

Differential tropism of immortalized and non-immortalized human neural stem cell lines in a focal demyelination model

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Human neural stem cells (hNSC) represent an optimal tool for the therapy of neurodegenerative diseases, since their ability to differentiate into neurons, astrocytes and oligodendrocytes. In experimental settings the slow proliferation rate of hNSC represent a limit that can be overcome by the use of immortalized hNSC lines, such as v-myc (v-IhNSC) or c-myc T58A (T-IhNSC) transduced hNSC. We previously showed that, compared with hNSC and v-IhNSC, T-IhNSC rise high percentages of oligodendrocytes soon after removal of mitogens and are prone to a precocious differentiation. Given the differential in vitro oligodendrogenic potential we analyzed the progeny of hNSC, T-IhNSC and v-IhNSC in an animal model of focal demyelination induced by LPC, to verify if local environmental cues inducing endogenous remyelination could address their integration and differentiation. The three lines were unilaterally transplanted in the subventricular zone (SVZ) of adult Sprague Dawley rats at 5 days from the lesion (subacute phase) induced by injection of lysolecithine. By immunohistochemical analysis and confocal microscopy we showed that non immortalized hNSC as well as immortalized T-IhNSC

and v-IhNSC were able to survive with a differential rate along the antero-posterior or medio-lateral axis and to migrate along the ventricular wall. In particular, after 15 days from transplantation, hNSC and T-IhNSC were able to reach the striatum and the corpus callosum differentiating into O4+ and MBP+ oligodendrocytes, with T-IhNSC colonizing the lesioned area, whereas v-IhNSC remained mainly confined in the SVZ. The three hNSC lines displayed differential survival rates and migration patterns, possibly depending on their intrinsic proliferative potential and differentiation ability. To note, a significant reduction of Iba1+ microglia activation together with a shift of the morphology of Iba1+ cells from the amoeboid macrophagic to the stellate resident phenotype was also observed in transplanted animals with respect to controls. This finding suggests an immunomodulatory effect of hNSC on the acute inflammatory reaction. These results support T-IhNSC line as a reliable cell model to study therapeutic applications of hNSC for demyelination disorders and show a differential tropism in vivo of hNSC depending on their intrinsic proliferation potential.

