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Piezoelectric material – A promising approach for bone and cartilage regeneration

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ABSTRACT

Bone and cartilage are major weight-bearing connective tissues in human and possesses utmost vulnerability for degeneration. The potential causes are mechanical trauma, cancer and disease condition like osteoarthritis and osteoporosis, etc. The regeneration/repair is a challenging, since their complex structures and activities. Current treatment options comprise of auto graft, allograft, artificial bone substituent, autologous chondrocyte implantation, mosaicplasty, marrow stimulation and tissue engineering. Were incompetent to overcome the problem like abandoned growth factor degradation, indistinct growth factor dose and lack of integrity and mechanical properties in regenerated tissues. Present, paper focuses on the novel hypothesis for regeneration of bone and cartilage by using piezoelectric smart property of scaffold material.

Introduction and background

The discovery of pyroelectricty [1] has shown path for transduction of energy. The first piezoelectric effect has been reported by Curie brothers in 1880 and name given from Greek word *piezein* means pressure [2,3]. Deformation of material by mechanical stress transduces into electrical energy is called piezoelectricity also known as direct piezoelectricity. In similar fashion, converse piezoelectricity is defined as electricitrical energy is tranasduced into mechnical deformation in material. The spectacle is first observed in many materials like, tourmaline, quartz, topaz, cane sugar, and Rochelle salt [4].

A piezoelectric material has broad applications comprise from very common applications such as tourmaline crystal used in household lighter [5], piezoelectric generator for wireless devices, etc. [7] and advanced applications like electromechanical SONAR transducer [6]. Apart from this, it has an extensive biological applications primarily piezoelectric composite transducer for diagnostic ultrasonography [8,9], Quartz Crystal Microbalance for immunological biosensors [10] and Ultrasonic nebulizer for pulmonary drug delivery system [11]. In humans, some tissues contain piezoelectricity and play a significant role mainly, bone containing piezoelectric collagen fibers and regulate the continuous stress-induced modifications [12]. Human dry skin containing collagen which is piezoelectric in nature [13]. Piezoelectric collagen type II is major constituent in articular cartilage, and it plays a significant role in regeneration/repair of the damaged cartilage [14].

Currently, medical fraternity faces unadorned problem for a degenerative disorder such as articular cartilage generation due to trauma, mechanical loading and disease like osteoarthritis (OA). Further, significant degenerative diseases include the bone degeneration; neuronal degeneration has a limited treatment option since treatment is the critical and regenerative capacity of these complex tissues are destitute [15].

Bone is an essential part of a musculoskeletal system, and it comprises of Extracellular matrix (ECM) and osteogenic cells. Basically, ECM consists of organic and inorganic materials, which includes flexible collagen maintains flexibility of bone and inorganic hydroxyapatite (HA) provides the strength. Osteogenic cells which are derived from a common type of mesenchymal stem cells (MSCs), particular osteoblast helps to bone formation, osteoclast responsible for bone reabsorption and the mature osteocytes assist the bone tissue the maintenance [16]. Bones are continuously remodel depending upon the application of a mechanical load to bear the stress [17]; more the mechanical load more the accumulation or reabsorption of an inorganic material and stronger the bone up to the certain limit [18]. Bone becomes porous when the application of stress or force is less or person is on resting stage [19,20]. Degeneration of bone takes place due to the mechanical fracture, osteoporosis, osteoarthritis, osteogenic sarcoma, and osteopenia, etc. [16], although blood supply is normal to still bone formation is slow. Common treatment options for bone regeneration/repair includes autograft substitution, but the limitations are

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morbidity and poor bone growth and further allograft implantation leads to serious immunological reaction and high rejection [21]. Besides the grafting, the most prominent treatment is ceramic scaffolding HA and Tricalcium Phosphate (TCP) due to lack of mechanical properties the success rate is limited.

The latest approach for bone regeneration is tissue engineering and growth factor based treatment, but the stability of growth factor is a critical issue and poor regenerative capacity of cells [22].

The articular cartilage is also one of the connective tissue as a bone in the skeletal system. Cartilage is a complex avascular and aneural type of tissue with about 2–4 mm thickness. Hence, it has low regeneration capability, due to an inadequate supply of nutrients. Unlike bone, it is composed of the specialized type of chondrocyte and chondroblast cells and ECM. ECM provides a microenvironment for cell–cell interaction, cellular proliferation, signal transduction. It also provides sponge-like structure to hold the different functional forces such as hydrostatic force, compression force, shear force, piezoelectric and electric force during stress transfer at joint without deformation [23,24]. EMC is composed of different component those are water which is near about 80% along with some trace ion includes sodium, potassium, calcium, and chloride [25]. Another major component is collagen especially type 2 collagen is major other are Collagen types I, IV, V, VI, IX, and XI in a minor [26]. Degeneration of the cartilage takes place due to the disease like OA, rheumatoid arthritis, and mechanical trauma; the treatment is very crucial since its complex structure [27].

Hypothesis

Regeneration/repair of skeletal tissues are multifaceted practice, since their complex structures and functionalities. Although, there are advanced treatment options to treat the damaged tissues, but the competence is not absolute. Primarily uncontrolled growth factor degradation, complicated growth factor dose optimization procedure, commercial viability and lack of integrity and mechanical properties in regenerated tissues are largely limited the attainments of the existed treatment options.

The proposed hypothesis may shows an alternative route for speedy regeneration of tissue in natural way by utilizing smart property of the material. The idea behind this strategy is to prepare a three dimensional piezoelectric biocompatible scaffold for regeneration of the tissue without addition of stimulating factors. The smart piezoelectric scaffold is subjected the predefined damaged site (Fig. 1), where the scaffold is experienced functional loads of the subject. The smart scaffold converts the functional stress into electrical signals by piezoelectric phenomenon. The generated synchronized electrical stimuli can modulate the Ca^{+2} channels, further it can enhance the synthesis of various molecules for rapid regeneration of the damaged skeletal tissue. Significantly, the natural negative feedback mechanism can control the regenerative mechanism.

Evaluation of hypothesis

Structurally bone is very complex and vascularized unlike cartilage; it composed of cells and ECM. Bone undergo continuous modification by the formation of osteocyte layer and reform depends upon the nearby environment. Bone is form by two methods: endochondral and intermembranous bone formation. In enchondral, bone formed from the native cartilage tissue with the various predefined sequential event and membranous, bone formed from the fibrous tissue rather than cartilage [28,29].

Remodeling of bone takes place under the activity of osteoclast and osteoblast in response to various stimuli such as mechanical stimuli, electrical stimuli, enzymatic activity, growth factor and different cytokines [30,31]. Osteoblasts and osteoclasts are responsible for bone formation and reabsorption, respectively and thereby control the bone remodeling. Bone deformation or fracture can happen due to various events like mechanical trauma, osteoporosis, osteomalacia, osteogenic imperfect, Paget disease, mineral imbalance and metabolic disorder [32].

Although bone has an intrinsic capability to regenerate and repair in response to the damage to some extent, it needs some clinical interventions for crucial complications. Bone substitution is one of the best practices for complex problems in which bone or artificial graft is implante at the damaged site [33]. The artificial graft material must have osteoconduction, osteoinduction and osteointegration property. In autograft bone or part of the bone has been transplanted in same patient and autograft is the gold standard technique. The major limitations for the autograft are less availability and donor site morbidity. Allograft is another most accepted practice, bone or part bone is collected from living, or non-living human for implantation. It provides good success rate, but it leads to distressed osteoinduction property due to the absence of growth factor, it also possesses immunogenicity effects and high rejection, further allograft spell infectiousness diseases like HIV and HBV, etc. [34]. Xenograft is similar to the allograft, but it was taken from other than human. The xenograft is prepare from Bovine bone which is freeze-dried or demineralized and deproteinized before clinical use. The principal problem with xenograft is poor osteoinduction, mechanical failure, immunogenicity and post-surgical infection [35,36].

Artificial bone substitute

Artificial bone substitute contains biomaterial that mimics the biological environment and stimulates the bone regeneration. It includes polymers, ceramics, blends and composite materials [37].

Some of the marketed product listed here are Healos® from Depuy; it contains HA and the collagen. Cortoss® which used at load bearing site and Rhakoss® used in spinal application both are resin based formulations [38]. Widely used biodegradable synthetic polymers are polyanhydrides, polypropylene fumarate, polycaprolactones (PCL), polyphosphazene, polylactide, polyglycolide, and associated copolymers (polylactide-co-glycolide) [39].Ceramic materials include Calcium phosphate, calcium silicate, calcium carbonate and bioactive ceramic like HA and bioglass [40,41]. Calcium hydroxyapatite and β-TCP is an excellent bond substitute and can be used for bone filling in autograft and allograft [41]. β-TCP is formulated in various form such microspore for regeneration of irregular tissue [42]. It is well documented that the significant structural and functional variations were observed in ceramic based bone substitute with respect to natural bone, and further it leads to various complications [42,43].

Tissue engineering approach

Currently, the tissue engineering is the most promising approach to regenerative medicine. It includes cell-based and growth factor-based therapy. Cell-based therapy includes stem cell Mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), adult stem cells, induced pluripotent stem cells (iPSC) embedding directly to damaged site [44]. Precise growth factors like Bone morphogenetic protein (BMP) specifically BMP-2 and BMP-7 (recombinant BMP-2 and Recombinant BMP-7) are added to the cells for the stimulating action of osteoinduction and ultimately regenerate the bone in a rapid manner [45,46]. Supplementary growth factors like Angiogenic, Transforming growth factor- α (TGF-α) and vascular endothelial growth factor (VEGF) also play a critical role in bone regeneration as well [47]. Even though the approach has offered