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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

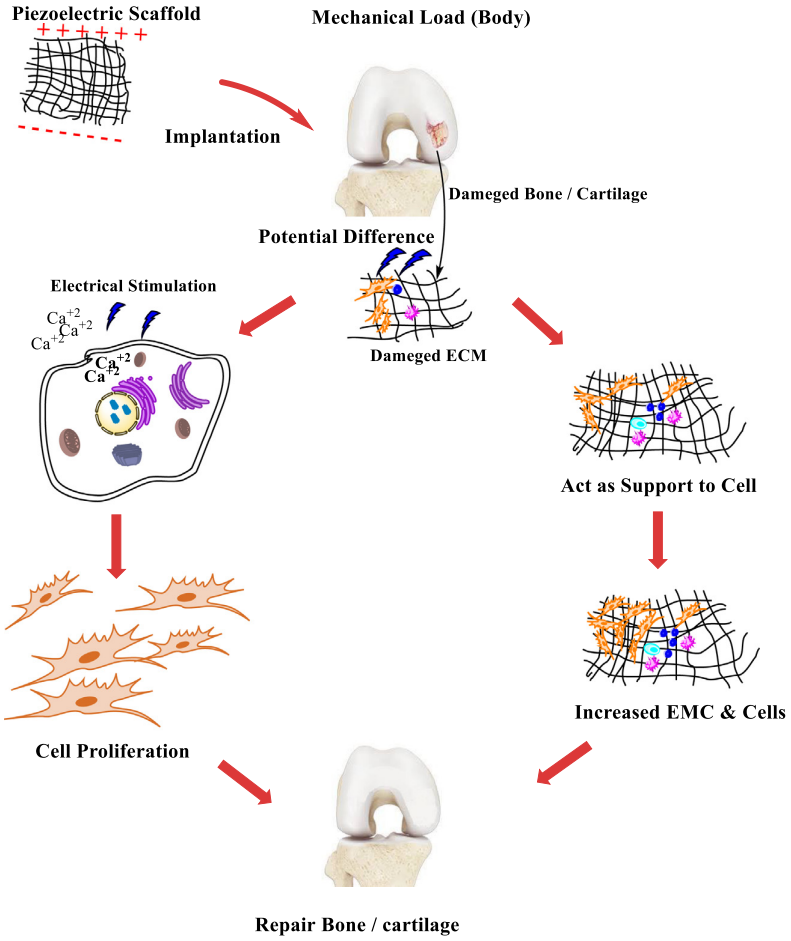

Fig. 1. The illustration show the possible mechanism of the proposed hypothesis; initially, the piezoelectric scaffold is implanted at the damaged skeletal tissue. The functional loads on the scaffold generates the electrical stimuli by piezoelectric phenomenon. Further, the electrical potential stimulates the activity of the Ca^{+2}- calmodulin pathway. Thereby, enhanced synthesis of biomolecules for rapid regeneration of damaged tissue.

huge advantages over conventional strategies, but it demonstrated deprived regenerative capacity and stability issues [48].

The application of piezoelectric mechanism in biomedical technology may produce radical outcomes. The rationale behind is when functional loads applied on the piezoelectric scaffolds can produce electric stimuli [3]. Various mathematical models have developed for the cell and cell-based piezoelectric scaffold by the consideration of elasticity tensor, dielectric tensor, and piezoelectric coupling tensor [49]. HA is one of the primary components of bone and HA-$BaTiO_3$(Barium Titanate) composite has been demonstrated enhanced biocompatibility and osteoinduction. Interestingly, increased the percentage of $BaTiO_3$ has shown improved D_{33} without any toxic effect [50].

Further, significant enhancement in mechanical strength and piezoelectric coefficient has been observed in PCL composite with the addition of three different perovskite fillers (calcium titanate, strontium titanate, and barium titanate) and the composite was demonstrated improved osteoblast proliferation [51]. Moreover, Poly(vinylidene fluoride-co-tetrafluoroethylene (PVDF-TrFE) and $BaTiO_3$ composite have shown better osteoinduction and osteogenesis as compared to the pristine polymer. Besides, the composite membrane has shown increased tensile strength, piezoelectric coefficient and bioactivity [52].

Numerous research takes place in this area in future piezoelectric biodegradable and biocompatible biomaterial by designing 3D prototype can be used for regeneration of bone by stimulating the natural mechanism of bone regeneration and remodeling with the advantage of the fulfillment of excellent osteoconductive, osteoinductive and osteogenic property without need cells and growth factor.

Cartilage regeneration

As articular cartilage is a particular type of hyaline cartilage major function is load bearing and lubrication of articulating surface. Articular cartilage is avascular, alymphatic and aneural tissue has the poor regenerative capacity, due to lack of nutrients supply. Structurally it is similar to bone, composed of EMC and cells. Major components of the EMC are water, collagen and proteoglycan which play a vital role in the maintenance of biomechanical and biochemical functions. Cartilage is secreted from specialized cells called as chondrocytes [53,54]. It is derived from the mesenchymal stem cells and is responsible for maintenance of turnover of the ECM. It is highly sensitive for various stimuli such as hydrostatic force, compression force, mechanical loading and piezoelectric stimuli. Another important characteristic of the chondrocyte is, it has limited replication potential due to its weak intrinsic regeneration capacity [55].

Structural morphology of articular cartilage consists of four type of zones (Fig. 2) namely superficial zone, transitional zone, a

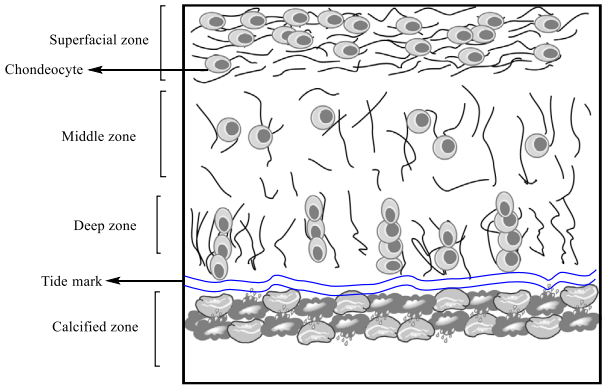

Fig. 2. Structure of Articular cartilage.

middle zone and calcified zone; these zone are structurally as well as functionally differ from each other. The superficial zone is uppermost fine and thin layer zone, and it occupies 10–20% of total cartilage. The primary function of the zone is to protect the inner layer from the shear force and due to its function cells are arranged in flattened in shape. Tightly arranged mess like the structure of collagen fibers has offered strong tensile, compression and shear strength to cartilage to resist the mechanical damage. The superficial layer is filled with a synovial fluid called Lubricin.

Below superficial zone immediate middle zone, it acts as a sandwich between superficial zone and deep zone. The key role of the zone is to provide resistance to compressive force by some structural specificity i.e. spherical shape and large diameter chondrocytes are arranged randomly in collagen fibers along with the high concentration of proteoglycans.

Cells with low density arranged columnar and parallel to the collagen fibril in deep zone provide strong resistance to compressive force. High-density collagen fibers are aligned perpendicular to the articular surface and it has high concentration proteoglycan and low water content. The line called tide mark distinguishes the calcified zone to the deep zone and it has particular affinity to basic dye such as toluidine. Mineralized Zone presents immediate to tide mark and it contains a metabolically less active subtle volume of cells [56–58].

Cartilage damage/injuries are classified into three categories, the first category is subchondral bone damage which is invisible mechanical disruption of the articular surface. The second one is articular surface damage; it confines to the articular surface and third is destruction of both surface and the subchondral bone [59,60]. Chondrocytes are responded to mechanical disruption and try to repair the damaged site but have limited capacity. The biochemical and chemical agent associated with the disease also damages the cartilage includes gaut, osteoarthritis, acromegaly and alkeptonuric ochronosis [61].

Regeneration of cartilage is very crucial and critical treatment option for the cartilage injury/ disease as follows:

Pharmacological & non pharmacological treatment

In general, based on the disease condition, first it treated with nonsurgical procedures. Non-pharmacological treatments are orthotics, local temperature modulation, exercise and physical therapy. Pharmacological treatments include anti-inflammatory,v iscosupplement, and corticosteroid. These treatments are symptomatic therapy also it has drug-associated side effect as well as it can not stop the further degeneration of the cartilage [62].

Surgical treatment

Bone marrow stimulation

Bone marrow stimulation has been created by debridement, drilling, spongialization and microfracture. The main motive behind these techniques is to make migration of the cell to damaged site to repair the tissue [63]. In microfracture practice, the damaged cartilage is removed completely and make a small microfracture at the subchondral bone. The subchondral bone microfracture initiate the cartilage regeneration, but it is reported that the generated cartilage has deprived biomechanical properties as compared to the original [64,65].

Mosaicplasty

The technique has been being administrated for osteochondral and subchondral defect regeneration since 1993. The chondral defect is filled with an osteochondral cylindrical structure called mosaicplasty osteochondral. The cylindrical tissues are collected from healthy cartilage of the same patient, but donor site morbidity and lack of further integrity lead to the poor attainment of the practice [66].

Autologous chondrocyte implantation (ACI)

It is the first cell-based therapy introduced by Gothenburg in 1984. In ACI the chondrocyte from healthy cartilage of the patient has been isolated and cultured in the laboratory under aseptic conditions. Subsequently, the cultured cells have injected into chondral defect site and it is covere with a periosteal patch. The process is not recommended for osteoarthritic subjects since ACI is highly prone to rapid degeneration. Today, various scaffold based technique were developed described under cell-based therapy [66–68].

Tissue engineering

Tissue engineering for cartilage regeneration has immense impotence, due to its rapid regeneration capability at avascular tissues and it has practiced with various additives such as drug molecules, growth factors and other stimulations. Different strategies are applied to regenerate the cartilage like chondrocyte derivation at the site of interest to repair the tissue by MSCs implantation with the suitable scaffold. Significant extracellular matrix production has been reported in rabbit model by implantation of *in vitro* cultured MSCs in gelatin sponge scaffolds, without immunological reactions [69].

Karkhaneh et al., are developed a mathematical model for growth factor release to relate the synthesis of glycosaminoglycan with respect to polymeric microsphere degradation [70].

Mechanical stimulation (compression of 1.27 ± 0.04 MPa) has well demonstrated the enhanced synthesis of proteoglycans and greater expression of SOX9 and COL2 In PCL and Polyvinyl alcohol (PVA) blended scaffold cultured with MSCs [71]. Besides, the scaffold has shown complete degradation in 30 days at physiological conditions. Similar kind of study has been reported by Merlin Rajesh Lal et al. [72], BMP-2 supplemented chitosan-agarose base scaffold has been cultured with Wharton's Jelly-Mesenchymal Stem Cells (HWJ-MSCs), and it has shown immense increment in chondrogenic potential.

Bone marrow derived Mesenchymal stem cell (BMSCs) are differentiated into chondrocytes when BMSCs are cultured on transforming growth factor- β1 (TGF β1) implanted 3D sodium alginate gel and consequently repair the damaged cartilage [73].

Increases proteoglycan synthesis has been observed by Davisson et al., [74] when chondrocyte-seeded that polyglycolic acid (PGA) scaffold was subjected to static and dynamic and force. Alike, substantial escalation of collagen and proteoglycan synthesis has reported in cell-seeded PGA scaffolds are subjected to low shear force [75]. A similar study is carried out by Mauck et al., with the application of the compression force on chondrocyte-based agarose scaffold wich shows that increase in the concentration of sulfated glycosaminoglycan and hydroxyproline concentration [76].

In recent times, there is a hand full of literature has been published on growth factors mediated tissue engineering. Blunk. T et. al. are documented that increased ECM production in bovine calf articular cartilage [77], formerly growth factor-supplemented (insulin-like growth factor (IGFI), interleukin-4 (IL-4), TGF β1 or platelet-derived growth factor (PDGF) PGA scaffold are cultured with Sieminski chondrocytes. Similar kind of results has been observed in PGA scaffold are supplemented with BMP-2 [78] BMP-4 as explant [79] and transfected BMP-7 with alginate [80].

The existed or reported methodologies have certain limitations. primarily, abandoned growth factor degradation, indistinct growth factor dose [81,82], lack of integrity and mechanical properties in regenerated tissues in cell-based therapies [83].

For better quality of treatment, it is essential to go for alternative strategies to counter the problem. In modern science, one of the best tools is the utilization of smart properties of material for regenerative medicine. The piezoelectric mechanism may be the best possible strategy to stimulate the regeneration of complex tissues like bone and cartilage. The piezoelectric scaffold at the site of damage experienced functional loads of the subject and generated electrical potential difference by piezoelectric effect [52]. The potential difference may further interact with cells and thereby stimulating the certain pathways by their signal amplitudes [84]. Certainly, the same phenomenon may regulate the bone remodeling and tissue regeneration by utilizing natural piezoelectric tissues [12], but the exact phenomenon is not yet established. While it was reported that piezoelectric collagen fibers promote the chondrocytes to generated the cartilage [17]. Considerably, a certain amount of electrical stimulations is activated the voltage-gated calcium channel of chondrocytes. The active channels promotes the influx of extracellular calcium and further activates the calmodulin, subsequently calcineurin and then dephosphorylation of a nuclear factor. Eventually, the action leads to expression of genes which are responsible for growth factor such as BMP-2, TGF-β, etc. synthesis. The secreted growth factors are responsible for regeneration of cartilage, Fig. 3. Shows the complete pathway for electrical and mechanical stimulation leads to growth factor synthesis [84]. Hence, the analogy of electrical stimulation to the synthesis of cartilage is best possible in the piezoelectric smart scaffold. The scaffold can absorb the functional stresses of the body and generate the electrical stimuli to activate the calcium channels.

The best conceivable procedure is implantation of the 3D piezoelectric scaffold at the damaged site. There are adequate number biocompatible ceramics and polymers are available to formulate the scaffold with proper physical and mechanical properties for the different biomedical application. The proposed hypothesis doesn't require any stimulating factors such as growth factors, drugs and biomolecules etc. Therefore, the strategy may be the best alternative for conventional therapies to repair/ regeneration of complex tissues like bone and cartilage.

Perspective

The proposed strategy has potenial advantages over the conventional stratageis. primerly, the mecahnisam adopts the natural

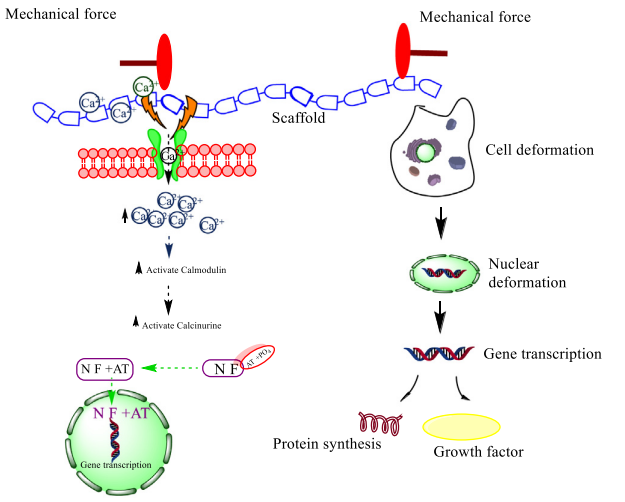

Fig. 3. Mechanism of stimulation cartilage regeneration by using piezoelectric scaffold.

pathway, methodology is highly cost effective and requres minmal surgical intervention. Numarous piezolectric biocomatable materils such as PVDF-TrFE, Poly(3-hydroxybutyrate-co-3-hydroxyvale rate), PCL and different perovskite (calcium titanate, strontium titanate, and barium titanate) can be subjected to biomedical applications. Moreover, there are numerous techniques for scaffold development like electrospinning technology, freez drying, sol–gel method, solvant evaporation and salt leaching method can be utilized for the three dimensional scaffolding. However, the critical part of the methodology is selction and fabrication of the scaffold for particular application. Therfore, the smart piezoelectic property of a material can show huge impact on regenarative medicine in an effectve manner.

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