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Fueling Neuroscience with Human Pluripotent Stem Cells

Editorial

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Since the discovery of the first embryonic stem cells (ESCs) from mice (Evans & Kaufman, 1981; Martin, 1981), *in vitro* study on the mechanisms of neural development and neural degenerative disorders never stops (Berberi et al., 2003; Kawasaki et al., 2000;Lee et al., 2000; Lu & Song, 2006; Lu et al., 2009;Pacherik et al., 2002; Strübing et al., 1995; Tropepe et al., 2001; Ying et al., 2003).With the isolation of the first human ESCs (Thomson et al., 1998), the dream of using these magic cells to understand the human being's brain and to treat the neural degenerative diseases starts showing in scientists' and clinicians' thoughts. In 2006 and 2007, Yamanaka group and Thomson group successfully generated mouse and human induced pluripotent stem cells (iPSCs) (Takahashi&Yamanaka, 2006; Takahashi, et al., 2007; Yu et al., 2007), which not only overcomes the ethical issues brought by the isolation human ESCs,but also may in theory avoid immunosuppression reactions after autologous transplantation. This creation makes it possible to study the individualized human cells *in vitro*, especially the neural cells in the central nervous system (CNS), which usually are hard to obtain from live human beings. Human pluripotent stem cells (PSCs) derived neural cells have been globally used in the two major areas in neurosciences: 1. Research on human neural system development and neural degenerative diseases' pathophysiologic process, which may help researchers find potential targets to treat diseases; 2. PSCs based pre-clinical/clinical cell therapies(a part of personalized medical treatments).

Understanding human neural development and neural diseases by PSCs

Till now, most knowledge on the mammalians' neural system development is obtained from non-human being animals, such as rodents and monkeys. And because of the ethical issues, neural diseases were usually modeled in the text of non-human being animals, for example, modeling brain serotonin deficiency using rodents(summarized inLu, 2013a). Although non-human being animals share similar development pathways and may have similar pathophysiological processes during neural system diseases with human beings, as the very specific species in the world, human beings use unique and more complicated mechanisms to develop the most important control system--- neural system, and the pathophysiological processes during the development of disease may be more complex. Before the discovery of human PSCs, researchers had hard time to obtain human neural cells for *in vitro* culture and study; and it is even difficult to understand the development processes from embryonic cells to matured neurons or glial cells. Human PSCs, which can mimic the *in vivo* human being development *in vitro*, offer scientists a very powerful tool to study human neural development(Zhang et al., 2001).One of the typical examples is the *in vitro* specification of the spinal cord motor neurons with human ESCs (Li et al., 2005). Human ESCs as very early embryonic cells develop into embryonic bodies (EBs), which mimic the three germ layers stages; with the treatment of fibroblast growth factor 2 (FGF2), retinoic acid (RA) and sonic hedgehog (SHH), HB9+/ChAT+ spinal motor neurons were generated from human ESCs. It is an interesting case to show how to use the knowledge from animals in the human *in vitro* development and how to use PSCs to demonstrate the unique properties of human being. Furthermore, human PSCs derived motor neurons make it possible to study the motor neuron related diseases, such as Amyotrophic lateral sclerosis (ALS) (Chen et al., 2014). Similar researches also happened on other neural diseases, such asDown syndrome (Weick et al., 2013) and Rett syndrome(Williams et al., 2014).

Application of PSCs derived neural cells for treating diseases

Another important function of human PSCs derived neural cells is to treat neural system diseases. One typical example is the cell therapy trials for Parkinson's disease (PD). Human ESCs could be efficiently differentiated into midbrain dopaminergic neuron progenitors and then transplanted into PD animal's brain (Kirkeby et al., 2012; Kriks et al., 2011). As for the autologous transplantation, researchers are conducting related studies using non-primate animals, such as Rhesus monkey (Emborg et al., 2013).

It should be admitted that there is still a long way to go before the cell therapy could be applied in clinical environment. Scientists are trying their best to optimize the graft cells, either by generating PSCs without transgene integration(Hou et al., 2013; Lu, 2014; Obokata et al., 2014), or by directlyconverting human somatic cells into neural progenitors with non-integration virus (Lu, 2013b; Lu, 2013c; Lu et al., 2013). Reprogramming the *in situ* somatic cells in the brain may be another potential treatment for neural diseases (Guo et al., 2014; Lu et al., 2014).

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