Study the effect of electrical stimulation through the conductive membranes on the wound healing gene expression in normal human dermal fibroblasts

Hyun Jin Park[1,2], Mahmoud Rouabhia[1], Denis Lavertu[2] and Ze Zhang[2]

[1]Groupe de Recherche en Écologie Buccale, Faculté de Médecine Dentaire, Université Laval, [2]Axe de médecine régénératrice, Centre de recherche du CHU de Québec, Département de chirurgie, Faculté de médecine, Université Laval, QC G1V 0A6, Canada

Statement of Purpose: Skin wound healing is a complex multi-stage process that orchestrates the reconstitution of the dermal and epidermal layers of the skin (1). During wound healing, fibroblasts are an important cell type participating the inflammatory and remodeling processes (1). Fibroblast activation involves different wound healing genes. These are grouped into different but complementary control pathways for collagen production, cell adhesion, remodeling and spreading, for the cytoskeleton, inflammatory cytokines and chemokines, and for growth factors and signal transduction (2). Genes can be modulated by various conditions, such as diabetes (3) or an exposure to exogenous stimuli, such as ultraviolet light (4) and electrical stimulation (ES). ES in its various forms has been shown to promoting wound healing by increasing the migration of keratinocytes and macrophages (5), enhancing angiogenesis (6), and stimulating dermal fibroblasts (7,8). Thus, the goal of this study was to determine the effect of ES on the expression profiles of the genes involved in the wound healing process in normal human dermal fibroblasts using electrically conductive PPy/HE/PLLA membranes.

Methods: Normal human fibroblasts were seeded on the heparin (HE)-bioactivated polypyrrole (PPy)/poly(L-lactic acid) (PLLA) conductive membranes, cultured, and subsequently exposed to ES of 50 or 200 mV/mm for 6 h. Following ES, the cells were used to extract RNA for gene profiling and the culture supernatants were used to measure the level of the different wound healing mediators.

Results: A total of 50 genes were affected (activated/repressed) by ES; among these, 42 were up-regulated and 8 were down-regulated. ES intensities (50 and 200 mV/mm) we tested did not activate/repress the same genes, at the same time. ES modulated the expression of genes involved in cell adhesion, remodeling and spreading, cytoskeletal activity, extracellular matrix, inflammatory cytokines and chemokines, and growth factors, as well as in molecules participating in signal transduction. The expression of wound healing genes was supported by protein production. Protein levels in the culture supernatant showed that ES increased CCL7, KGF, and TIMP2 but reduced MMP2.

Conclusions: This study demonstrated that ES modulates the expression a variety of genes involved in the wound healing process, confirming that ES is a useful tool in regenerative medicine.

References:
1. Broughton G 2nd, Janis JE, Attinger CE. Plast Reconstr Surg 2006: **117**: 12S–34S.
2. Velasquez LS, Sutherland LB, Liu Z *et al*. Proc Natl Acad Sci USA 2013: **110**: 16850–16855.
3. Peplow PV, Chatterjee MP. Cytokine 2013: **62**: 1–21.
4. Houreld NN, Ayuk SM, Abrahamse H. J Photochem Photobiol B 2013: **130C**: 146–152.
5. Wang E, Zhao M, Forrester JV *et al*. Exp Eye Res 2003: **76**: 29–37.
6. Zhao M, Bai H, Wang E *et al*. J Cell Sci 2004: **117**: 397–405.
7. Shi GX, Zhang Z, Rouabhia M. Biomaterials 2008: **29**: 3792–3798.
8. Rouabhia M, Park H, Meng S *et al*. PLoS One 2013: **8**: e71660.