Exogenous Adult Post Mortem Neural Precursors attenuate secondary degeneration, and promote myelin sparing and functional recovery following experimental spinal cord injury

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Neural stem cells from the subventricular zone of the forebrain, because of their proliferation and differentiation characteristics, are a good tool for tissue replacement therapies. We recently isolated a subclass of neural progenitors, capable of surviving a powerful ischemia insult: these cells were named Post Mortem Neural Precursor Cells (PM-NPCs). Differentiation yield mostly neurons (about 30-40%) compared to regular NPCs. Also the cholinergic yield is higher. PM-NPCs are particularly sensitive to mTOR activity. The average dose of rapamycin normally used to inhibit mTOR is 5 ng/mL but we observed that the effect was significantly evident with a dose 100 fold lower. The higher ERK activation observed in undifferentiated PM-NPCs is also involved in their differentiation process, since the exposure to ERK inhibitor PD98059, downregulates significantly the extent of neuronal differentiation. PM-NPCs but not classical NPCs synthesize EPO that it is known to be active as a signalling molecule promoting stem cell-derived neurogenesis and neuronal differentiation, the effect is not observed in astrocytes. Blocking the EPO pathway by means of monoclonal antibodies anti-EPO or anti-EPOR markedly inhibits the differentiation of PM-NPCs towards the neuronal phenotype. Differently the exposure of regular NPCs to exogenous EPO increases their differentiation ability close to level of PM-NPCs.
The potential of PM-PCs in terms of replacement therapy was investigated in a mouse model of spinal cord injury. 1x 10^6 of PKH 26 labelled PM-PCs, kept from animal 6 hours after death (T6), were administered intravenously within 2 hours after the traumatic injury of the cord. The improvement of animal functional recovery and the transplanted cells fate were studied. 30 days after transplantation animals treated with T6 PM-NPCs show a remarkable improvement of the rate of hind limb function evaluated by Basso Mouse Scale compared with animals treated with placebo. PM-NPCs migrate predominantly at the injury site, survive and differentiate predominantly into cholinergic neurons, reconstitute a rich axonal and dendritic network and promote a marked axonal regeneration across the injury site of monoaminergic fibers. Moreover the molecular analysis of the lesion site show that PM-NPCs induce a remodulation of inflammatory response and release of neurotrophic factors. Pro-inflammatory cytokines (IL-6, MIP-2 and TNF-alpha) levels significantly decrease after 48 hours from spinal cord injury and PM-NPCs transplantation, while after 7 days we observe a small increase of IL-6 and TNF alpha. In conclusion, we purified a new class of neural precursors able to survive after a powerful ischemic insult (PM-NPCs). Their neuronal differentiation requires the activity of mTOR and MAPK and is prevented by exposure to anti-EPO and anti-EPOR antibodies. Moreover, these cells represent a liable source for cellular therapy in neurodegenerative disorders, specially on spinal cord injury.