Chemical Transdifferentiation: a New Strategy in the Fight against Neurodegenerative Disease

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Cell transdifferentiation of somatic cells directly into desirable cells has sprung up in recent years, which also has provided an alternative cell source for cell therapy in regenerative medicine, comparing with cell reprogramming. However, the conventional strategy for generating target cells through transdifferentiation was mainly based on viruses expressing exogenous transcription factors, which was unavoidably related with safety issues when translated into clinical application. Small molecules with more advantages in manipulating cell fate changes has attracted attentions of researchers in regenerative medicine. Especially the advent of chemically-induced pluripotent stem cells [1] opens a new era of regeneration medicine. Based on our VCR induction protocol, Hu et al. added more chemical compounds with VCR to generate neural stem cells from mouse fibroblasts, which includes VPA, CHIR99021, A83-01, BIX01294, RG108, PD0325901, and Vitamin C [3]. Interestingly, Baharvand et al. induced human fibroblasts in suspension culture into neural progenitor cells only in the presence of 5-Aza [4]. Based on our VCR induction protocol, Hu et al. added small molecules known to promote neural progenitor cell differentiation to directly convert adult normal and Alzheimer’s disease human fibroblasts into neuronal cells. The additional compounds are Forskolin, SP600125, GO6983, and Y-27632 [5]. Besides, functional neurons can also be induced from human fibroblasts by alternative recipe containing SB431542, CHIR99021, VPA, LDN193189, DAPT, Tzv, TTNPB, SAG, and Purmo [10].

Both Alzheimer’ Disease (AD) and Parkinson’s Disease (PD) belong to neurodegenerative disorder, partially due to losses of functional neurons. Transplantation of isolated neural stem cells or differentiated sub-specific neurons is proven to be helpful in alleviating symptoms in rodent models of AD and PD [11]. However, cell transplantation has been limited to cell sources. Chemical transdifferentiation of easily accessible somatic cells into neuronal cells in vitro successfully help solving this issue, which will provide unlimited and clinically safe cells for individual patients. Except for that, the other issues related with transplantation of engineered cells into central nervous system are delivery strategy and integration efficiency. To bypass these obstacles, transdifferentiation in vivo of resident cells into functional cells to repair damaged tissues is thought to be the ultimate goal in regenerative medicine. For neurodegenerative disease, glial cells, especially astrocytes proliferate, accompanying by losses of nearby neurons after damage. Thus, many groups have worked on delivery of viruses expressing exogenous transcription factors in vivo to convert local astrocytes into neuronal stem cells or neuro blasts or neurons [12-16]. Without introduction of viruses delivering exogenous genes, which are also involved in safety issues, the cocktails of small molecules even cocktail of pharmaceutical drugs identified in astrocytic-neuronal conversion in vitro assay might be applied by local delivery or systemic administration to achieve in transdifferentiation in situ. It is worth to mention that glial cells can be converted into neurons in vivo after brain injury at low efficiency by VPA alone [17], which is a drug to treat epilepsy and bipolar disorder. Although the side effect of the small molecules needs to be fully considered before clinical application, chemical transdifferentiation brings us promising prospects to the treatments of neurodegenerative disease, including AD and PD [18] (Figure 1).

All the above neuronal cell transdifferentiation reported so far was initiated mainly from fibroblasts both in mouse and human. Due to neural cells and fibroblasts belong to distinct germ layer ectoderm and mesoderm individually, generated neural cells often remain the epigenetic memory of starting fibroblasts, which indicates incomplete transformation between cells and also hinders the clinical translation of these chemically induced cells. Considering the proximity in lineage distance among neuronal cells, astrocytes are one of the ideal starting candidate cell type for generating neural stem/progenitor cells or neurons. Recently, we found that combination of VPA and Repsroxx was able to convert mouse astrocytes into neuro blasts and neurons in vitro [9]. Beyond that, Zhang et al. demonstrated that cultured human astrocytes can also be induced efficiently into functional neurons under sequential exposure to cocktail of SB431542, CHIR99021, VPA, LDN193189, DAPT, Tzv, TTNPB, SAG, and Purmo [10].

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Figure 1: Generation of neuronal cells through chemical transdifferentiation.

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