Background

Traumatic brain injury (TBI) can lead to necrosis, apoptosis and autophagic cell death of neurons following by multiple events such as opening of the blood-brain or blood-spinal cord barrier, inflammation, edema, ecotoxicity, increase in free-radicals, altered cell signaling and gene expression The microenvironment of the injured brain includes different cell types such as normal and dysfunctional neurons (surviving bodies and dead axons or synapses), denervated intact neurons, senescent cells, blood capillaries, glial scars, free-radicals, neuroinflammatory and neurotrophic factors, and the extra-cellular matric. Thus, the repair and reconstruction of the brain tissue is the ultimate goal for the treatment of brain injury. As part of the acute injury response, glial cells (astrocytes and microglia) migrate to the injury site to repair BBB and SCB and isolate the site of injury. However, the same cells start producing inhibiting growth factors limiting axonal regeneration. The design of neural injury response strategy needs to promote favorable factors and simultaneously inhibit adverse factors. Endogenous neural stem cells (NSCs) can migrate from the subventricular zone (SVZ), dentate gyrus (DG), and striatum to the injury site where they differentiate into neurons, oligodendrocytes, and astrocytes. Axon formation is a critical step to neural connection and synaptogenesis. Axon can grow and sprout from new neurons derived from NSCs.

However transplanting stem cells in-vivo is a complex and difficult operation: 1) these cells have low capacity of migration and tend to form clusters close to the targeted site and 2) they have to integrate into the host neuronal network and survive; overall this process of migration, differentiation and integration has yet to be fully understood. Direct cell reprogramming, or transdifferentiation, is the conversion of a somatic cell into another without inducing pluripotency, using typically defined transcription factors (TFs). For both techniques, the main concerns are risk of tumor formation, and spread of foreign new derived neurons in unintended sites, however cell transplantation is a more involved process with a risk of triggering an immune-rejection from the host and comes with a high-cost involved in production of clinical grade cells for transplantation. Yet direct reprogramming in-vivo still faces difficulties which need to be addressed:

1) Careful selection of the target cell for reprogramming to avoid depletion of the cells being reprogrammed: cells to be reprogrammed need to be carefully selected as not to impair the their functional role.
2) Identify transcription factors (TFs) which promote conversion to identified neuronal cells.
3) Design of a precise and safe gene delivery system.

In the study we will address each of these points.

Design of an efficient and specific strategy which promotes reprogramming of astrocytes to neuroblasts in the adult brain after TBI with a low-risk gene delivery system.

Wenze Niu et al., in their study, selected astrocytes for cell reprogramming since they are one of the most abundant non-neuronal cells in the CNS. And following a TBI, they aggregate to form glial scars which physically and chemically obstruct axonal regeneration. Among the eight TFs (SCLA1, BRN2, KLF4, MYC, MYT1L, OCT4, SOX2 and ZFP521) and the four microRNAs (miR9, miR124, miR125 and miR128), they found that SOX2, by itself, induces the most significant number of DCX^+ cells, adult neuroblast cells (iANBs). Next, they showed that iANBs were only localized in the injected striatal regions and they were not the result of any migration of DCX^+ cells coming from areas surrounding the injection site like lateral ventricle. With various transgenic (Tgs) mice and an inducible reporter *Cst3* gene expression they demonstrated that the iANBs originated form the cells transduced by lentivirus under hGFAP promoter and not from $IBA1^+$ microglia or N2-glia, additionally they also proved that SOX-2 induced iANBS did not originated from neurons going through dedifferentiation and becoming DCX^+ neuroblasts. Then they investigate iANBs characteristics demonstrating that the neuroblasts derived from non-dividing astrocytes and pass through a proliferating state. Finally, after co-injecting BNDF-Nog-expressing lentivirus with SOX2-lentivirus, the researchers performed a whole-cell patch-clamp which exhibited mature neurons with full electrophysiological function. In the course of the experiments, they did not observe any tumor formations confirming that the newly converted neurons have been successfully integrated into the local neuronal network without immediate side-effects.

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