Stretch-growth and cell therapy: a novel combinatorial approach for treating spinal cord injuries

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Abstract
Spinal Cord Injury is a pathological condition with devastating physical and socio-psychological consequences [1], but effective treatments are lacking due to the complex pathophysiology. Recent investigations in the field of regenerative medicine show the therapeutic potential of neuroepithelial stem (NES) cells to treat this type of injury [2], while advancement in nanotechnologies enables the development of novel nanomedical tools. Previous studies investigated the use of magnetic nanoparticles (MNPs) and magnetic field to induce stretch-growth (SG), i.e. the stimulation of axonal outgrowth by mechanical stimuli [3][4][5]. The purpose of this work is to validate a novel combinatorial approach to treat spinal cord injuries based on the use of SG and cell therapy. Indeed, the success of stem cell-based therapies depends on the capacity to promote axonal growth, which is necessary to reconstitute lost neural circuits. Our data concern mechanically induced stretch growth of MNP-labelled human-derived differentiating neurons both in vitro and microinjected in the ex vivo model of mouse spinal cord (SC) organotypic slices. Our data demonstrate that we can manipulate elongation and guidance of the neurites of stretched NES cells both in vitro and in the SC tissue. We are also developing an innovative platform of cortico-spinal assembloids to model the cortico-spinal tract (CST) in vitro. After performing an injury of the assembloids, these will be used to test the effective regenerative potential of our approach in a human 3D cytoarchitectural context.

References

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Figures

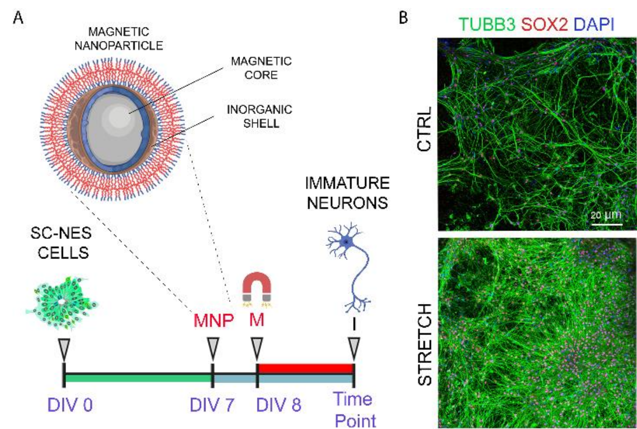

Figure 1. (A) Schematic representation of stretch growth protocol: SC-NES cells are labelled with MNPs at DIV 7 of differentiation; at DIV 8 external magnetic field is applied. Cells are fixed at specific time points: DIV 10 for short term assay; DIV 60 for long term assay. (B) Representative images of DIV 60 neurons in control (upper image) and stretch (lower image) condition.

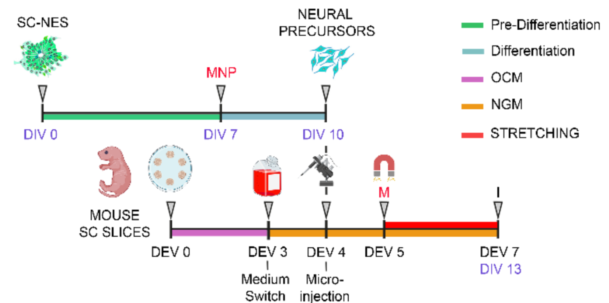

Figure 2. Schematic representation SC-NES cell transplantation protocol into mouse spinal cord organotypic slices. Cells are labelled with MNPs prior to transplantation. The external magnetic field is applied for two days (short term assay), then cells are fixed for further analysis.

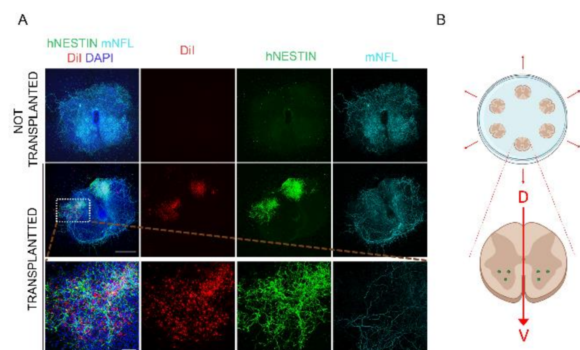

Figure 3. (A) Immunofluorescence staining for human-NESTIN (green) to detect human SC-NES cell-derived neural precursors transplanted into the mouse spinal cord organotypic slices. (B) Co-culture organization design: up to 6 SC slices are placed concentrically with the dorso-ventral axis (red arrow) in the radial direction (centrifugal) and human SC-NES cells are microinjected in the ventral horns (3 injections per horn- green dots).