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Short Communication

Biophysical Stimulation for Bone Regeneration

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Tissue engineering involves the restoration of tissue structure or function through the use of cells, scaffolds, and regulators to stimulate growth [1]. The central paradigm in bone tissue engineering involves the use of a biomaterial scaffold, which can include osteoprogenitor cells and growth factors to stimulate bone growth. Tissue on this scaffold can be grown *in vitro* and then implanted (red route, Figure 1), or it can be directly implanted to facilitate bone regeneration *in vivo* (black route, Figure 1). A major goal in the design of this formulation is to promote healing by recreating the bone tissue microenvironment, which is responsible for regulating the osteoprogenitor cell function to maintain homeostasis [1]. Essential to this micronenvironment are stimulating factors that promote the osteoinductive capacity of the scaffold and which include biochemical, mechanical and electromagnetic stimuli. There have been significant efforts in the past decade to develop tissue engineering strategies based on this paradigm to regenerate bone tissue damaged as a result of injuries or conditions such as caneurysmal bone cysts, enchondroma and congenital pseudarthrosis [2]. This has required the formation of multi-disciplinary teams that apply principles of engineering and the life sciences to restore tissue structure and function. Although there have been progress in delivering these solutions to the clinic, the promises of tissue engineering 20 years ago have still to come. There is high urgency for tissue-engineered products which can achieve these expectations [3,4]. One of the essential components of the bone tissue microenvironment is biochemical and biophysical stimulation that promote the osteoinductive capacity of the scaffold. Most efforts have focused on the delivery of exogenous biochemical stimuli such as growth factors. Effective delivery of these biochemical stimuli has proven a challenge because of loss of bioactivity, limited control over dose administration, non-targeted delivery, and lack of availability of required growth factors [5]. An area in bone tissue engineering that has not been given the proper attention is the application of biophysical cues, such as the forces that result from weight-bearing exercise or the application of electromagnetic fields. This has prompted an opportunity in the search for mechanical and electromagnetic stimulatory alternatives for bone tissue regeneration.

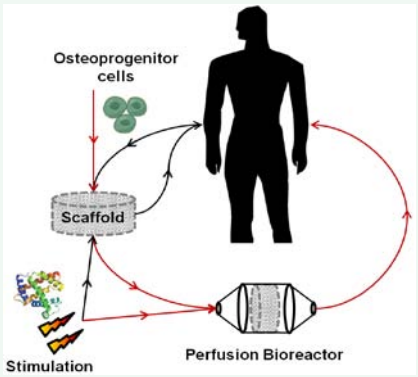

Figure 1 The bone tissue engineering central paradigm.

Mechanical stimulus is part the bone tissue microenvironment and it is essential for maintaining bone health and homeostasis [6]. The process by which cells transduce these force-induced signals into biochemical responses is known as mechanotransduction and it leads to variations in gene expression, cell function and morphology, and extracellular matrix (ECM) remodeling. Bone tissue consists of a network of osteocytes, osteoblasts and osteoclasts, where the first serve as sensory cells responsible for mechanotransduction, while the others function as effector cells involved in bone remodeling. When a load is applied to bone it causes pulsatile fluid flow through the microscopic canals between the lacunae of ossified bone where osteocytes reside. The shear stress and mechanical strain generated by this flow is sensed by the cells, which then through paracrine signaling modulate osteoclast and osteoblast bone remodeling [7]. Here the mechanical strain is due to hydrostatic pressure and compression and relaxation of the ECM, while the shear stress on the surface of the cells is due to the pulsatile fluid flow [8]. A problem in simulating this effect is that since bone loading and unloading *in vivo* generates all of these forces concurrently, the effects of transient pressure waves cannot be separated from those of fluid shear stress or cell strain. This is especially relevant for bone tissue engineering constructs consisting of 3D scaffold seeded with osteoprogenitor cells that require the use of perfusion bioreactors to impart these compressive or tensile loading mechanisms to stimulate the production of ECM prior implantation [9].

Efforts towards understanding the effect of these mechanical forces include the application of cyclic hydrostatic pressures [10,11], fluid shear stress [12], and more recently the stimulation mechanosensitive membrane receptors using magnetic nanoparticles [13]. A shared result by all these studies is that

cell response is affected by the intensity and duration of the mechanical stimuli. It is clear that the underlying signaling mechanisms are complex and that development of a mechanical stimulation device for clinical applications is yet to come. This is due to the limited understanding of the signaling events involved, and to the complexity of this varied and dynamically changing mechanical environment. Further investigations on the effect of stimuli intensity and duration are needed to allow the development of therapies that will allow clinical applications.

Early studies related to the effect of mechanical stress on the electrical properties of bone demonstrated that compression caused a negative potential between inserted electrodes, which lead to bone resorption, while tension generated a positive potential, which lead to bone growth [14,15]. These findings lead to the development of different methods for electrical stimulation of bone: direct current, capacitive coupling, and inductive coupling [16] (Figure 2). Direct current stimulation is an invasive procedure, which involves the surgical placement of electrodes, with the cathode placed in the defect and the anode place in proximate soft tissue. Although bone growth has been demonstrated using currents between 5 and 100 μA, because of the invasive nature of the procedure, direct current stimulation has the risk of infection and tissue reaction [17]. Capacitive coupling is a non-invasive procedure that consists of electrodes placed on top of the skin across from the defect or fracture. Bone growth has been demonstrated using potentials of 1-10 V at frequencies 20-200 kHz, which generate electric fields of 1-100 mV/cm [17]. Another non-invasive procedure is inductive coupling, which enhances bone healing by using electromagnetic fields generated using Helmholtz coils placed across from the defect or fracture [18]. These electromagnetic fields are induced at right angles to the coil base by the electricity passing through them. The stimulation of bone growth has been shown using electromagnetic fields 0.01-2.0 T in strength with electrical field of 1-100 mV/cm at the fracture site [19]. In addition to the stimulation of bone growth, low-frequency pulsed electromagnetic fields (PEMF) have been shown to induce vascular growth [20]. The have also been shown to increase the expression of the osteogenic transcription factor Runx-2 and a decrease of the expression of the adipogenic factor PPARγ in mesenchymal stem cells, which are co-repressed [21]. This effect is especially significant when considering that the balance between these cell populations is believed to be related to diseases such as osteoporosis and diabetes [22]. At the cellular level, low-frequency PEMF stimulation is thought to modulate the expression level of endogenous osteogenic cytokines and their

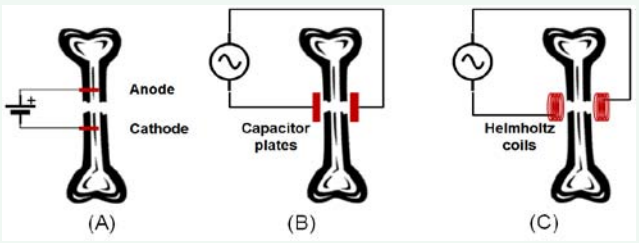

Figure 2 Electrical stimulation methods: (A) DC current using two electrodes and a battery, (B) capacitive coupling using two capacitor plates, and (C) inductive coupling using Helmholtz coils and a power source.

receptors [23-25]. Although similarly to mechanical stimulation, the underlying mechanisms involved in this type of biophysical stimulation are complex and remain elusive. There is high urgency in developing tissue-engineered products that can be brought to the clinic for bone regeneration applications. The development of non- to minimally invasive biophysical stimulatory methods shows great potential in being able to answer this call and should be explored more closely, keeping in mind that the importance of understanding the underlying cellular processes involved.

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