same cells that produced them via autocrine signaling. In addition, the cells adhered to the biomaterial could affect neighboring cells through cell-to-cell adhesions, such as gap junctions.

elemental constituents, and the incorporated ions, especially carbonate and fluorine [78,79]. Electron-provoked modifications to SFE via photoluminescence and surface photovoltage spectroscopy are reportedly effective for improving surface properties [81]. Extracellular stimulation, such as CC, IC, and combined electromagnetic fields, can induce electrical stimulation affecting cell attachment, adhesion, and motility [81].

Surface wettability affects the adhesion of cells to most biomaterials in addition to apatites, such as polymers [82], poly (methyl methacrylate) [76], inorganic glass microscope slides [83], partially stabilized zirconia (PSZ) [84], and Ti metals [80,85]. Whatever the substrata and methods are chosen for surface modification, wettability of biomaterials increase cell spread [86]. Optimum wettability for cell adhesion generally occurs at the contact angle of 50°–60° [87]. The wettability of HA improved by polarization at 600 °C was too high and inhibited cell adhesion to the surface. Electric stimulation to bone has been demonstrated to effectively enhance bone healing [88–92].

Polarization of piezoelectric materials generates localized electric fields that couple to the plasma membrane and open mechanosensitive and voltage-gated ion channels (e.g., Piezo1 and Ca^{2+}-activated channel complexes), elevating intracellular Ca^{2+} to trigger calmodulin/ERK and PI3K/Akt cascades that reshape cytoskeleton dynamics and transcriptional programs [93,94]. These fields simultaneously engage integrin receptors at the protein–material interface, activating focal-adhesion signaling (FAK, Src, talin, vinculin/ILK) that strengthens adhesion and coordinates traction forces for migration [95]. Downstream, mechano-electrical cues promote YAP/TAZ nuclear translocation and Hippo-pathway crosstalk, reinforcing adhesion-dependent gene expression that supports persistent motility and growth guidance [96–98]. Functionally, these polarization-driven electric fields bias cell movement (electrotaxis/galvanotaxis) and alignment, enabling directed migration of diverse cell types during regeneration and repair, as shown across model systems and engineered bioreactors [99,100]. In biomedical applications, piezoelectric polymers and hydrogels (e.g., PVDF/PLLA-based or collagen-composite systems) have leveraged this ion-channel/integrin synergy to enhance adhesion, orchestrate Ca^{2+} signaling, and steer tissue-specific growth in bone, cartilage, wound, and neural contexts, highlighting a path to self-powered, stimulus-responsive implants [101–105]. Collectively, the evidence supports a unified mechanism in which piezoelectric polarization shapes ion-channel gating and integrin-FAK signaling to promote robust cell adhesion, directed migration, and guided growth for regenerative medicine.

Surface polarization is also reported to enhance osteoclast resorption

on CA in vitro [106]. Osteoclasts shape giant multinucleated cells of bone-resorbing differentiated from precursor monocyte/macrophage lineage, crucial for development and turnover of bone as well as calcium homeostasis [107]. Resorption is dependent on the formation of the actin cytoskeleton in an actin-rich structure called a sealing zone for osteoclasts to anchor onto a biomaterial. Activated osteoclasts are categorized into five patterns of vinculin distribution by the morphology of the resorbing phases [107]. The podosome belt of mature osteoclasts can proceed to the sealing zone of actively resorbing osteoclasts to form a large circular actin band for tight attachment to the bone and sealing-off the resorption pit, which secretes proteases and proton [107]. The morphologies of human monocytes cultured with the osteoclast differentiation factors receptor activator of nuclear factor-kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) varied among several types of materials. Osteoclast precursors derived from peripheral blood were found to fuse to multinuclear giant cells on HA, CA, a glass coverslip, and TiO_2 after culture with M-CSF and RANKL [108]. Actin ring structures were formed by osteoclasts on CA and bone slices. Although both FBGCs and osteoclasts are important for biomaterial research [109], it is difficult to distinguish between these cell types because both are derived from the monocyte/macrophage linkage and have common features, such as the presence of podosome belts and production of tartrate-resistant acid phosphatase (TRAP) [110,111]. However, these cell types differ in resorption capability [112].

The piezoelectric effect exerts a profound influence on osteoclast function by coupling mechanical stress to localized electric fields, which directly modulate cell signaling and cytoskeletal dynamics. Electrically polarized apatite and polymeric scaffolds generate surface charges that increase surface energy and wettability, thereby enhancing protein adsorption and creating favorable conditions for osteoclast adhesion and resorption activity [106]. These polarization-induced electric fields also activate voltage-gated Ca^{2+} channels, elevating intracellular Ca^{2+} oscillations that are essential for osteoclastogenesis; however, excessive or sustained electrical stimulation can destabilize podosome clusters and actin ring structures, resulting in impaired bone resorption [113]. In parallel, piezoelectric polarization intersects with osteoclast differentiation pathways: studies using electromagnetic field analogs—mimicking endogenous piezoelectric cues—show suppression of RANKL–RANK signaling and downstream NF-κB, MAPK, and NFATc1 activation, accompanied by decreased expression of TRAP, cathepsin K, and MMP-9, key effectors of osteoclast resorptive function [114,115]. Notably, these effects extend beyond osteoclasts themselves, as piezoelectric polarization modulates the osteoblast–osteoclast crosstalk by altering the OPG/RANKL balance, ultimately tipping bone remodeling dynamics toward regeneration or resorption depending on the electrical environment [72]. Collectively, these findings highlight piezoelectric polarization as a potent regulator of osteoclast differentiation and activity, functioning not only through direct modulation of ion channels and cytoskeletal organization, but also via systemic control of signaling pathways that coordinate bone resorption and formation—underscoring its therapeutic potential in treating osteoporosis and enhancing bone regeneration.

7. Current status and future perspective of piezoelectric scaffolds for tissue engineering

Some case studies increasingly demonstrate the translational potential of piezoelectric ceramics in regenerative medicine, with several reports highlighting their efficacy in bone and soft tissue repair. For example, polarized hydroxyapatite and barium titanate ceramics have been shown in animal models to accelerate bone healing by enhancing osteoblast differentiation, collagen deposition, and mineralization at defect sites [116] [117] [72]. In a rat calvarial defect model, polarized calcium phosphate ceramics significantly promoted new bone formation compared with nonpolarized controls, underscoring the clinical relevance of piezoelectric surface charges [118].

Beyond hard tissues, case studies using polarized piezoelectric scaffolds and composites for soft tissue repair have reported enhanced angiogenesis [119], fibroblast proliferation, and wound closure [120], suggesting broader applicability in dermal and vascular regeneration [73]. Early-stage translational studies also point to the promise of piezoelectric ceramics in load-bearing orthopedic implants and self-powered therapeutic devices, where their mechanoelectric responsiveness provides continuous bioelectric stimulation without external power sources [74]. Collectively, these findings emphasize that piezoelectric ceramics have advanced from bench-top studies to preclinical and early translational contexts, offering a unique strategy to actively regulate cell behavior and tissue regeneration in clinically relevant settings.

Because of its excellent mechanical properties, PSZ is widely considered as a material in the orthopedic and dental fields [121,122]. However, there are two major limitations to the clinical application of PSZ; bioinertness of poorly direct bonding to natural bone in vivo and low temperature degradation (LTD) [123]. The LTD arises from the tetragonal-to-monoclinic phase transformation at a low temperature lower than 400 °C even in humid or steam ambience [121,122]. The polarization was effective in the inhibition of the tetragonal-to-monoclinic transformation of ZrO_2; the phase transformation was more largely depressed after alkaline treatment on positively charged PSZ surfaces than negatively charged and untreated surfaces [121]. Polarization derives O^{2-} from the positively charged to the negatively charged side, resulting in the accumulation of oxygen vacancies on the positively charged side and resultantly the increase of Zr–OH formation when exposed to an alkaline solution. Those formed Zr–OH reduce water adsorption onto the surface, leading to diminish of the Zr–O–Zr bond cleavage.

The bioactivity of PSZ can be provided with combination of electrical polarization with acidic or alkaline treatment [56], as was confirmed by the simulated body fluid tests to evaluate growth of apatite layers on the surfaces. Combining polarization with the chemical treatment promoted the in vitro bioactivity of PSZ with increase of osteoblast adhesion to PSZ surfaces, leading to improved bioactivity. The above-mentioned surface modification can be effectively applied to produce PSZ clinical devices with bioactivity. As seen above, polarization brings mechanical, chemical and biomedical advantages to practical applications.

From materials engineering viewpoint, as introduced above, bone is a highly functional device where minerals are highly organized with biopolymers. Although electrically polarized piezoelectric ceramics have emerged as promising biomaterials with the potential to substantially advance bone regeneration [124,125,44,126], several technological and translational challenges must be resolved before their clinical application can be realized to fully replace the superior bone function. Among these, a pressing concern can be the stability of polarization-induced charges in vivo; surface charges generated by electrical polarization may be prone to decay under physiological conditions due to ion exchange, protein adsorption, and interactions with body fluids, thereby limiting their long-term efficacy [127,4,128]. Regarding the concern, very recent study successfully disclosed the long durability of polarized hydroxyapatite ceramic by an over a decade longitudinal study. As a polarized piezoelectric material can be reasonably considered to comprise of numerous μm-sized grain electrets, protein-covered, dissolution-damaged, or mechanically-cleaved surfaces can be almost originally revived under numerous grain electrets [60].

Also presumed issue is the difficulty in achieving uniform and reproducible polarization, particularly within porous scaffolds or complex geometries, where localized charge inhomogeneities may compromise biological responses. Ceramic biomaterials are usually as porous bodies or granules for clinical uses as artificial bones and teeth, the polarization technique should be analyzed using those complex-shaped specimens. Furthermore, the molecular mechanisms underlying charge-mediated effects remain insufficiently understood. While evidence suggests that surface charges can influence protein conformation, intracellular signaling pathways, and osteogenic activity, the

precise molecular processes remain unresolved, constraining the rational design of next-generation materials. It is actually an overwhelming study to elucidate intracellular signaling pathways, on the other hand, a recent study gives a clue to polarized hydroxyapatite using osteogenic cells [129]. A translational perspective requires long-term safety and efficacy studies regarding chronic tissue responses, inflammatory risks for clinical adoption. International standards for polarization protocols, charge intensity, and evaluation methods will be presented for reproducibility and regulatory approval. Beyond this, applications outside bone regeneration, such as bone–cartilage junctions or soft–hard tissue interfaces will be explored in the future.

Despite these challenges, the outlook is highly encouraging. Advances in nano-structuring and spatial patterning techniques are expected to enable site-specific control of surface charge distribution, thereby allowing precise modulation of bone formation, angiogenesis, and immune responses [130–134]. Combining polarized hydroxyapatite with bioactive molecules, cytokines, or stem cells also holds promise for synergistically enhancing tissue regeneration and integration with host tissues. Importantly, growing insights into charge-mediated immune regulation—such as macrophage polarization and inflammatory modulation—open new avenues for incorporating immune control into regenerative medicine. Looking forward, the application of polarized ceramics is likely to extend beyond orthopedics into dentistry, cartilage repair, and even neural and muscular regeneration. The development of patient-specific scaffolds with tunable microscale charge distributions may further align this technology with the goals of precision regenerative medicine.

The clinical translation of polarized hydroxyapatite ceramics holds considerable promise for improving outcomes in bone regeneration and repair. By providing sustained bioelectric cues, these materials may accelerate bone healing, reduce reliance on autografts or allografts, and minimize complications associated with conventional bone substitutes. Their potential application in challenging clinical scenarios—such as large bone defects, osteoporotic fractures, and revision surgeries—highlights their relevance to unmet medical needs. Beyond orthopedics, polarized ceramics may enhance osseointegration in dental implants, support cartilage regeneration at osteochondral interfaces, and even contribute to neuromuscular tissue repair, thereby broadening their therapeutic scope. However, successful clinical adoption will require not only rigorous preclinical validation but also well-designed clinical trials that establish long-term safety, efficacy, and cost-effectiveness. In this regard, collaboration between material scientists, clinicians, and regulatory bodies will be crucial to accelerate the translation of this technology from bench to bedside.

8. Conclusions

The basic consideration of bone tissue engineering stands on the use of the natural biological responses of the host. Bone tissue utilizes an electrical potential produced by piezoelectricity due to displacement of collagen fibrils, which can be stored as energy both in collagen fibrils and apatite minerals. Such electrical energy stored in apatite minerals are sufficient to stimulate osteogenic cells during bone remodeling. The electrical properties of bone tissue and synthesized apatite indicate that carbonate incorporation in bone minerals is an important factor in determining bone piezoelectricity.

The application of an external voltage can polarize bone tissue as well as synthesized inorganic biomaterials. Electrical polarization improves surface wettability by increasing the SFE, while neither change was observed in the surface roughness, or microstructural elements of grain morphology and crystalline phase. The half periods of the electrical potentials stored in biomaterials are calculated at 10^7–10^{11} years at body temperature. Differences in surface characteristics affect cell behaviors. In piezoelectric scaffolds, an increase in SFE enhances protein adsorption and osteoblast adhesion. Carbonate incorporation in apatite crystals induces osteoclast differentiation from monocytes. Piezoelectric scaffolds could have long-term effects on cell behaviors at biointerfaces. Understanding the interactions between cells and biomaterials will facilitate the design and selection of new biomaterials for implantation to endure the lifetime of recipients.

CRediT authorship contribution statement

Miho Nakamura: Writing – review & editing, Writing – original draft, Resources, Project administration, Conceptualization. **Kimihiro Yamashita:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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

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Data availability

Data will be made available on request.

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