Restore cell balance in the aged brain after stroke by direct in vivo reprogramming technology

Restabilirea echilibrului celular dupa accident vascular in creierul batran prin reprogramare genetica in vivo

Ischemic stroke is the second leading cause of death and the primary reason for sustained disability worldwide for which no cure exists. After stroke, neurons are frequently lost in the infarct core. Astrocytes, on the other hand, become reactive and proliferative, disrupting the neuronal vs non-neuronal cell balance in the lesioned area, especially in the aged brain. Therefore, restoring the balance between neurons and non-neuronal cells within the post-stroke perilesional area is crucial for post-stroke recovery. In addition, proliferating glia become reactive and build up gliotic scars that are initially protective by confining the damaged area. In the long-term, however, the gliotic scar is deleterious by acting as a barrrier to neural regeneration. "Melting" glial scars has been attempted for decades with little success. Alternative strategies include transforming inhibitory gliotic tissue into an environment conducive to neuronal regeneration and axonal growth. The latter idea has gained momentum following the discovery that in vivo direct lineage reprogramming in the adult mammalian brain is a feasible strategy for reprogramming non-neuronal cells into neurons; this exciting new technnology emerged as a new approach to circumvent cell transplantation. However, the potential of this new methodology has not been tested to improve restoration of structure and function in the hostile environment caused by the fulminant inflammatory reaction in the brains of aged animals following stroke. To this end, we will be using commercially available retroviral/lentiviral delivery systems encoding transcription factors, *SOX2* or *NeuroD1* or two transcription factors (*Neurog2 and Bcl-2)* to target astrocytes in the neocortex of aged rats. Successful direct in vivo reprogramming of reactive glia into *neuroblasts and mature neurons* will be assessed by cellular phenotyping and behavioral recover.Since there is no restorative treatment available for stroke, and given the overwhelming importance of stroke therapy for both patients and society, this approach, if successful will be a breakthrough in the field.

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