Cell-based therapies for neural replacement strategies in stroke-related neurodegeneration: neurophysiological insights into stem progenitor cell neurogenesis within a host environment

The restricted neurogenesis limits the brain ability to overcome neurotional cell death following ischemic lesion: Failure of the damaged brain to regenerate following cerebral ischemia results in functional deficits that are most often irreversible and can further deteriorate, causing mortality and severe disability, progressive memory loss and cognitive impairments, known as dementia. This is caused by massive neuronal cell death and neurotoxicity following limited blood supply to the brain. Ischemic death of brain neurons (acute or delayed after lesion) has been the etiology of vascular dementia, the second most common type of dementia after Alzheimer’s disease. Multiple types of vascular dementia exist, common in cognitive decline that gradually worsens and variable in where strokes happen (subcortical dementia) or how severe lesions are (e.g., major stroke, series of small strokes or brief transient ischemic attacks). It has emerged as a synergistic driver of Alzheimer’s disease and vascular disease that often comes (mixed dementia). For over the last three decades after the ischemia-induced neuronal cell death had been discovered, intense research has been focused on withdrawing or, at least, attenuating neurodegeneration to improve restoring function in experimental models of post-stroke cognitive impairments while mimicking focal ischemia, permanent or transient brain lesions, hypertension or reproducing Alzheimer’s disease combined with vascular pathology [for review (Hainsworth et al., 2017)]. Long-standing perspectives that ischemic neuronal death might be potentially suspended through activation of endogenous neuroprotection stay with genomic reprogramming and/or gene activation for de novo protein synthesis, relied on the hypoxia-activated signaling pathways (Dirnagl et al., 2009). On the other hands, pre-clinical studies, including our own works (Kopach et al., 2016; Bybachuk et al., 2017), have reported functional impairments at the later times (weeks) post-ischemia (as in principal neurons (Kopach et al., 2018)). Instead, multipotent NSPC differentiation has been prompted versus post-stroke brain regions (subpopulations of neurons, other neural cell types).

Post-ischemic environment regulates neurogenesis of NSPC grafts: An in vivo protein kinase C (PKC) and CaMK pathways, and phospholipase for feasibly exploring the ischemia-induced neuronal cell death together with managing therapeutic approaches for targeted interventions in the organized brain tissue. In translational neuroscience, this methodology benefits with a meaningful consideration of variable experimental modifications utilized to mimic ischemic insult and onset of cell death (depending on how severe and complex the ischemic impairments are, diverse stem cell origin, etc.). In our study of an in situ modeling of cerebr ischemia optimized for a delayed death of principal neurons [within 2 weeks instead of acute CA1 neuronal death (Rybachuk et al., 2017)], we have traced the functional properties of NSPC grafts over the time in the hippocampal tissue subjected to ischemia (Figure 1; Kopach et al., 2018). The post-ischemic environment influenced neurogenesis of NSPC grafts in different ways. Neuronal maturation has been delayed, both excitability and synaptogenesis, at each time points tested (for over 3 weeks in total; Figure 1). Instead, multipotent NSPC differentiation has been prompted towards the non-neuronal phenotype – we have identified the NSPC-derived glial cells as fast as within a week in the post-ischemic tissue. Such principal difference in the stem cell fate between control and post-ischemic environments implies the determinant, yet underestimated, regulatory role of the host tissue in neurogenesis of NSPCs, both differentiation profile (neuronal vs. non-neuronal) and neurophysiological maturation.

Endogenous facilitators of stem cell fate: Ischemic cell damage results in the glutamate-induced excitotoxicity followed by massive neuronal death and overwhelmed neurotoxicity. Ultimately, different signaling molecules and mediators are released those levels became dramatically heightened, overwhelming the extracellular matrix and activating post-ischemic signaling pathways, with an immense variety of molecular mechanisms being involved. Moreover, during neuronal cell death, necrotic, pro-apoptotic factors and mediators of inflammation activate pro-inflammatory signaling, including nuclear factor-kappa B (NF-κB) pathway and others, pertinent to overactivated astrocytic response featuring the post-ischemic brain. Numerous signaling cascades can thus, contribute to how the ischemia-subjected environment governs the fate of NSPC grafts. The notable regulatory roles in stem cell differentiation have been evidenced for phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (Akt), Ca2+–dependent Ca2+/calmodulin-dependent protein kinase (CaMK)/cycadine monophosphate (cAMP) response element-binding protein (CREB), and Wnt signaling pathways in in vitro and in vivo studies, among the involved signaling targets with the transcriptional status of C and D signaling activation (Le Belle et al., 2011; Telezhkin et al., 2016). Therefore, pharmacological or genetic manipulations modulating presently dissecting signaling pathways, providing multiple growth facilitators, such as neurotrophins, to support intrinsic growth capacity of differentiating neurons, neutralizing high levels of endogenous reactive oxygen species (ROS) in the post-ischemic tissue can accelerate neuronal maturation of NSPC grafts. Further, the supposed beneficial effects may include neurogenesis of the resident neuronal stem cells of the brain for activating endogenous self-renewal. By opposition, these signaling pathways, with managing therapeutic approaches for targeted interventions in the organized brain tissue. In translational neuroscience, this methodology benefits with a meaningful consideration of variable experimental modifications utilized to mimic ischemic insult and onset of cell death, yet underestimated, regulatory role of the host tissue in neurogenesis of NSPCs, both differentiation profile (neuronal vs. non-neuronal) and neurophysiological maturation.

Figure 1 The experimental scheme of neural stem progenitor cell (NSPC) administration in an in situ model of stroke. A cartoon shows the time course for functional assessment of the NSPC-derived neural maturation in a host tissue (organotypic hippocampal tissue subjected to oxygen-glucose deprivation of 10 minutes duration, with onset of the therapy after 2 hours (h) of re-oxygenation). W: Week(s).

Figure 2 The current concept of NSPC-therapy in stroke-related neurodegeneration encompasses the multipotent differentiation of NSPC grafts in a host tissue for replacement of various neuronal phenotypes after ischemia-induced cell loss for restoring the function in multiple ways.

Functional restoration via multipotent NSPC function: Outcome after cell therapy is mediated by diverse mechanisms underlying functional improvements in the post-stroke recovery. Our study implies that NSPC therapy comprised primarily of promoted neurogenesis to a glial lineage that emerges shortly after initiating the therapy in the ischemia-subjected brain tissue (Kopach et al., 2018). This initial stage includes supplying the damaged tissue with the NSPC-derived astrocytes and oligodendrocytes – the output assuming the glia-related neurotrophic and neuroprotective effects. The glial-derived astrocytes enhance the viability of brain cells by secreting various neurotrophic factors and supporting cell regeneration, evidenced for improving neurological function of post-stroke brain (Jiang et al., 2013), whereas oligodendrocytes’ role has been proven in re-myelination and axon regeneration, both essential to synaptic networking (Figure 2). Such glial-directed differentiation of NSPC grafts, driven by overactivated master regulators that heavily burden the post-ischemic tissue, may mirror endogenous mechanism of boosting the glia-mediated tissue clearance following ischemic neuronal cell death. As the cellular debris cleared and pro-apoptotic and inflammatory mediators recede, multipotent NSPC neurogenesis towards neuronal maturation takes place, which is the longer lasting process. Indeed, the ability of multipotent stem cells to mature with higher efficacy to neurons in astrocyte co-cultures had been evidenced. Other roles of glial cells have included the active astrocytic contribution to synapse formation, plasticity and remodeling that should facilitate network remodeling in the post-stroke tissue.

Conclusions and future perspectives: Ischemia-induced neuronal cell death is one of the leading causes of the brain damage that results in high rate of mortality and severe disability in patients after stroke (series of strokes). The stroke-related neurodegeneration gives rise to numerous neurological disorders, including cognitive decline (vascular dementia), motor disability (paralysis), and others associated with a wide range of impairments. Massive neuronal death after stroke could be barely overcome only by pharmacological interventions, but requires also implementation of cell therapies for replacement strategies. Although the long history of stem cell research had provided conceptual advances and clinical relevance of cell-based therapy, it has been less understood the neurophysiological basis of such tremendous effects of stem cells on the post-stroke recovery of brain function. Because recovery of the brain is not a single process, it is essential to clearly define the precise timing required for maturing of neurophysiological activity, ranging from intrinsic excitability to network function, for the entirely different stem cell-derived phenotypes. Dissecting this would expand the knowledge about stem cell therapy to find how best to use multiple routes of the therapy (induced pluripotent or embryonic stem cells) for the stroke-related neurodegeneration. More work is needed on defining the regulatory role of pathological physiological environment on stem cell neurogenesis to provide the field with a meaningful consideration of cell therapy in context of promoting ‘self-repair’ of the post-stroke brain by engaging endogenous brain recovery mechanisms to power self-renewal. The perspective remains in accelerating neurophysiological maturation of neuronal phenotypes in the post-ischemic tissue tailored to enhancing the functional influence and, thereby, maximizing beneficial effects. Understanding the regulatory role of pathophysiological environment on stem cell grafts will foster cell therapy to augment therapeutic interventions in stroke-related neurodegeneration and to improve ultimate outcome.

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