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Editorial

Progress in Clinical-Grade Induced Human Neural Stem Cells: An Editorial

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One of the major breakthroughs in regeneration medicine is the generation of human induced pluripotent stem cells (iPSCs) from differentiated somatic cells by defined transcription factors [1,2], which leads to the exploration of cell therapy [3] and in vitro disease modeling [4]. This kind of reprogramming concept has extended into the field of transdifferentiation from one differentiated cell type into another through overexpression of lineage related transcription factors [5-12]. However, because of the little or no proliferation potential, the potential utilities of these transdifferentiated somatic cells are limited. Direct conversion of somatic cells to lineage-committed stem/progenitor cells, such as neural stem/progenitor cells, would allow production of sufficient cells for downstream research or application and overcome the potential risk for tumor formation by iPSCs. Approaches for generating clinical-grade human somatic stem cells show great application values.

In the neuroscience field, human neural stem/progenitor cells have been generated from fibroblasts by overexpressing neural transcription factors, or Yamanaka factors or similar cocktails of transcription factors [13,14]. Because of the use of integrating lentiviruses or retroviruses, which could disrupt endogenous gene expression and are associated with the risk for tumor formation due to potential spontaneous reactivation of the viral transgenes [15], it limits the potential application of these cells in the clinical environments.

In order to avoid using integrating viruses, episomal vectors were applied to generate human induced neural stem cells. Pei and colleagues generated iNPs from human urine cells using oriP/EBNA episomal vectors [16]. They used a set of six factors that have been used for iPSC generation [17], and the iNPs were generated on Matrigel (a mixture of different coating materials). However, interestingly, it is stated in the report that the protocol does not apply to human dermal fibroblasts. Although the method of episomal vectors avoids using viruses, there still exists the possibility of genomic integration and consequentially potential mutation.

Recently, we used Sendai viruses (SeV) carrying four Yamanaka factors to generate iNPs from human and monkey fibroblasts [18]. SeV is a RNA virus. To date, there is no report of pathogenicity associated with SeV in primates, and its safety could be further enhanced by the F-deficiency [19]. SeV-based vector has been used in clinical gene therapy for cystic fibrosis [20,21] and vaccine delivery [22]. Additionally, the temperature-sensitive nature of the RNA virus [23] offers another safeguard step to ensure the removal of viral genomes. The SeV derived-iNPs were generated and cultured in laminin-coated plates with a chemically defined medium. They exhibit characteristic morphology, gene expression patterns, growth rate, as well as predictable in vitro and in vivo differentiation potentials. Furthermore, the regional information of these iNPs was carefully examined. The stable expandable iNP lines carry a hindbrain identity and can differentiate into hindbrain neurons and, when caudalized, an enriched population of spinal cord motor neurons. Regional specific human iNPs are another effort towards clinical application.

The ideal way to generate clinical-grade human iNPs may be using some non-virus, non-integration ways, such as artificial RNAs, in an animal-free and chemically defined environment. And the iNPs should be well characterized, especially the regional identities, because as for neurodegenerative diseases, usually they needed accurate region-targeted treatment. Furthermore, how to maintain the stability of the human iNPs is another important issue for the future industry production and clinical application.

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