

Sonic Hedgehog, Stem Cells and Neural Disorders

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For the last decade or so, as the concept of regenerative medicine has become particularly prominent, a great deal of attention has been focused on rebuilding tissue via the addition of new cells (i.e., cell therapy). This has been enhanced by the increased understanding or, at least, the increased controversy surrounding the use of embryonic stem cells.

An entirely different approach takes advantage of the understanding that tissue development in the embryo is predominantly controlled by a small number of powerful regulatory pathways. One of these is the signaling pathway activated by the three peptide ligands of the hedgehog pathway. The most well known of these is sonic hedge hog which controls the number and differentiation of many ventral neural types including motor neurons, dopaminergic neurons and a variety of midbrain and cortical neurons. We have identified a family of small molecule hedgehog pathway agonists that have sub-nM EC₅₀'s, are orally available and CNS permeant. These agonists reproduce Shh activity in all embryo-based in vitro and in vivo assays. They have also shown impressive neuroprotective activity in different adult rodent CNS disease models ranging from Parkinson's disease to stroke. In addition to being neuroprotective, they have the ability to stimulate proliferation of adult CNS stem cells. Thus, activating the hedgehog pathway may have a unique ability to both protect the adult CNS from damage and to stimulate its repair.