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Glial-Neuron Transformation by "Chemical Cocktail"

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ABSTRACT: Repairing of brain damage is a challenging task due to the limited regenerative potential of complex network of neurons interspersed with glial cells. To address this issue, a number of approaches are in progress. Here we discuss a fascinating approach in which reactive astrocytes generated during any brain injury can be transformed into functional neurons using a mixture of small molecules or "chemical cocktail". This "chemical cocktail" leads to the conversion of reactive astrocytes into neurons by targeting two very important transcription factors, NeuroD1 and NeuroG2. This chemical approach opens up a new direction in development of regenerative medicine.

KEYWORDS: *Astrocyte, neuron, regenerative medicine, chemical cocktail, brain injury*

The human brain is an inexplicable machine, which contains networks of millions of neurons surrounded by a large number of glial cells with neuroprotective functions. This amazing machinery acts as an integrated precise machine that maintains physiological, motor, and cognitive functions. Any damage or even slight perturbation to this complex machinery due to stress, injury, or neurodegenerative disorders causes severe malfunction in our psychological, motor, and cognitive functions. The indigenous repairing mechanism of the brain is limited due to its inadequate regenerative capabilities and complexities, which makes repair of damage even more challenging. Thus, novel approaches in this direction are extremely important. Various approaches have been attempted, and some of them are promising. Among them, stem-cell-based approaches have shown maximum promise in repairing and regenerating the damage caused in neurons.[1] These approaches are unique due to their regeneration and repairing capability including replacement of damaged cells, restoration of neuronal circuitry, reduction of inflammation/gliosis, and induction of axonal regeneration.[2] Recently, interesting approaches involving reprogramming of reactive astrocytes into functional neurons using multifaceted approaches have emerged as a new strategy. This approach is attractive, given the fact that it reduces the multiple steps of regeneration and transplantation of neurons involved in the stem-cell based approaches. This approach is beneficial due to the resident population of reactive astrocytes already present in the damaged area of brain which will aid in their simultaneous conversion into functional neurons. In this direction, Guo et al., have reported a rather interesting approach to repair the brain damage by reprogramming the reactive glial cells into functional neurons by targeting a single neural transcription factor NeuroD1.[3] This has been achieved by retroviral transfection of NeuroD1 in vivo in the reactive glial cells present in the cortex of stab injured or Alzheimer's disease (AD) mice model. In an interesting turn of events, the resident astrocytes produce glutamatergic neurons while NG2 cells are transformed into glutamatergic and GABAergic neurons. Not only this, but the neurons produced also prove their functionality by integrating into the innate neural circuit. Apart from this, we are now well acquainted with the fact that epigenetic regulation and transcriptional activation of two transcription factors, NeuroD1 and NeuroGENIN2, play an important role in glial to neuron conversion. While reprogramming of reactive astrocytes into neurons using gene transfection still remains a viable option, new approaches using chemical cocktails might hold the key to the future of regeneration studies.

Here we discuss two such interesting works that demonstrate how chemical cocktails have been used for reprogramming the glial cells to functional neurons (Figure 1). Cheng et al. reported that a mixture of three small molecules known as VCR (Valproic acid, CHIR99021 and Repsox) can cause reprogramming of cultured astrocytes to NeunN$^+$ functional neurons through the activation of NeuroG2 and

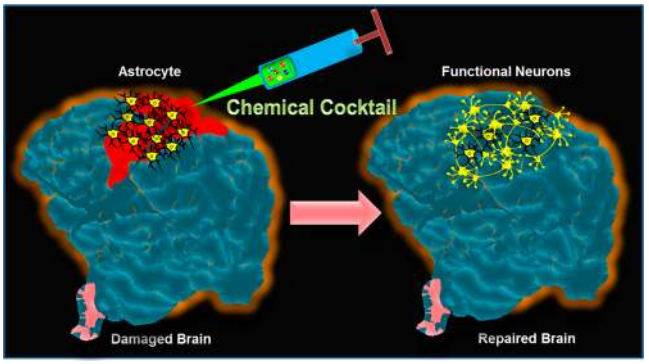

Figure 1. Cartoon representing chemical cocktail induced transformation of reactive astrocytes of a damaged brain area into functional neurons. Potential approach for repairing brain damage.

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NeuroD1 transcription factors.[4] Later, they observed that this combination named VCR also works in the brain of adult mice by converting resident astrocytes into functional neurons, thereby suggesting a practical utility of such chemically induced conversions in vivo.[4] In another intriguing study, Zhang et al. reported the chemical-induced conversion of reactive human astrocytes into functional neurons using a cocktail of nine small molecules that inhibits the glial cells but activates the neuronal signaling pathways to successfully generate a horde of reprogrammed neurons.[5] This chemical reprogramming is also governed by epigenetic regulation and activation of transcription factors NeuroD1 and NeuroG2. These astrocyte derived regenerated neurons are functional for more than 5 months and are able to form functional synapses with the resident neurons. Moreover, these reprogrammed neurons are functional for more than a month after transplantation in the mice brain and integrate successfully in the neuronal circuit.[5]

In summary, these studies offer vast scope in the field of brain damage repair through an alternate route of chemical transformation of reactive glial cells into functional neurons. These chemical cocktails offer many advantages in the repair of brain damage including direct administration of the drug in situ at the injured site, higher chance of BBB permeability when administered through i.v. injection, low chance of graft rejection, and no ethical or other issues concerning their transplantation. However, this approach is relatively new and suffers from quite a few inadequacies like any other emerging methods. Some of the areas of future investigations include the effect of these cocktails on other cells (neurons, oligodendrocytes, normal tissues, etc.), effect of the individual molecules in the cocktail, and the optimum number of molecules with defined concentrations that are required for the successful production of regenerated functional neurons. This chemical approach of reprogramming opens up a new field of immeasurable opportunities that can lead to great discoveries in the arena of regenerative medicine.

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Notes

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