Clinical Neuroscience & Neurological Research International Journal
ISSN: 2689-6001

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Mini Review *Volume 5 Issue 1*

Unlocking the Potential of Dermal Fibroblast: Direct Differentiation to Functional Neuron

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Received Date: October 30, 2024; **Published Date:** November 06, 2024

Abstract

Neurodegenarative diseases are slow and progressive. Human nervous system is much more complicated than any animals. In human patients the disease courses don't reflect in animal models and the variability and mutation are not alike. While focusing on neurological research for disease mechanism or drug testing, the data of animal models and their limitations severely impact on cell type specific contribution to disease. Hence, induced pluripotent stem cells (iPSCs) derived neurons used as valuable tools for studying disease mechanism or chemical testing for neurotoxicity. However, various disadvantages like the clonal selectivity, loss of epigenetic markers and time are the factors that impact on research achievements. Hence use of skin fibroblasts for direct conversion following rapid methods facilitates differentiation into astrocytes, neurons and oligodendrocytes. These fibroblast generated neuronal cells are of pure population at large numbers that are used for numerous neurological and neurodegenerative disorders. In this review author put some methods and their significances in the current technology.

Keywords: Skin Fibroblast; iPSCs; Neuron; Neurodegenerative Diseases

Introduction & Background

For studying underlying mechanism of neurological diseases and to screen the chemicals for its neurotoxic potential, animal models are being used historically as gold standard. However, the data generated are often shows limited feat with human physiological system. There are several reasons for variability such as display of disease phenotypes, genetic background, mutations and variation in drug sensitivity. Further many of the neurological disorders are rare and only seen in human and for these no animal models are existing. Hence use of appropriate cell type of human would be more relevant and that would facilitate pre-clinical research for drug testing, screening and safety testing of chemicals. Since last few decades, cellular reprogramming technology developed rapidly and successfully used for various researches in neurological and neurodegenerative diseases. Using four transcription factors (Sox2, Oct4, KLF4 and c-Myc), Yamanaka and Takahashi showed for the first time that these four factors are capable of redirecting somatic fibroblasts to form iPSCs [1]. Through traditional methods, fibroblast cells can be reprogrammed to induced pluripotent stem cells (iPSCs) and are capable of differentiating into various cell types of the body and all three germ layers [2]. Both intrinsic and extrinsic factors can determine the cell fate [3]. These cues can be altered or reprogrammed by using lineage specific transcription factors that can convert somatic cells into neuron [4].

Different types and combinations of transcription factors were used by various researchers to reprogram directly to differentiate into neurons. The results of reprogramming

gives induced neural progenitor cells (iNPCs) and these iNPCs can differentiate into astrocytes (iAs) [5], neuron (iNs) [6] and oligodendrocytes (iOs) [7]. The reprogrammed donor fibroblasts which become neuron retain the functional properties of age matched normal as well as age related neurodegenerative and neurological disorders [8]. This powerful conversion protocol is used for evaluation of novel therapeutic approaches for pre-clinical drug screening, neurotoxicity assays and age-related neurological and neurodegenerative diseases.

Discussion and Future Perspectives

The nervous system of human is the most complex one among all the animals. Hence to study the neurological aspects or functional assays, human cells are the most relevant ones that can predict the closer views. For our beneficial research point of views, direct conversion of human skin fibroblast using small molecules cocktails gives functional neurons and astrocytes. The chemically induced neurons retain neuronal properties like expression of neuronal cell marker proteins, synaptic proteins, in terms of electrophysiological functional properties and gene expression pattern. Therefore, it is established that somatic fates can be converted by manipulating the cell signaling pathways. The cocktails of chemical used for endogenous fate determination without the help of any endogenous or exogenous transgenes [9].

It is well established that master transcription factors are responsible for determining the specific cell and also small molecule cocktails are sufficient to activate the required neuronal genes to facilitate neurotransmitter and neuronal signals [10]. Recently, it has been demonstrated that the neuronal cell fate can be determined by neuron-fate-determining proneural genes, small molecules and additional transcriptional factors [11]. Direct reprogramming by small-molecule-driven fibroblasts to neuron is a sequential ordered transcriptional activation process. In this efficient gene activation process of cell-fate- determination, the neuronal-specific transcriptional auto-regulatory loops get activated and establish neuronal functional properties. The development of chemical induced or small molecule cocktails suggests a general strategic differentiation pattern that manipulates cell fate through lineage specific genetic reprogramming for desirable neuronal specific genes. Also it silences initial fibroblast specific gene expression. To move forward for chemical reprogramming it may be possible to identify other small molecules that can do neuronal plasticity and synaptic function. The direct lineage specific reprogramming may maintain the neuronal properties for longer period using other survival factors for neuron. For studying neurological disease mechanism, drug testing and pre-clinical research this method may be useful.

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