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Short Communication

Mechanisms of Extra Low Frequency Electromagnetic Field (ELF-EMF) on Human Bone Marrow Stem/Stromal Cell (hBM-MSC) Differentiation

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Abstract

The differentiation of human Bone-Marrow Mesenchymal Stem/Stromal Cells (hBM-MSCs) is dependent on exposure to biophysical and biochemical stimuli that favor early and rapid activation of the in vivo tissue repair process [1]. Exposure to exogenous stimuli such as an electromagnetic field (EMF) can promote differentiation of hBM-MSCs via ion dynamics and small signaling molecules. The plasma membrane is often considered to be the main target for EMF signals, and most results point to an effect on the rate of ion or ligand binding due to a receptor site acting as a modulator of signaling cascades.

INTRODUCTION

Human bone marrow stem/stromal cells (hBM-MSCs), also known as bone marrow-derived mesenchymal stem cells are a population of progenitor cells that contain a subset of skeletal stem cells (hSSCs), able to recreate cartilage, bone, and stroma that supports hematopoiesis and marrow adipocytes. There is also growing evidence that these same cell types can differentiate to nerve-like tissue. Due to the variability in their differentiation capacity, hBM-MSCs are widely used in a number of cell therapies. Exposure to low-frequency electromagnetic fields (EMFs) has been reported to affect their regenerative capacity by increasing the rate of osteogenic, chondrogenic, and neurogenic differentiation [1].

Mechanisms of Action

During human development, lineage-committed cells of the three embryonic germ layers migrate and proliferate in the form of endogenous ionic currents, giving rise to electric fields (EFs) [2]. While endogenous EFs are present in all developing and regenerating animal tissues, their existence and potential impact on tissue regeneration and repair have been largely ignored. Exposure to EMF activates intracellular and extracellular mechanisms. The mechanisms through which EMF exchanges information between cells, and how the conversion of this biomechanical signaling is translated, have been researched for decades showing that EMF can permeate both the plasma and nuclear membranes of cells, thereby affecting a variety of cell functions and tissue types [3-5]. The concept that the plasma membrane may be sensitive to EMF was first proposed by Adey in 1974 [6]. Electrical properties such as membrane surface charge and potential are especially influenced by extra low-frequency (ELF) EMF (<100 Hz) [7]. For example, ELF-EMF can induce depolarization in the cell membrane followed by an increase or decrease in intracellular calcium $[Ca^{2+}]_i$ [7]. As a second messenger, Ca^{2+} ions are involved in regulation at all stages of cellular growth and development, including proliferation and differentiation, as well as in the assembling and disassembling of cytoskeletal elements [7]. Ion fluxes are closely involved in differentiation control as stem cells move and grow in specific directions to form tissue and organs. EMF affects numerous biological functions such as gene expression, cell fate, and cell differentiation, but specific cell functions only respond to certain frequencies and field strengths.

EMF Parameters (Frequency, Intensity and Time Specific)

Years of research have shown that the parameters through which the human body resonates provide biological windows of opportunity that must be adhered to in order for the desired effect to occur. The effect of EMF on stem/progenitor cell differentiation depends on specific parameters such as time duration, frequency, field strength (intensity), and also cell type [8,9]. Effective EMF

stimuli are coherent, presenting a series of recurring signals that must be present for a minimum amount of time [10]. This effect is also tissue specific [11,12].

From electroencephalograms (EEGs) it is known that brain waves operate between 0-30 Hz, corresponding from low Delta to high Beta brainwave frequencies. Adey and Bawin [13], and also Sisken and Walker [14], reported that cells and tissues respond to these same frequencies. Also these researchers found that field strengths between 33-66 micro Tesla work most effectively and are the safest for individual cell types. Time of exposure must correspond with the biological function of the cell activity. If, for instance, it takes a cell 15 min to effect a certain biological change, then the EMF exposure needs to be that same amount of time. Often investigators will apply the EMF for hours or even days, when the change they are trying to exact takes only minutes to occur *in situ*. Prolonged exposure can negate the effect. While much of the EMF research has focused on the differentiation of hBM-MSCs to bone, it appears that the same 15 Hz frequency stimulates hBM-MSCs to initiate chondrogenesis, however the field strength is more intense (5mT versus < 2mT)

[15]. Since cartilage formed by hBM-MSCs typically undergoes hypertrophy or directly forms bone [16,17] it is not surprising these two tissues would respond to the same frequency; however it is interesting to note that the field strength is more than double for chondrogenesis than that of osteogenesis.

EMF Field Resonance and Signal Transduction

Studies in developmental biology have identified key regulators of morphogenetic properties, indicating where endogenous EMF is located in the action potentials of nerves and heart tissue, as well as in skeletal muscle vibrations, with frequencies elicited by rhythmic activities throughout the human organism [2]. Liboff suggests that the transport of Ca^{2+} through channels of the cell membrane involves a resonance-type response to the applied EMF, which is the mechanism that activates ion flux, receptors, kinases, and even transcription factors [18]. Ca^{2+} efflux transported from the cytosol to the plasma membrane has been found to be initiated by exposure to EMF and, as reported by McLeod et al., to transport Ca^{2+} across the membrane [19]. This modulation of Ca^{2+} creates a harmonic resonance pattern in which the innate ions follow the wave function of the exogenously applied EMF. Ion cyclotron resonance (ICR) helps regulate biological information in ways that biochemical remedies and pharmaceuticals cannot [20,21]. Experiments in resonance effects involve generating cell communication signals by using

ELF-EMF triggered specific biological pathways. The resonant frequencies applied to hBM-MSCs are able to strongly affect their differentiation processes [20]. Different harmonics of known therapeutic treatments can affect cell differentiation; however, the first harmonic is by far the strongest, with each subsequent harmonic diminishing in intensity [22]. Because the human body defies chaos to avoid entropy, it maintains a high degree of order and coherence. In physics, field potentials represent the guidance cues for electricity and magnetism, whereby scalar and vector potentials are information based phase relationships forming organization and structure. Due to the harmonic nature of PEMF therapies, ELF-EMF is capable of affecting neural differentiation through constructive interference.

ELF-EMF exposure of MSCs has been suggested as a clinically therapeutic option for treating neurodegenerative diseases

[23]. Using 50 Hz frequency, 5 mT field strength, 60 min per day for 12 days, EMF was reported to facilitate differentiation to MSCs expressing neuronal-specific markers and genes, forming synaptic junctions and pulsed excitatory postsynaptic currents [24]. Studies using this same frequency, but amplitude of 1 mT, showed the expression of neural markers such as neurofilament (NF-L), microtubule associated protein 2 (MAP2), and NeuroD1 increased at 6 days, and phosphorylation of Akt and CREB, but not ERK, increased at 90 min in BM-MSCs. The Akt (Protein kinase B) Pathway, (aka PI3K-Akt Pathway), is a signal transduction pathway that promotes survival and growth in response to extracellular signals. Results suggest that EMF induced neural differentiation through the activation of the epidermal growth factor receptor (EGFR) signaling and mild generation of reactive oxygen species (ROS) [25].Reports also suggest that exposure of MSCs to ELF-EMF increases the expression and function of voltage-gated Ca^{2+} channels while Ca^{2+} influx through Ca (v)1 channels play a key role in promoting the neuronal differentiation of neural stem/progenitor cells (NSCs) [26]. In cultures of differentiating NSCs exposed to 50 Hz, 1 mT

EMF, the percentage of cells displaying immunoreactivity for neuronal markers (beta-III-tubulin, MAP2), and for Ca(v)1.2 and Ca(v)1.3 channels was markedly increased. NSC-differentiated neurons in EMF-exposed cultures also exhibited significant increases in spontaneous firing in the percentage of cells exhibiting Ca^{2+} transients in response to potassium chloride (KCl) stimulation, and in the intensity of these transients and of Ca^{2+} currents generated by the activation of Ca (v) 1 channels [27].

CONCLUSION

While it remains difficult to alter the expression of genes to rebuild damaged tissues in humans, especially when considering the use of controversial treatments such as stem cell and gene therapies, a systems-based view of development and regeneration may provide suitable therapeutic alternatives.

Exposure from EMF provides a field-based treatment that is non-linear and non-reductionist. Because these systems (osteogenic, chondrogenic or neurogenic) use complex interactions of multiple genetic substances that give rise to physical cues, they must be stimulated by systems-based approaches in order to receive effective differentiation cues. In contrast to biochemical approaches, mechanical and electrical signals are relatively easier to control and implement in order to guide repair and regeneration [1]. ELF-EMF therapies could provide an auxiliary approach to enhancing cellular activities for tissue regeneration by stimulating hBM-MSCs with both EMF and the proper chemical signals (differentiation media and growth factors) to promote cellular responses synergistically.

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