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DEVELOPMENT OF ADVANCED RELEASE SYSTEMS FOR MESENCHYMAL STEM CELLS

ABSTRACT

The increasing need for more efficient and less invasive treatment of damaged or diseased tissue is stimulating the development of new technologies in the field of tissue engineering and regenerative medicine (TERM). By applying combinations of biomaterial scaffolds, cells and bioactive molecules, regeneration of damaged or diseased tissue can be facilitated, leading to their functional regeneration.

Stem cells are defined by their combined ability to self-renew and to allow multi-lineage specific differentiation (e.g. bone, cartilage, fate, muscle and tendon). Nowadays, they are the most versatile and promising cell source for the regeneration of aged, injured or diseased tissue. Therefore, a major goal in TERM is the development of new culturing methods, using advanced biomaterial scaffolds, which closely mimic the natural structuring and, simultaneously, promote differentiation or proliferation of specialized stem cells without loss of their "stemness".

Electrospinning has attracted tremendous interest in the research community as a simple and versatile technique to produce synthetic polymeric ultrafine fibers with diameters ranging from tens of nanometers to a few micrometers. In addition, electrospun non-woven meshes can physically mimic the ECM structure of native tissues. Those remarkable properties render electrospun nanofiber meshes useful for many applications, particularly those related to the field of biomedical engineering such as scaffolding and drug release systems.

The controlled release of bioactive molecules from biodegradable scaffolds can enhance the efficacy of TERM approaches. Locallized drug delivery systems are used to improve the therapeutic efficacy and safety of drugs, and enhancing the quality of life of patients, by delivering them to the site of action at a rate dictated by the need of the physiological environment. Nanoparticle-based systems have the facility to diffuse through cytoplasmatic cell membranes, allowing controlling or modifying the cell activity. Examples of those release systems include liposomes, solid nanoparticles or polymeric carriers (e.g. dendrimers, micelles).

Liposomes, a nanoparticle release system, hold tremendous promise for the development of release strategies in various therapeutic contexts. They present a great potential to finely control the drug release profile, to fuse with the cytoplasmatic cell membrane and to prolong the presence of drugs in circulation. Furthermore, through the encapsulation of bioactive compounds (e.g. growth factors, DNA, siRNA) in a nanocarrier such as a liposome, the total amount of drug used may be significantly reduced when compared with the systemic administration. This results in a decrease in the amount and types of nonspecific side effects, and an increased effectiveness of the drug used. Although there is a great interest in the systemic use of liposome systems, it is important to note that significant challenges still exist, namely the successful targeting of drug-loaded liposomes to specific tissues.

The combination of biomaterial scaffolds with loaded liposomes seems a reliable strategy. We propose herein the development of multi-functionalized electrospun nanofiber meshes for TERM approaches. Specifically, new strategies to control MSCs' differentiation will be developed by the incorporation of liposomes carrying lineage-specific growth factors into the electrospun meshes or by its

immobilization at the surface of electrospun nanofiber meshes. These combined systems will allow the convenient adhesion and proliferation of MSCs, as well as the local control over their differentiation by the release of lineage-specific growth factors. When implanted in the defect site, those multi-functional systems are intended to act as carriers for MSCs' and also to attract endogenous MSCs and induced their tissue-specific differentiation. Both in vitro and in vivo experiments will be performed to confirm the efficacy of the proposed strategy.