Electroconductive nanofiber strategies for biomaterial-based approaches to tissue engineering

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Nanofibrous scaffolds are versatile nanosystems which can be tailored into scaffolds for tissue engineering strategies. These scaffolds are perfect for the design of artificial extracellular matrices as they have high surface areas and can be easily produced through electrospinning from individual or blends of materials into single structured (monoaxial) or multilayer (coaxial) fibers. Such strategy is important do developed nanostructured materials not only to support successful cell transplantation but also to create multifunctional systems (e.g. signal to stimuli transducers, biosensors and drug delivery systems).

The role of electrical stimulation in enhancing the efficacy of cell-based therapies has been established using both *in vitro* and *in vivo models*. Electroconductive polymers are a class of materials capable of conducting electrical current, and therefore are an important component in designing multifunctional nanofibrous systems. Electroconductive coaxial fibers are an example of such system, having several advantages including tuneable mechanical properties (to boost biocompatibility), the ability to entrap sensitive drugs in the inner core layer, ease of functionalization through chemical modification and be made biodegradable.

Our group has focused on the development of electroconductive and biodegradable coaxial fibers. These systems are not only important for the development of better *in vitro* models for studying disease progression and drug testing, but also for the successful development of tissue engineering based therapies for neurological diseases. This coaxial fiber consists of a shell layer of polycaprolactone (PCL) blended with polyaniline (PANI), cladding to a core layer composed of poly(glycerol sebacate) (PGS). The development of coaxial fibers was undertaken in three sequential steps:

1. Study the effect of PANI to PCL ratio used on electrospun fibers electroconductivity vs NSC biocompatibility profile;
2. Study of the solvent system used on fiber production with electroconductivity enhancement;
3. Production of an optimal electrospun electroconductive coaxial fiber and assess its application in supporting neural differentiation of induced pluripotent stem cell (iPSC).

PCL-PANI fibers can be obtained from trifluoroethanol (TFE) solutions, with an electroconductivity plateau reached for PCL-PANI ratios 88:12, 91:9, 93:7, 94:6 and 95:5, with conductivity values in the range of 0.014 to 0.077 S cm-1. All combinations tested are biocompatible for NSC culture. However, electroconductivity was dependent on environmental humidity [1].

The solvent system for PCL-PANI fibers was optimized using TFE and hexafluoropropanol (HFP). The best combination was used to produce electrospun fibers with higher electroconductivity (0.2 S cm-1) at a higher humidity (50%). This effect was attributed both to synergic changes in PCL packaging during fiber formation and the pseudo-doping of PANI by HFP, a process that was also studied in PANI films. The AC electrical stimulation of NSCs was also performed and neural marker expression (MAP2) was improved.

Finally, coaxial PCL-PANI/PGS fibers were produced successfully. The average diameter was 951 ± 465 nm and the electroconductivity was 0.063 ± 0.029 S cm-1. The mechanical properties (ε of 1.3 MPa) and hydrophilicity (38 º) were also favorable for NSC culture. iPSC differentiation towards the neural lineage was favored by the presence of the coaxial fibers as shown by the upregulation of DCX, NCAM, NEUN and GAD67 neural markers.

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