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Stem cell interactions with the injured brain

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Skandiasalen, Astrid Lindgrens Barnsjukhus.

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ABSTRACT

Neurodegenerative diseases such as Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis and acute neurological disorders such as brain ischemia and traumatic injury yearly affect millions of people. Neural stem cell (NSC) grafting is an emerging strategy to treat and potentially cure these conditions for which today no effective remedies exist. The restoration of function might occur both by replacement of lost neural cell populations and by rescue of host cells at risk. In this thesis we have investigated the early interactions between grafted NSCs and the injured brain and characterized potential mechanisms that underlie the functional improvements seen after NSCs grafting. For these aims, we employed an organotypic culture (OC) system to model injured neural host tissue and grafted both murine and human NSCs to this model. First, we recognized that the OC was a suitable model system to study the early interactions between NSCs and the host. After NSC grafting we observed a reduced host cell damage using metrics like astrogliosis, apoptosis and necrosis. The grafted NSCs also integrated functionally and participated in host calcium signaling networks. Employing a combination of immunohistochemistry, RNA interference, pharmaco-logical blockers, calcium imaging and dye coupling assays we identified gap-junctional graft-host couplings as the mechanism that conveyed both the beneficial impact on the host and the early functional interactions. We recognized that gap junction expression in the grafted NSCs and the injured host cells were highly dynamic processes. The investigations of the graft and host gap junction expression indicated a temporal window of opportunity for successful NSC engraftment. Finally, we noticed that graft-host gap-junctional couplings could be increased by treating the human embryonic stem cells with a Rho-associated kinase inhibitor. This was paralleled by an increased beneficial impact on the damaged host cells. The main conclusion in this thesis is that that gap-junctional coupling appears to be one of the first steps by which graft and host cells establish functional and beneficial interactions. This precedes the formation of more complex communication like chemical synapses. The direct cell-to-cell contact allows reciprocal exchange of a multitude of different health promoting substances and neutralization of pathological processes by diffusion of harmful substances. Increased knowledge of the exact molecular mechanisms involved in the interplay between the graft and host, and also how to direct them, can ultimately benefit the potential future use of NSCs grafts for the treatment of neurodegenerative disorders.

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