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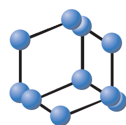
PERSPECTIVE



A Potential Application of Glia-to-Neuron Conversion for the Treatment of Neurological Disorders

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1. INTRODUCTION

In recent years, an *in vivo* cell conversion technique has been developed to regenerate new functional neurons in rodent adult brains by directly converting glial cells to neurons [1-3]. Glial cells are the most abundant cells in the mammalian adult brain, and they constitute more than half of the brain cells. Compared to non-dividing neurons, glial cells have the intrinsic proliferative capability and thus can serve as source cells for neuroregeneration. On the other hand, using endogenous glial cells for generating new neurons could avoid transplantation of external cells and has no risk of immunorejection [4]. To date, *in vivo* direct glia-to-neuron conversion has been successful in astrocytes and Müller glia [1-3]. The following methods have been used to convert glial cells into neurons in the central nervous system (CNS): 1) using shRNA-mediated knockdown of polypyrimidine tract-binding protein, an RNA-binding protein, to convert midbrain astrocytes into dopaminergic neurons [1], 2) using AAV-mediated ectopic expression of NeuroD1 and Dlx2 transcription factors to convert striatal astrocytes into GABAergic neurons [2], 3) using CRISPR-mediated knockdown of a single RNA-binding protein Ptbp1 to convert Müller glia into retinal ganglion cells [3]. These state-of-the-art approaches have been shown to effectively improve neuronal functions in animal models of neurodegenerative diseases.

2. FUTURE PERSPECTIVES

To develop a novel therapy for neurological disorders using the glia-to-neuron conversion approach, we need to ascertain that newly converted neurons can be integrated into functional neural circuits in the CNS. Currently available techniques, including optogenetic stimulation or chemogenetic manipulation and *in vivo* calcium imaging with miniaturized fluorescence microscopes (miniscopes), are powerful to analyze the integration of the converted neurons into neural circuitry and functional recovery after glia-to-neuron conversion. By combining with AAV-mediated specific expression of light-sensitive proteins or designer receptors exclusively activated by designer drugs (DREADDs) on the converted neurons, optogenetic stimulation or DREADDs-based chemogenetic manipulation can be used to specifically activate or inhibit the converted neurons in the CNS. Meanwhile, *in vivo* calcium imaging with miniscopes can monitor real-time neuronal activity modulated by optogenetic stimulation or chemogenetic manipulation of neural circuits integrated with the converted new neurons. Alternatively, two-color spectrometer-based *in vivo* fiber photometry can be employed to record cell-specific dynamic neurotransmitter release and calcium influx-indicated neuronal activity in the CNS while optogenetic stimulation or DREADDs-based chemogenetic manipulation of a rewired neural circuit, which can provide experimental evidence to show synaptic activities in the rewired neural circuit. Together, we will be able to characterize the integration of new neurons following *in vivo* direct glia-to-neuron conversion and demonstrate functional recovery resulting from neural circuitry rewiring after such cell conversion.

Moreover, it is critical to know the types of new neurons generated from the glia-to-neuron conversion approach. It has been reported recently that the converted neurons in different brain areas can be developed into different types of neurons, which suggests that local environmental cues may play an important role in specific new neuron development at certain brain regions [1]. Non-coding genetic variation is a key factor to control phenotypic diversity, and cell type-specific promoter-enhancer interactomes may underlie region-specific differentiation of new neurons [5]; however, the cellular and molecular mechanisms for the effect of the local environment remain unclear. Therefore, future studies focusing on exploring such mechanisms will advance our understanding of how different types of new neurons are developed through the glia-to-neuron conversion in the CNS.

Additionally, myelination of neuronal axons enables fast nerve conduction and provides a structural basis for normal signal transmission in the CNS. It is still unknown whether the new neurons generated from the glia-to-neuron conversion approach are myelinated, and if so, how the myelination is regulated. As we know, oligodendrocytes produce myelin sheath to wrap around neuronal axons in the CNS [6]. The function of myelinating oligodendrocytes is regulated by

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some genetic and epigenetic mechanisms [7, 8]. For instance, epigenetic regulation (*e.g.*, DNA methylation, histone modification, and chromatin remodeling) contributes to multiple aspects of oligodendrocyte development and regeneration [9-11]. It is interesting to unravel the involvement of oligodendrocytes in the development of new neurons following glia-to-neuron conversion. Investigating the underlying mechanisms for the myelination of the converted neurons will identify potential molecular targets that can be used to develop a novel approach to enhance functional activities of the new neurons during the cell conversion treatment.

CONCLUSION

In summary, a glia-to-neuron conversion is a novel approach that can be developed into a potential therapy for neurological disorders. However, several issues, such as integration of the converted new neurons into functional neural circuits, local environment-dependent differentiation of the converted new neurons, and possible myelination of the converted new neurons, should be addressed by further studies for fine-tuning the glia-to-neuron conversion approach.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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