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Small molecules approach for conversion into the neuronal lineage

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Over the past years, manipulation of cell identity to derive a desired organ specific cell type has become a major research interest since efficient reprogramming via forced expression of transcription factors had been achieved. The major aim of these studies is to obtain any somatic cell type that can be used in drug discovery and regenerative medicine, but genetic manipulation of cells by the use of tissue-specific transcription factors poses unknown risks and is therefore associated with safety concerns. Recent work showed that trans differentiation can be also achieved with a gene-free approach using small, chemically defined molecules. In my work presented here, it can be shown for the first time that human fibroblast cells can be converted into cells of the dopaminergic lineage with a cocktail of small molecules containing epigenetic modifiers targeting histone acetylation and histone methylation, kinase inhibitors, and a regulator of cAMP levels. The converted fibroblasts exhibit neuron specific gene expression pattern at the mRNA and protein level, and also produced dopamine indicating this fundamental functional property. A crucial part in the protocol is the inhibition of TGFβ, BMP and GSK3β signaling in order to convert fibroblast into the neurons, which could be modulated by the small molecule inhibitor E738. High levels of AKT1 and GSK3β phosphorylation in the absence of CREB activation indicated an important new cross talk between AKT1 and GSK3β signaling for the neuronal lineage. Activation of Chk2 and HSP27 did not differ significantly from non-induced fibroblast, confirming low toxicity of the cocktail used. Induced fibroblasts did not exhibit a transient progenitor cells phase. On the other hand, postnatal mouse glia cells treated with a similar cocktail of small molecules as used for fibroblast trans differentiation, were converted into semi-functional neurons through a proliferative, "de-differentiated", stage via adding the small molecules BIX. We observed that de-differentiated glia cells possessed neuronal stem cell like properties indicated by gene expression, self-renewal and neurosphere generation properties, other neuronal specific markers and half Na+ channel current. Taken together, the results presented here clearly show that using well defined combinations of small chemical molecules can be sufficient to obtain functional neurons of the dopaminergic lineage by reprogramming from human fibroblast. Moreover, with minor adjustments, a similar cocktail of small molecules was sufficient to obtain semi-functional neurons starting with postnatal glia cells without the introduction of exogenous genetic factors.

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