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Neural stem cell engraftment

Functional interactions, brain repair and gap junctions

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ABSTRACT

Neural stem cell (NSC) engraftment therapies show increasing promise as potential cures for several of the diseases of the central nervous system. Traditionally, functional improvements after NSC engraftment have been attributed to replacement of lost neurons and astrocytes, remyelination and support of adjacent cells at risk. How grafted NSCs and their progeny integrate into recipient brain tissue and functionally interact with host cells is as yet not fully understood.

In this thesis we have investigated the early and beneficial interactions between grafted NSCs and neural host cells. Initially the use of organotypic striatal slice cultures as an *ex vivo* experimental model to study integration of NSCs grafted to striatal tissue was evaluated. Using this model we recognized that NSC engraftment had a positive impact on the host tissue estimated by reductions of host cell astrogliosis, apoptosis and necrosis. Growth factor overexpression and serum free culturing conditions affected both the differentiation of the exogenous NSCs as well as their interactions with the host.

We observed that one of the first and essential ways in which grafted murine as well as human NSCs integrate functionally into host neural circuitry and affect host cells, even before consummation of neuronal differentiation, is via gap-junctional coupling. In addition to providing a potential template for subsequent mature electrical coupling, the gap junctions permit exogenous NSCs to exchange ions and molecules with host cells and participate in host network activity, including synchronized calcium transients in fluctuating networks. In both murine and human NSCs grafted to slice cultures and rodent models of neurodegeneration, gap junction formation was associated with the rescue of host cells. Both *in vitro* and *in vivo* the beneficial actions of the NSCs were abrogated by suppressing gap junction formation and function via pharmacologic and/ or RNA-inhibition strategies.

After mechanical injury to the host tissue and successive NSC engraftment the expression of connexins, the substrate for gap junction formation, changed significantly in both graft and host cells. The temporal connexin expression pattern suggested that a window of opportunity for successful host cell rescue by added NSCs exists.

Finally we show that controlled hypoxic preconditioning of NSCs prior to engraftment is a reliable and clinically relevant method to increase NSC hemichannel expression and function and thereby improve the engrafted NSCs' ability to interact with and potentially rescue host cells at risk.

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