Applications of Piezoelectric smart biomaterials

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Piezoelectric materials have a wide variety of electronic applications such as transducers, actuators and sensors. Moreover, piezoelectric materials have significant applications in tissue engineering as an electro-active scaffold for tissue repair and regeneration. They can deliver variable electrical stimulus without an external power source. The electrical stimulation resulting from piezoelectric scaffold can regenerate and repair the tissues by definite pathways. The piezoelectric scaffolds with optimized properties can produce suitable bioelectrical signals, similar to the natural extracellular matrix (ECM), which has observed during remodeling phenomenon in bone and cartilage .

The electro-active scaffolds are most significant in tissue engineering where the electrical stimulation is relevant for the tissue repair or regeneration, such as, neuronal tissue repair, bone and cartilage repair and regeneration etc. Tissues like bone, cartilage, dentin, tendon and keratin can demonstrate direct piezoelectricity. Collagen is a fiber-like structure and it is major constituent in bone and cartilage, responsible for the piezoelectric property. Due to the piezoelectric property of collagen, it can generate electric signals in response to internal force.

These signals transmitted through ECM to the voltage-gated channels in the cell membrane. Mainly, the osteocyte cells are involved in mechano transduction and they communicate with other cells such as osteoblasts and osteoclasts. The activation of these channels transmits the intracellular signals to the nucleus, leads to the activation of signaling cascades, responsible for the cellular events such as matrix production, cell growth and tissue repair . Hence, the electro-active scaffolds, which mimics the piezoelectric coefficients of natural tissues may be a suitable approach for the repair and regeneration of skeletal tissues like bone and cartilage.

Bone and cartilage are dense connective tissues, which consist mainly cells and extracellular matrix (ECM) (Figure). In general, ECM consists two main cell types immature and mature, the immature cell in cartilage and bone are chondroblast and osteoblast, respectively. Vitally, the blast cells have the capacity to cell division and further it secretes the ECM. Subsequently the blast cells differentiate into mature cells like chondrocytes and osteocytes, in cartilage and bone respectively. Matured cells are mostly encompassing in conserving the matrix and it has limited capacity for cell division and matrix production. Other cells present in the matrix are fibroblasts, macrophages, adipocytes and mast cells.

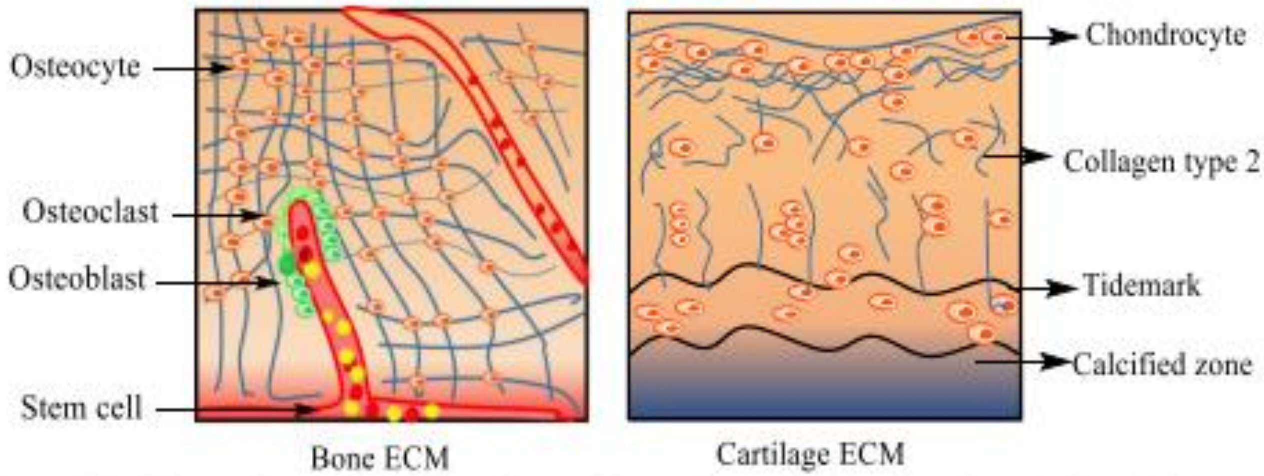


Fig. 1 Illustration shows the highly vascularized ECM of bone (Bone ECM) and avascular ECM of cartilage (cartilage ECM)

The bone

has abundant ECM, composed of 25% water, 25% organic collagen fibers and 50% crystallized mineral salts . The inorganic mineral salts in the form of microcrystalline, such as hydroxyapatite [Ca10 (PO4)6 (OH)2] confer the hardness and mostly rigidity of the bone. The mineral salts like calcium hydroxide and calcium phosphate combined to form centrosymmetric hydroxyapatite nanocrystals, which further combines with other mineral salts and ions such as magnesium, fluoride and manganese. These crystals were deposited in the network of collagen fibers, which further undergoing a process called calcination. The entire process is initiated by bone formation cells (osteoblasts) . Compact bone has mostly type I collagen and has the piezoelectric coefficient approximately 0.7pC/N .

The ECM of cartilage

comprises of collagen (type II, VI, IX, X and XI), proteoglycan, non-collagenous proteins and tissue fluid. Collagen is strong and flexible structure and can resist the pulling forces [18]. Among all, cartilage is compose of 90–95% type II collagen and the primary function is to resist tension [19]. The piezoelectric collagen can influence the cell membrane receptors and ultimately the nucleus owing to electrical charge alterations in response to functional loads .

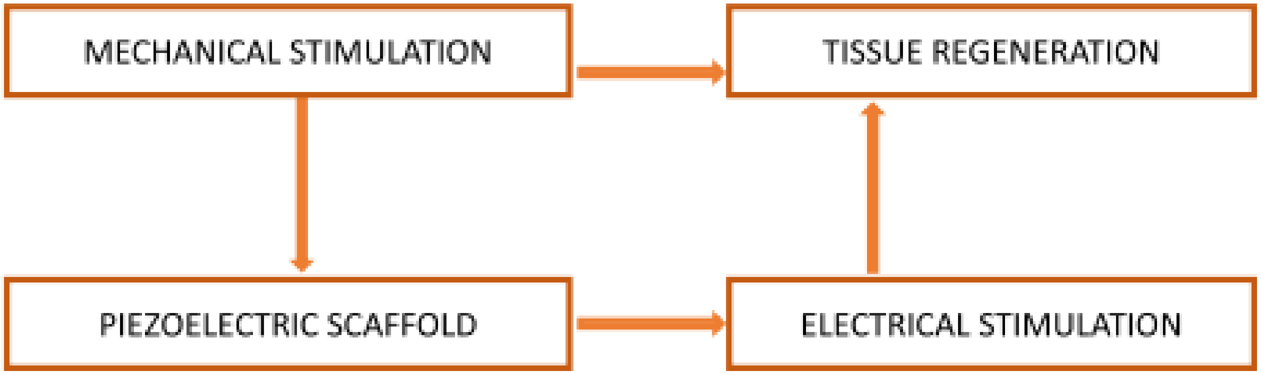
The deformities and injuries in hard tissues like, bone and cartilage can occur, primarily, due to mechanical trauma and various disease conditions. The osteoporosis, paget disease, ricket, osteomalacia, osteoarthritis, osteomyelitis, and osteosarcoma mainly contribute bone degeneration . Cartilage degeneration is primarily, due to gaut, osteoarthritis, acromegaly and alkeptonuric ochronosis .

Conventional therapies include pharmacological treatments such as, estrogens and selective estrogen receptor modulator et al. However, major limitation of the pharmacological therapies are disease dependent, less effective in case of critical degeneration, lack of site specificity and drug associated toxicity . Surgical intervention is an important treatment choice; the major practices are autograft, allograft, xenograft, bone marrow stimulation, mosacoplsty and autologous chondrocyte implantation.

The surgical practices have success rate up to some extent, the major limitations come from; donor site morbidity, due to secondary surgery associated with autograft and allograft. Furthermore, immunogenic rejection and disease transmission as consequence of allograft and xenograft practices. Bone marrow stimulation has poor regenerative capacity and the regenerated cartilage has low biomechanical integrity , the donor site morbidity also associated with mosiacplasty . The autologous chondrocyte implantation is a costly practice and complicated process, it is not recommended for osteoarthritis

Piezoelectricity has shown its strong effectiveness in natural pathways, specifically at the site where the collagen implicated activities. The compressive force on collagen triggers the re-organization of dipole moment and generates negative charges on the surface The generated charge prompts the electrical stimulation to the cells, leads to the opening of voltage-gated calcium channels. The increased activity of intracellular calcium concentration activates the calmodulin, which subsequently stimulates the activation of calcineurin. The calcineurin dephosphorylates NF-AT (Nuclear Factor of Activated Cells), which further translocate into the nucleus, where it binds co-operatively with other transcription factors to regulatory regions of the inducible genes. These genes further induce the translation of several growth factors like Transforming Growth Factorβ (TGF β), Bone Morphogenetic Protein (BMP) etc. which are responsible for the regulation of ECM production as well as up/ down regulation of several proteins and cellular metabolism

In general, tensile/compression forces acting on the piezoelectric scaffolds generates the electrical stimulation and transfers it to the surrounding cells, promotes the cell signaling pathways, responsible for the growth factor synthesis (Scheme 1). The mechanism behind the conversion of mechanical stimuli into biochemical signals remains elusive .It is well evident that the piezoelectric collagen stimulates the cell proliferation (tissue regeneration) by electrical stimuli via mechanotrasduction. The collagen possesses polar hexagonal crystalline unit and it is primarily responsible for piezoelectricity . The literature strongly suggests that the collagen rich bone converts the functional stresses into electrical stimulations for regeneration and remodeling. The electrical stimulation is largely contributes in cell phynotypic change. Mechanical stimulation has some major constrains like, sensitization of bone cell, age related issue like higher the age poor the regenerative capacity



Scheme 1 Representing the tissue regeneration in response to the mechanical stimulation on the piezoelectric scaffold. The mechanical force on the piezoelectric scaffold generates the electrical stimulus for enhanced tissue regeneration. At the same time, applied mechanical stress can simultaneously augments the tissue regeneration in predefined signaling pathways

Piezoelectric bio-materials

To induce piezoelectric property in the scaffold, the best possible way is to select appropriate piezoelectric material; either, piezoelectric polymer or ceramic or polymer-ceramic composite for fabrication of bio-scaffold. Hence, piezoelectric materials are best suits for biomedical applications, where the electromechanical transduction involves. The property possesses to the material due to lack of center of symmetry . The deformation of such materials results in the development of charges of opposite polarity on opposite faces of crystals. Fundamentally this is due to the separation of the center of neutrality of charges on the crystal lattice as the material is deformed along certain axes. The term applies to some polycrystalline, inorganic materials and some inorganic substances . Piezoelectric materials can also be classifies as piezoelectric polymers and piezoelectric ceramics. The piezoelectric ceramics are included in the polycrystalline class . Piezoelectric materials are using either alone or as a composite in tissue engineering.

Piezoelectric polymers

The properties of piezoelectric polymers are different from inorganic crystals, since these possess the advantage of processing flexibility. Mechanically, polymers have high strength and high impact resistance as compared to inorganic materials. Structural requirements of piezoelectric polymers are:

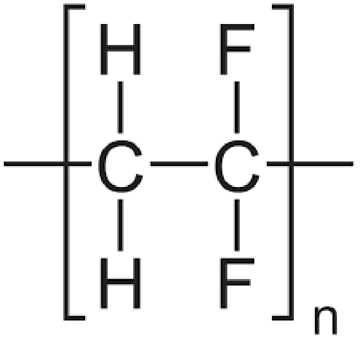
(1) the presence of permanent molecular dipoles.

(2) the ability to align or orient the molecular dipoles.

(3) the ability to sustain the alignment once it is achieve .

(4) the ability of the material to undergo large strains when mechanically stressed . The piezoelectric polymers, which are used in tissue engineering for cartilage and bone as follows:

1- PVDF (poly(vinylidene fluoride)) $C_2H_2F_2)_n$



PVDF is a best known piezoelectric copolymer with the piezoelectric coefficient of 20 pC/N . Due to its high flexibility and non-toxicity, PVDF have been used for a variety of biomedical applications, from tissue engineering scaffolds to implantable self-powered devices . PVDF-TrFE and barium titanate piezoelectric composite membrane has been reported as charge generator to promote the bone regeneration . The piezoelectric PVDF scaffold has been largely promoting the osteogenic differentiation of human adipose-derived stem cells . A novel piezoelectric actuator device based on PVDF has been demonstrated to effectively stimulate the bone growth at the bone-implant interface by the use of converse piezoelectric effect . Furthermore, PVDF and PVDF-TrFE has been reported for neural tissue regeneration. The PVDF is well known biocompatible thermoplastic polymer. It has high chemical and physical resistance. Still when it expose to the extreme alkaline condition it tends to degrade but not suitable for biological environment . However, the PVDF is a non biodegradable polymer which limits its applicability in tissue engineering .

2-Polyamides

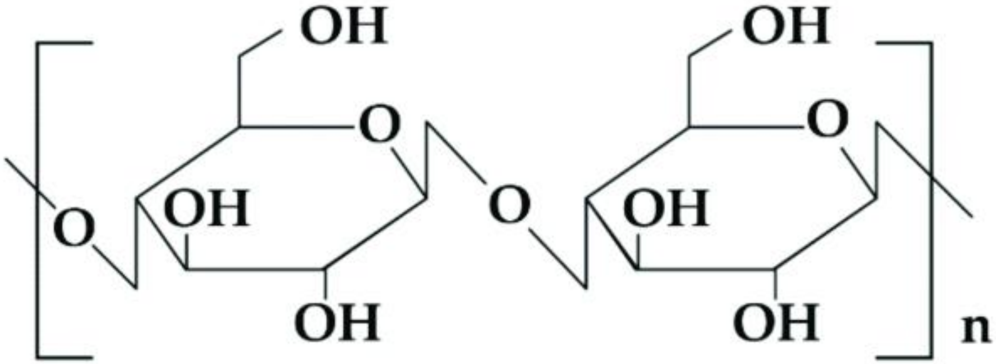
Polyamides and polypeptides possess piezoelectricity by odd numbered Nylons and peptide (CONH) bonds, respectively . Odd nylons (nylons-5, nylons-7) contains even numbered methylene groups and one amide group on each monomer unit. Due to the presence of one amide group, odd numbered nylon results net dipole moment (3.7 D) . The piezoelectric polarization proceeds as a consequence of the stress-induced internal rotation of the peptide bonds [83]. The piezoelectric coefficient (d31) for nylon is 3 pC/N at 25 °C and 14 pC/ N at 107 °C . Wang et al., have been reported that polyamide-hydroxyapatite composite promotes the osteogenesis by 12 weeks of implantation . Also studies had been reported that the polyamides are applicable for cartilage repair or regeneration as a polymeric matrix. But proper modifications are required to promote the cell attachment and proliferation of chondrocytes . Lack of degradation pattern of the polyamides has limited applications in tissue engineering.

3- Natural polymers

Biopolymers Natural polymers are gaining more importance in tissue engineering because of their degradability and low toxicity. More than that, the polymers have offer biological signaling, cell adhesion, cell responsive degradation and remodeling . Meanwhile, their use as a unique scaffold material has often compromise owing to their inadequate physical properties, together with the possible loss of biological properties during formulations. Moreover, appropriate screening and processing are required to avoid the disease transmission and immune rejection. While suitable chemical or physical processing will help to overcome these issues

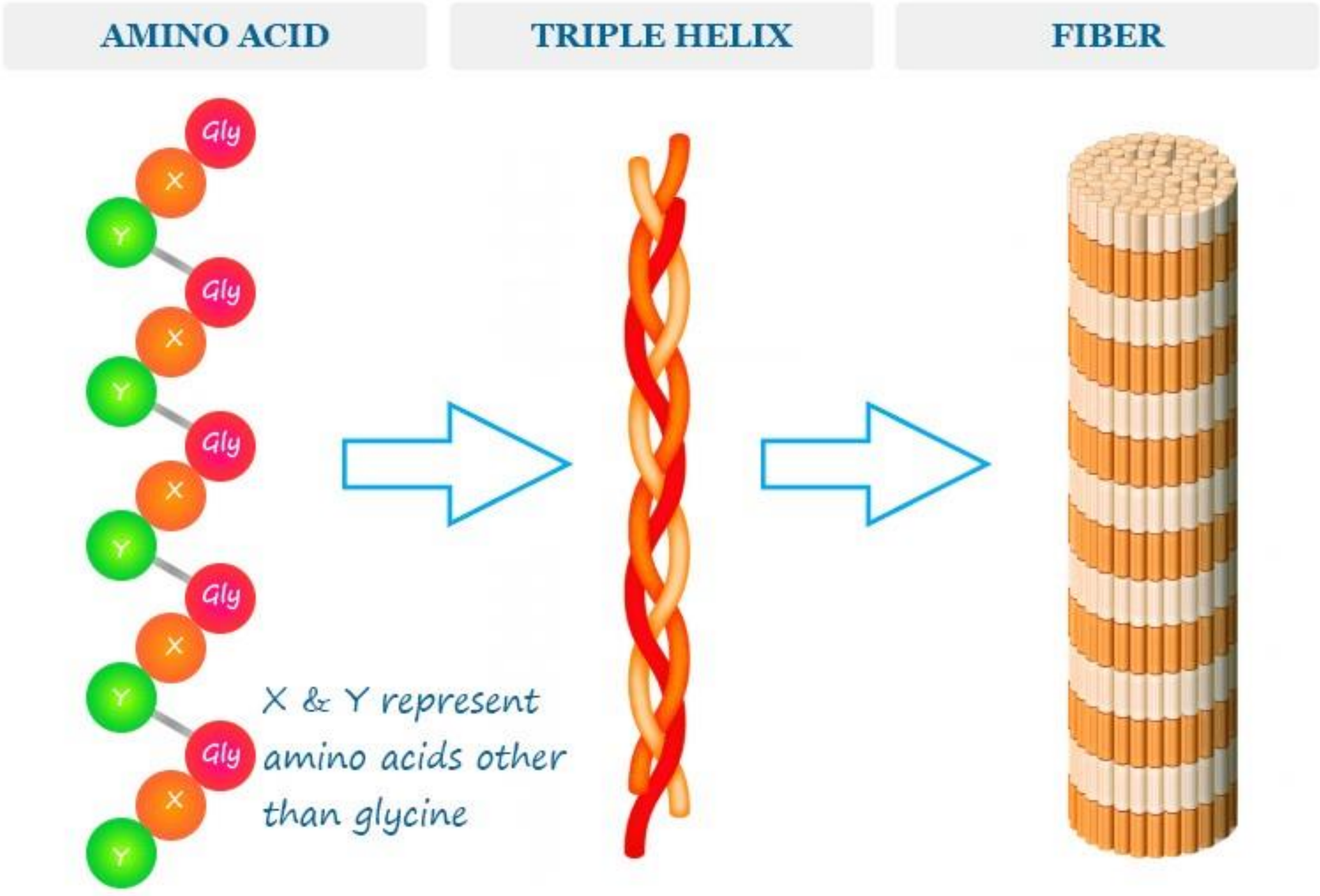
A) Cellulose

Cellulose is the most abundant natural polymer on earth . it is made up of un branched chains of glucose molecules linked via beta 1-4 glycosidic bonds and it has a piezoelectric property with a shear piezoelectric coefficient (d14) 0.2 pC/N . It has large number biomedical applications, due to excellent biocompatibility, high tensile strength and impersonates with biological environment, despite its water content and nanofibrous structure. While, it has a small pore size or the dense mesh formation of fibers limits the cell infiltration. However this can be overcome by the incorporation of proper porogens. Moreover, studies have been demonstrated that the ability of cellulose to promote cellular adhesion particularly chondrocytes, osteocytes, endothelial cells and smooth muscle cells [89]. Hence, it is appropriate piezoelectric material for both bone and cartilage tissue engineering



B)Collagen

Collagen is a biological protein has three parallel polypeptide strands in a left-handed, polyproline II-type (PPII) helical conformation coil about each other with a one-residue stagger to form a right-handed triple helix and vital component of the ECM like bone, cartilage, tendon, teeth and blood vessels, where it responsible for the structural and mechanical support. It is a natural piezoelectric material with piezoelectric coefficient ranges from 0.2 to 2.0 pC/N . Additionally, it is suitable as a biomaterial in tissue engineering due to its biocompatibility, good cell binding properties, hydrophilicity, low antigenicity, absorbability in the body etc. . The researchers had been reported the application of collagen scaffold in bone healing . Similarly the collagen-hydroxyapatite piezoelectric composite scaffold has been proved as a suitable structure for cellular growth and bone healing . Also the collagen-calcium phosphate composite scaffolds are reported for cartilage tissue engineering. Studies with collagen-calcium phosphate composite scaffolds are demonstrated the average filling ratio of the defect area with the newly formed cartilage tissue at week eight and twenty is about 81% and 96%, respectively [80]. However, it has certain limitations like low mechanical stiffness, rapid degradation and toxicity by addition of crosslinking agents.



Structure of Collagen

C) Chitin

Chitin is a natural polysaccharide and is the structural component of the cuticles of crustaceans, insects and mollusks. It has a piezoelectric structure with piezoelectric coefficient ranges from 0.2–1.5 pC/N depending upon its source . Chitosan is a polymer which is obtained by the de acetylation of chitin, has a number of biomedical applications such as wound healing and carriers for controlled drug delivery etc. . By making it composite with other suitable filler components it is suitable for bone and cartilage regeneration. Chitin largely favors for biomedical applications, since it is a hydrophilic material, which promotes cell adhesion, cell proliferation, differentiation and it offers well biocompatibility . But, low mechanical properties and inability to maintain predefined shape, limits its use in tissue engineering particularly for hard tissue applications.