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Sommario/riassunto

Stroke remains one of the most devastating diseases in industrialized countries. Recanalization of the occluded arterial vessel using thrombolysis is the only causal therapy available. However, thrombolysis is limited due to severe side effects and a limited time window. As such, only a minority of patients receives this kind of therapy, showing a need for new and innovative treatment strategies. Although neuroprotective drugs have been shown to be beneficial in a variety of experimental stroke models, they ultimately failed in clinical trials. Consequently, recent scientific focus has been put on modulation of post-ischemic neuroregeneration, either via stimulation of endogenous neurogenesis or via application of exogenous stem cells or progenitor cells. Neurogenesis persists within the adult brain of both rodents and primates. As such, neural progenitor cells (NPCs) are found within distinct niches like the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the dentate gyrus. Cerebral ischemia stimulates these astrocyte-like progenitor cells, upon which NPCs proliferate and migrate towards the site of lesion. There, NPCs partly differentiate into mature neurons, without significantly being integrated into the residing neural network. Rather, the majority of new-born cells dies within the first weeks post-stroke, leaving post-ischemic neurogenesis a phenomenon of unknown biological significance. Since NPCs do not replace lost brain tissue, beneficial effects observed in some studies after either stimulated or protected

neurogenesis are generally contributed to indirect effects of these new-born cells. The precise identification of appropriated cellular mediators, however, is still elusive. How do these mediators work? Are they soluble factors or maybe even vesicular structures emanating from NPCs? What are the cues that guide NPCs towards the ischemic lesion site? How can post-ischemic neurogenesis be stimulated? How can the poor survival of NPCs be increased? In order to support post-ischemic neurogenesis, a variety of research groups have focused on application of exogenous stem/progenitor cells from various tissue sources. Among these, cultivated NPCs from the SVZ and mesenchymal stem cells (MSCs) from the bone marrow are frequently administered after induction of stroke. Although neuroprotection after delivery of stem/progenitor cells has been shown in various experimental stroke models, transplanted cells are usually not integrated in the neural network. Again, the vast amount of grafted cells dies or does not reach its target despite profound neuroprotection, also suggesting indirect paracrine effects as the cause of neuroprotection. Yet, the factors being responsible for these observations are under debate and still have to be addressed. Is there any “optimal” cell type for transplantation? How can the resistance of grafted cells against a non-favorable extracellular milieu be increased? What are the molecules that are vital for interaction between grafted cells and endogenous NPCs? The present research topic seeks to answer - at least in part - some of the aforementioned questions. Although the research topic predominantly focuses on experimental studies (and reviews alike), a current outlook towards clinical relevance is given as well.