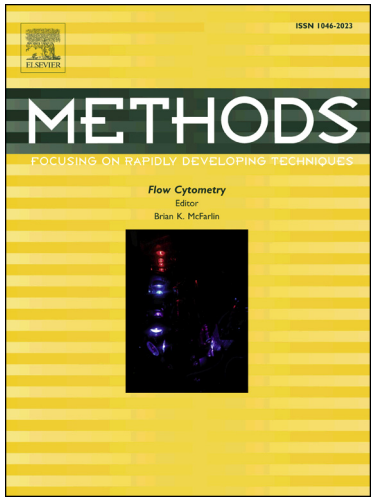

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Methods of reactivation and reprogramming of neural stem cells for neural repair

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Abstract:

Research on the biology of adult neural stem cells (NSCs) and induced NSCs (iNSCs), as well as NSC-based therapies for diseases in central nervous system (CNS) has started to generate the expectation that these cells may be used for treatments in CNS injuries or disorders. Recent technological progresses in both NSCs themselves and their derivatives have brought us closer to therapeutic applications. Adult neurogenesis presents in particular regions in mammal brain, known as neurogenic niches such as the dental gyrus (DG) in hippocampus and the subventricular zone (SVZ), within which adult NSCs usually stay for long periods out of the cell cycle, in G0. The reactivation of quiescent adult NSCs needs orchestrated interactions between the extrinsic stimulis from niches and the intrinsic factors involving transcription factors (TFs), signaling pathway, epigenetics, and metabolism to start an intracellular regulatory program, which promotes the quiescent NSCs exit G0 and reenter cell cycle. Extrinsic and intrinsic mechanisms that regulate adult NSCs are interconnected and feedback on one another. Since endogenous neurogenesis only happens in restricted regions and steadily fails with disease advances, interest has evolved to apply the iNSCs converted from somatic cells to treat CNS disorders, as is also promising and preferable. To overcome the limitation of viral-based reprogramming of iNSCs, bioactive small molecules (SM) have been explored to enhance the efficiency of iNSC reprogramming or even replace TFs, making the iNSCs more amenable to clinical application. Despite intense research efforts to translate the studies of adult and induced NSCs from the bench to bedside, vital troubles remain at several steps in these processes. In this review, we examine the present status, advancement, pitfalls, and potential of the two types of NSC technologies, focusing on each aspects of reactivation of quiescent adult NSC and reprogramming of iNSC from somatic cells, as well as on progresses in cell-based regenerative strategies for neural repair and criteria for successful therapeutic applications.

Keywords: neurogenesis; reactivation; adult neural stem cell; reprogramming; induced neural stem cell

1. Introduction

Injuries, along with many other diseases, in the central nervous system (CNS) of adult mammalian are liable to cause death or permanent disability due to the loss of neurons and glial cells [1-3]. To repair the damage requires being able to regenerate the correct cell types in the injured areas. The discovery of neural stem cells (NSCs) that can differentiate into neurons and glia has opened a new avenue for potential neural repair, which, conceptually, can be achieved either by stimulation of NSCs inhabitant in adult brain or through transplantation methods with induced NSCs (iNSCs). Adult NSCs are found mostly in two regions of the anterior brain, subgranular zone (SGZ) within the hippocampus dentate gyrus and the sub ventricular zone (SVZ) lining the lateral ventricles [4]. Both two niches consisted of diverse cell types and structures, such as neurons, glia, axon projections and blood vessels. The main function of the niches is to create an opposite environment that keeps most of stem cells in a quiescent and undifferentiated state [5]. Most of the