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Editorial

Biophysical Stimulation with Pulsed Electromagnetic Fields as Innovative Approach for Functional Tissue Engineering of Cartilage

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Abbreviations Extracellular Matrix (ECM); human Mesenchymal stem cells (hMSCs); Insulin-Like Growth Factor (IGF); interleukin (IL); Prostaglandin E2 (PGE2); Proteoglycans (PGs); Pulsed Electromagnetic Fields (PEMFs).

Abstract

The tissue engineering is a multidisciplinary field with the aim to repair the tissue combining the use of stem cells and biomaterials, whose activity can be controlled by the addition of signal molecules, such as growth factors or modulated by physical stimuli. Tissue engineering requires two phases: an in vitro phase to develop the construct in culture and an in vivo phase including the surgical implantation of the construct to repair the tissue defect and the outcome evaluation.

It is known that pulsed electromagnetic fields (PEMFs) (1.5 mT, 75Hz) plays several positive effects on cartilage and bone tissues and they are used in orthopedics with benefit for patients.

The rationale for using PEMFs in tissue-engineering techniques for cartilage repair is based on two important findings: [1] the increase in anabolic activity of chondrocytes and cartilage explants exposed to PEMFs and [2] preventing the catabolic effects of inflammation due to surgical trauma at the site lesion itself, thanks to the agonistic activity for the A2A adenosine receptor. More recently, PEMFs have been studied on human Mesenchymal stem cells (hMSCs) and it has been shown that PEMFs can favour chondrogenic differentiation in the presence of an inflammatory microenvironment counteracting the de-differentiating activity of proinflammatory cytokines.

On the basis of these considerations, PEMFs may be useful in promoting the formation of new cartilage in the engineered construct during its preparation in vitro, to protect the construct when surgically implanted in an inflammatory environment and to favor its integration with the surrounding host tissue. However, several gaps have been highlighted from the clinical outcome evaluation and they deserve attention to improve the use of PEMFs as an useful tool for cell-based regeneration of cartilage defects in orthopedics.

Tissue engineering is an interdisciplinary field that uses the combination of cells, biomaterials, and suitable biochemical factors to improve or replace biological functions and it is addressed to the repair of tissues. Specialized connective tissues, such as cartilage, require certain mechanical and structural properties for proper functioning. Powerful developments in tissue engineering have yielded a novel set of tissue replacement parts and implementation strategies. Scientific advances in biomaterials, stem cells, growth factors, have created opportunities to fabricate tissues in the laboratory from combinations of scaffolds, cells, and biologically active molecules. Among the major challenges now facing tissue engineering is the need for more complex functionality, as well as both functional and biomechanical stability in laboratory-grown tissues destined for transplantation.

Considering that cartilage, a specialized connective tissue not vascularized, has very limited regeneration capability, the improvement of cartilage repair procedures is required.

To treat articular cartilage damage effectively, it is necessary to fill the defect with a repair tissue with the same mechanical and functional characteristics of hyaline cartilage and to promote the integration of the repair tissue with the host cartilage and the subchondral bone. To these aims, several procedures have been proposed also by using human Mesenchymal Stem Cells (hMSCs). So far, clinical research has failed to identify surgical procedures that can reproduce the biological composition and biomechanical properties of native cartilage. Tissue-engineering procedures aim at overcoming the current limitations of traditional surgical treatment by offering functional regeneration in the defect region. They require an initial step of in vitro culturing of chondrocytes or hMSCs, alone or in the presence of natural or synthetic Extracellular Matrix (ECM)-based scaffolds, followed by a second step consisting in the surgical implantation of the engineering-construct into the cartilage defect. By taking into consideration and controlling all the scaffold- and cell-related critical factors, the final laboratory phase requires the evaluation of the tissue substitute's biomechanical and biological properties before it is implanted; the in vivo result depends on the capability of functional remodeling and integration with host tissue [1]. However, the lesion site scenario completely differs from the strictly controlled in vitro tissue conditions. In fact, in the joint environment, potent catabolic mediators could severely impact chondrocyte metabolism and ECM

maintenance [2]. Most cartilage tissue engineering is being done for trauma, which alters the physiological joint environment, leading to an increase of proinflammatory cytokines such as interleukin (IL)-1 and IL-6 in the acute phase of inflammation. These cytokines counteract the differentiation of hMSC in chondrocytes. In the long term, the chronic presence of elevated levels of IL-1 and IL-6 in the synovial fluid could be responsible for cartilage catabolism, leading to development of osteoarthritis. In addition, increased IL-1 concentration has been documented after joint surgery and to correlate with the severity of cartilage damage, showing the importance of controlling the joint environment for clinical success following tissue engineering procedures. In the presence of IL-1, hMSCs differentiation is directed toward the fibroblast rather than chondrocyte phenotype and transplanted chondrocytes synthesize fibrocartilage instead of hyaline cartilage, with a loss of functional properties of articular cartilage. In an inflammatory environment, prostaglandin E2 (PGE2) is released and it promotes chondrocyte apoptosis. This implies that even transitory exposure to chemical factors, which may arise from inflammation, might have long-lasting effects on the development of immature tissue within the joint.

Several in vitro, in vivo, and clinical studies have shown that biophysical stimulation with pulsed electromagnetic fields (PEMFs) plays a regulatory role of connective tissue, particularly cartilage, bone and synovia with a global positive effect on the joint tissues [3-7]. Most of these studies have shown that PEMFs affect chondrocytes in several experimental models (monolayers, cartilage explants, and 3D scaffolds), by significantly increasing cell proliferation and synthesis of specific cartilage ECM components, including Proteoglycans (PGs) and collagen type II. Further, PEMFs counteract the IL-1β-triggered cartilage ECM degradation in healthy and osteoarthritic-joint-derived cells. Moreover, using human cartilage explants, we showed that PEMFs increase PGs synthesis of the same magnitude as that induced by the Insulin-Like Growth Factor (IGF)-1, the main cartilage anabolic growth factor [6]. Together, these in vitro data support the active role of PEMFs in the phase of development and manipulation of the construct in culture, suggesting that the combination of tissue engineering and low-frequency PEMFs might improve cartilage repair techniques.

The effect of PEMFs can be important also in the surgical phase to control and limit the inflammatory microenvironment. It has been shown that PEMFs inhibit the negative effect of the cytokine IL-1β on the production of ECM components in cartilage explants. These results suggest that PEMFs stimulation during the implantation phase may prevent the catabolic effects induced by inflammatory molecules on both implanted and host cells, thus protecting the construct in the long term. Recent data suggest that the IL-1β inhibitory activity on the expression of specific chondrocyte markers, including aggrecan and type II collagen and accumulation of PGs during TGFβ3-induced chondrogenic differentiation of bovine and human MSCs, can be counteracted by PEMF exposure [1,8]. PEMFs may act also on cell membrane receptors and may affect membrane protein distribution. In particular, in vitro PEMFs mediate the up-regulation of A2A adenosine receptors on chondrocytes and synoviocytes enhancing their anti-inflammatory effects as they reduce cyclooxygenase 2 expression and PGE2 production in bovine and human synoviocytes [5,7]. These effects could be attributed to the capability of PEMFs to potentiate the density and functionality of A2A adenosine receptors, which, in turn, inhibit the NF-kB signaling pathway, resulting in decreased synthesis of inflammatory molecules.

In conclusion, the rationale for using PEMFs in tissue-engineering techniques for cartilage repair is based on two important findings: [1] the increase in anabolic activity of chondrocytes and cartilage explants exposed to PEMFs and [2] preventing the catabolic effects of inflammation due to osteoarthritis or surgical trauma at the lesion itself, thanks to the agonistic activity for the A2A adenosine receptor.

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