

The Homeostatic Pressure exerted by stem cells in Degenerative or Injured CNS Environments

Evan Snyder, M.D., PhD, Burnham Institute for Medical Research, La Jolla, CA, USA

Dr. Snyder has most recently been studying an intriguing phenomena with possible therapeutic dividends that has begun to emerge from his observations of the behavior of neural stem cell (NSC) clones in various mouse and primate models of CNS injury & degeneration. During phases of active neurodegeneration, factors seem to be transiently elaborated to which NSCs may respond by migrating (even long distances) to degenerating regions & attempting to restore homeostasis. This may include differentiating towards the replacement of degenerating neural cells of multiple types, not only neurons but also requisite non-neuronal “chaperone” cells, all of which are essential for the proper development and reconstitution of function. NSC’s are drawn to inflammatory niches. These "repair mechanism" may reflect the re-expression of basic developmental programs (particularly during temporal "windows" following injury) that may be harnessed for therapeutic ends. There is an enormous amount of “programmed” cross-talk between stem cells and the milieu that add complexity but also enrich therapeutic promise to the system. In addition, NSCs in their native state (as well as following genetic-engineering) may serve as vehicles for protein delivery allowing for the possibility of simultaneous cell replacement & gene therapy (e.g., with factors that might enhance differentiation, neurite outgrowth, connectivity, neuroprotection, anti-inflammation, anti-scarring, and angiogenesis,).

Cell-cell contact with communication through gap junctions appears to represent another mode of cross-talk. Multi-model approaches to most neurological conditions are likely required. The stem cell may serve as the “glue” for these. When combined with certain synthetic biomaterials, NSCs may be even more effective in "engineering" the damaged CNS towards reconstitution. Not only gene expression programs, but also an epigenetic chromatin modification programs seem critical for dictating plasticity and potency. These chromatin structures appear to influence the expression of various stemness genes, including some novel zinc finger proteins that influence the unfolding of various developmental programs along the continuum from pluripotency (as ES cells) to multipotency (as somatic stem cells, e.g., NSCs) to cell type commitment (e.g., as neural cell types).