Chemical conversion of human fibroblasts into neuronal cells: dawn of future clinical trials

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Major causes of human death in developed countries are atherosclerosis[1] and carcinogenesis.[2] Atherosclerosis finally leads to a variety of diseases such as myocardial infarction and cerebral infarction. The essence of these pathologic processes is largely due to free radical reactions or oxidative stress due to our persistent use of oxygen in the presence of iron,[3–5] and the products can be literally rust in our body.[6] Heart may be replaced with transplantation from another person with brain death under his/her own permission, but it is currently impossible to transplant brain. Additionally, highly ethical issues, severe donor deficiency and immunological rejections are always present with transplantation.[7]

If brand-new cells and organs of any type to be replaced and of their own immunophenotype were freely available, all the people on earth would benefit from this novel technology. Induced pluripotent stem cells can be established from differentiated somatic cells by the forced induction of four transcription factors: *Oct3/4*, *Klf4*, *Sox2* and *c-Myc*.[8] However, premature termination of reprogramming might lead to cancer development through altered epigenetic regulation.[9]

Recently, the concept of directly converting one type of somatic cell into another has attracted much attention.[10] However, one of the major drawbacks linked to the current strategies is that they are also based on ectopic expression of important developmental genes (transcription factors, etc.),[11] which might cause unexpected undesired effects. In the present issue of *Journal of Clinical Biochemistry and Nutrition*, Dai *et al.*[12] for the first time describe a highly efficient chemical conversion of human fibroblasts to neuronal cells with defined six chemical compounds (Fig. 1). Their protocol used five inhibitors to block distinct signaling pathways including transforming growth factor (TGF)-β (SMAD pathway), bone morphologic protein (BMP), glycogen synthase kinase (GSK)-3β, MEK-ERK and p53, together with a cAMP stimulator. Moreover, the authors emphasize that this protocol shortens the time required for differentiation into neuronal cells to 3 weeks in comparison to the reported protocols[10,13] with ~90% efficiency.

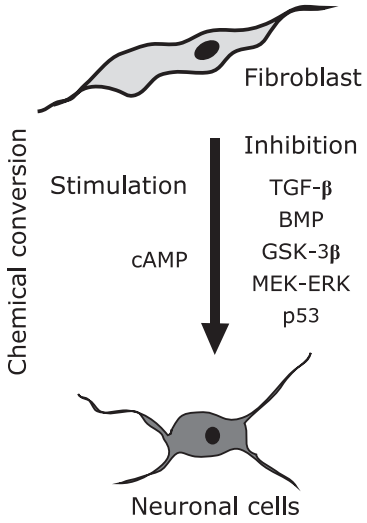

Fig. 1. Chemical conversion of human fibroblasts into neuronal cells. Refer to text for details.

I believe that this is the dawn of regenerative neurology. In a few years or so, human clinical trials would be performed by the use of this technique. Target diseases would be neurodegenerative diseases[14] such as Alzheimer's and Parkinson diseases, motor neuron diseases such as amyotropic lateral sclerosis, and cerebral infarction/hemorrhage. Simultaneously, we always have to consider how we can load these new neuronal cells with long-time experience and memory of the recipient if necessary.

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