Neuron Stem Cell

Ma Hongbao [1], Margaret Young [2], Yang Yan [1]

[1] Brookdale Hospital, Brooklyn, New York 11212, USA; [2] Cambridge, MA 02138, USA
ma8080@gmail.com

Abstract: The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell.
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Normally, stem cells are classified as 4 types according to their plasticity: totipotent stem cell, pluripotent stem cell, multipotent stem cell, and the adult stem cell: (1) Totipotent Stem Cells. When a sperm cell and an egg cell fuse, it forms a fertilized egg called zygote. The fertilized zygote is a totipotent stem cell, which has the potential to give rise to any and all animal cells, such as blood, heart, brain, skin lung, liver cells, etc. It can even give rise to an entire functional organism. The first few cell divisions in embryonic development produce more totipotent cells. In human, after 4 days of embryonic cell division, the cells begin to specialize into pluripotent stem cells. (2) Pluripotent Stem Cells. Pluripotent stem cells are can give rise to all tissue types, but cannot give rise to an entire organism. In the human, on the 4th day of development, the embryo forms into two layers, an outer layer which will become the placenta, and an inner mass which will form the tissues of the developing human body. These inner cells, though they can form nearly any human tissue, cannot do so without the outer layer; so are not totipotent, but pluripotent. As these pluripotent stem cells continue to divide, they begin to specialize further. (3) Multipotent Stem Cells. Multipotent stem cells give rise to a limited range of cells within a tissue type. The offspring of the pluripotent cells become the progenitors of such cell lines the adult cells, such as nerve, blood, heart, lung, kidney and skin cells, etc. They can become one of several types of cells within a given organ. (4) Adult Stem Cells. The adult stem cell (also called somatic stem cell) is a multipotent stem cell in adult humans that is used to replace the cells that have died or lost function. It is an undifferentiated cell exits in differentiated tissue. It renews itself and can specialize to yield all cell types present in the tissue from which it originated. So far, adult stem cells have been identified for many different tissue types such as mesenchymal, neural, hematopoetic, endothelial, muscle, skin, gastrointestinal, and epidermal cells, etc.

Recently, Harvard Stem Cell Institute (HSCI) researchers reported that they have devised two methods for using stem cells to generate the type of neurons that help regulate behavioral and basic physiological functions in the human body, such as obesity and hypertension, as well as sleep, mood, and some social disorders. This work collaborates with researchers from New York, Toronto, and Tokyo. This stem cell work was done by Florian Dr. Merkle and colleagues that first time to use live hypothalamic neurons as the targets for drug discovery and therapeutic cell-transplantation efforts for conditions related to stress, reproduction, puberty and immune function, and they can be sued as hypothalamic neurons (Robbins, 2015).

The hypothalamus is conserved brain structure and it plays a basic brain function, even it makes up only about 0.3%. The hypothalamus serves as a regulator for numerous basic physiological functions. It is difficult to observe live hypothalamic cells (Merkle, 2015). Researchers could use these new tools to grow hypothalamic neurons from patients with a specific disease. Studying the development and death from those neurons could provide researchers with the information necessarily to understand a disease's origins (Robbins, 2015).

For the stem cells growth, there is another phenomenon transdifferentiation. Abstract: Transdifferentiation is a non-stem cell transforming into a different type of cell, or a differentiated stem cell changing to another type of cells. Transdifferentiation is a type of metaplasia, which includes all cell fate switches, including the interconversion of stem cells. There are about 300 different types of cells, each specialized for a specific function. Most of our cells are matured cells, i.e. adult cells, rather than stem. The importance of the

trandifferentiation is to transform the non-stem cell into a different type of cells. If we can transform the old cells to a young cell, we can keep the life living eternally and keep the life body in the younger stage forever. This is the really biological immortality – living eternal – we will not die (Yang and Ma, 2010). In the transdifferentiation, the adult stem cells can differentiate into different cell types, such as brain stem cells can differentiate into blood cells or blood-forming cells can differentiate into cardiac muscle cells. In the transdifferentiation, the adult cell can be reprogrammed into other kind of cells, which is possibly involved in the damage recover. The transdifferentiation could to offer a way for the life body to convert the life line process, i.e. to cause the life processing from older to younger. This possibly happens in a jellyfish Turritopsis nutricula. Turritopsis nutricula is a hydrozoan that can revert to the sexually immature (polyp stage) after becoming sexually mature. It is the only known metazoan capable of reverting completely to a sexually immature, colonial stage after having reached sexual maturity as a solitary stage. It does this through the cell development process of transdifferentiation. This cycle can repeat indefinitely that offers it biologically immortal. It is not clear if stem cells are involved in this immortality or not. Up to now, there is little academic report in the Turritopsis nutricula studies. To study the mechanism of the biological immortality of Turritopsis nutricula possibly supplies the way finding the biological immortality for human (Ma and Yang, 2010). The transdifferentiation is an important biological event, but still has debate.

The following give some recent reports in the cancer studies.

Arber, C., S. V. Precious, et al. "Activin A directs striatal projection neuron differentiation of human pluripotent stem cells." Development **142**(7): 1375-86.

The efficient generation of striatal neurons from human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs) is fundamental for realising their promise in disease modelling, pharmaceutical drug screening and cell therapy for Huntington's disease. GABAergic medium-sized spiny neurons (MSNs) are the principal projection neurons of the striatum and specifically degenerate in the early phase of Huntington's disease. Here we report that activin A induces lateral ganglionic eminence (LGE) characteristics in nascent neural progenitors derived from hESCs and hiPSCs in a sonic hedgehog-independent manner. Correct specification of striatal phenotype was further demonstrated by the induction of the striatal transcription factors CTIP2, GSX2 and FOXP2. Crucially, these human LGE progenitors readily differentiate into postmitotic neurons expressing the striatal projection neuron signature marker DARPP32, both in culture and following transplantation in the adult striatum in a rat model of Huntington's disease. Activin-induced neurons also exhibit appropriate striatal-like electrophysiology in vitro. Together, our findings demonstrate a novel route for efficient differentiation of GABAergic striatal MSNs from human pluripotent stem cells.

Binder, E., D. Natarajan, et al. "Enteric neurospheres are not specific to neural crest cultures: implications for neural stem cell therapies." PLoS One **10**(3): e0119467.

Enteric neural stem cells provide hope of curative treatment for enteric neuropathies. Current protocols for their harvesting from humans focus on the generation of 'neurospheres' from cultures of dissociated gut tissue. The study aims to better understand the derivation, generation and composition of enteric neurospheres. Gut tissue was obtained from Wnt1-Cre;Rosa26Yfp/Yfp transgenic mice (constitutively labeled neural crest cells) and paediatric patients. Gut cells were cultured either unsorted (mixed neural crest/non-neural crest), or following FACS selection into neural crest (murine-YFP+ve/human-p75+ve) or non-neural crest (YFP-ve/p75-ve) populations. Cultures and resultant neurospheres were characterized using immunolabelling in vitro and following transplantation in vivo. RESULTS: Cultures of (i) unsorted, (ii) neural crest, and (iii) non-neural crest cell populations generated neurospheres similar in numbers, size and morphology. Unsorted neurospheres were highly heterogeneous for neural crest content. Neural crest-derived (YFP+ve/p75+ve) neurospheres contained only neural derivatives (neurons and glia) and were devoid of non-neural cells (i.e. negative for SMA, c-Kit), with the converse true for non-neural crest-derived (YFP-ve/p75-ve) 'neurospheres'. Under differentiation conditions only YFP+ve cells gave rise to neural derivatives. Both YFP+ve and YFP-ve cells displayed proliferation and spread upon transplantation in vivo, but YFP-ve cells did not locate or integrate within the host ENS. Spherical accumulations of cells, so-called 'neurospheres' forming in cultures of dissociated gut contain variable proportions of neural crest-derived cells. If they are to be used for ENS cell replacement therapy then improved protocols for their generation, including cell selection, should be sought in order to avoid inadvertent transplantation of non-therapeutic, non-ENS cells.

Haile, Y., M. Nakhaei-Nejad, et al. "Reprogramming of HUVECs into Induced Pluripotent Stem Cells (HiPSCs), Generation and Characterization of HiPSC-Derived Neurons and Astrocytes." PLoS One **10**(3): e0119617.

Neurodegenerative diseases are characterized by chronic and progressive structural or functional loss of neurons. Limitations related to the animal models of these human diseases have impeded the development of effective drugs. This emphasizes the need to establish disease models using human-derived cells. The discovery of induced pluripotent stem cell (iPSC) technology has provided novel opportunities in disease modeling, drug development, screening, and the potential for "patient-matched" cellular therapies in neurodegenerative diseases. In this study, with the objective of establishing reliable tools to study neurodegenerative diseases, we reprogrammed human umbilical vein endothelial cells (HUVECs) into iPSCs (HiPSCs). Using a novel and direct approach, HiPSCs were differentiated into cells of central nervous system (CNS) lineage, including neuronal, astrocyte and glial cells, with high efficiency. HiPSCs expressed embryonic genes such as nanog, sox2 and Oct-3/4, and formed embryoid bodies that expressed markers of the 3 germ layers. Expression of endothelial-specific genes was not detected in HiPSCs at RNA or protein levels. HiPSC-derived neurons possess similar morphology but significantly longer neurites compared to primary human fetal neurons. These stem cell-derived neurons are susceptible to inflammatory cell-mediated neuronal injury. HiPSC-derived neurons express various amino acids that are important for normal function in the CNS. They have functional receptors for a variety of neurotransmitters such as glutamate and acetylcholine. HiPSC-derived astrocytes respond to ATP and acetylcholine by elevating cytosolic Ca2+ concentrations. In summary, this study presents a novel technique to generate differentiated and functional HiPSC-derived neurons and astrocytes. These cells are appropriate tools for studying the development of the nervous system, the pathophysiology of various neurodegenerative diseases and the development of potential drugs for their treatments.

Hugh, R., F. Bender, et al. "Activated K-Ras, but not H-Ras or N-Ras, regulates brain neural stem cell proliferation in a Raf/Rb-dependent manner." Stem Cells.

Neural stem cells (NSCs) give rise to all the major cell types in the brain, including neurons, oligodendrocytes, and astrocytes. However, the intracellular signaling pathways that govern brain NSC proliferation and differentiation have been incompletely characterized to date. Since some neurodevelopmental brain disorders (Costello syndrome, Noonan syndrome) are caused by germline activating mutations in the RAS genes, Ras small GTPases are likely critical regulators of brain NSC function. In the mammalian brain, Ras exists as three distinct molecules (H-Ras, K-Ras, and N-Ras), each with different subcellular localizations, downstream signaling effectors, and biological effects. Leveraging a novel series of conditional activated Ras molecule-expressing genetically-engineered mouse strains, we demonstrate that activated K-Ras, but not H-Ras or N-Ras, expression increases brain NSC growth in a Raf-dependent, but Mek-independent, manner. Moreover, we show that activated K-Ras regulation of brain NSC proliferation requires Raf binding and suppression of retinoblastoma (Rb) function. Collectively, these observations establish tissue-specific differences in activated Ras molecule regulation of brain cell growth that operate through a non-canonical mechanism.

Lee-Kubli, C. A. and P. Lu "Induced pluripotent stem cell-derived neural stem cell therapies for spinal cord injury." Neural Regen Res **10**(1): 10-6.

The greatest challenge to successful treatment of spinal cord injury is the limited regenerative capacity of the central nervous system and its inability to replace lost neurons and severed axons following injury. Neural stem cell grafts derived from fetal central nervous system tissue or embryonic stem cells have shown therapeutic promise by differentiation into neurons and glia that have the potential to form functional neuronal relays across injured spinal cord segments. However, implementation of fetal-derived or embryonic stem cell-derived neural stem cell therapies for patients with spinal cord injury raises ethical concerns. Induced pluripotent stem cells can be generated from adult somatic cells and differentiated into neural stem cells suitable for therapeutic use, thereby providing an ethical source of implantable cells that can be made in an autologous fashion to avoid problems of immune rejection. This review discusses the therapeutic potential of human induced pluripotent stem cell-derived neural stem cell transplantation for treatment of spinal cord injury, as well as addressing potential mechanisms, future perspectives and challenges.

Liu, C., Y. Huang, et al. "Tissue-engineered regeneration of completely transected spinal cord using induced neural stem cells and gelatin-electrospun poly (lactide-co-glycolide)/polyethylene glycol scaffolds." PLoS One **10**(3): e0117709.

Tissue engineering has brought new possibilities for the treatment of spinal cord injury. Two important components for tissue engineering of

the spinal cord include a suitable cell source and scaffold. In our study, we investigated induced mouse embryonic fibroblasts (MEFs) directly reprogrammed into neural stem cells (iNSCs), as a cell source. Three-dimensional (3D) electrospun poly (lactide-co-glycolide)/polyethylene glycol (PLGA-PEG) nanofiber scaffolds were used for iNSCs adhesion and growth. Cell growth, survival and proliferation on the scaffolds were investigated. Scanning electron microcopy (SEM) and nuclei staining were used to assess cell growth on the scaffolds. Scaffolds with iNSCs were then transplanted into transected rat spinal cords. Two or 8 weeks following transplantation, immunofluorescence was performed to determine iNSC survival and differentiation within the scaffolds. Functional recovery was assessed using the Basso, Beattie, Bresnahan (BBB) Scale. Results indicated that iNSCs showed similar morphological features with wild-type neural stem cells (wt-NSCs), and expressed a variety of neural stem cell marker genes. Furthermore, iNSCs were shown to survive, with the ability to self-renew and undergo neural differentiation into neurons and glial cells within the 3D scaffolds in vivo. The iNSC-seeded scaffolds restored the continuity of the spinal cord and reduced cavity formation. Additionally, iNSC-seeded scaffolds contributed to functional recovery of the spinal cord. Therefore, PLGA-PEG scaffolds seeded with iNSCs may serve as promising supporting transplants for repairing spinal cord injury (SCI).

Xue, F., E. J. Wu, et al. "Biodegradable chitin conduit tubulation combined with bone marrow mesenchymal stem cell transplantation for treatment of spinal cord injury by reducing glial scar and cavity formation." Neural Regen Res **10**(1): 104-11.

This study examined the restorative effect of modified biodegradable chitin conduits in combination with bone marrow mesenchymal stem cell transplantation after right spinal cord hemisection injury. Immunohistochemical staining revealed that biological conduit sleeve bridging reduced glial scar formation and spinal muscular atrophy after spinal cord hemisection. Bone marrow mesenchymal stem cells survived and proliferated after transplantation in vivo, and differentiated into cells double-positive for S100 (Schwann cell marker) and glial fibrillary acidic protein (glial cell marker) at 8 weeks. Retrograde tracing showed that more nerve fibers had grown through the injured spinal cord at 14 weeks after combination therapy than either treatment alone. Our findings indicate that a biological conduit combined with bone marrow mesenchymal stem cell transplantation effectively prevented scar formation and provided a favorable local microenvironment for the proliferation, migration and differentiation of bone marrow mesenchymal stem cells in the spinal cord, thus promoting restoration following spinal cord hemisection injury.

Zhang, P. X., X. R. Jiang, et al. "Dorsal root ganglion neurons promote proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells." Neural Regen Res **10**(1): 119-23.

Preliminary animal experiments have confirmed that sensory nerve fibers promote osteoblast differentiation, but motor nerve fibers have no promotion effect. Whether sensory neurons promote the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells remains unclear. No results at the cellular level have been reported. In this study, dorsal root ganglion neurons (sensory neurons) from Sprague-Dawley fetal rats were co-cultured with bone marrow mesenchymal stem cells transfected with green fluorescent protein 3 weeks after osteogenic differentiation in vitro, while osteoblasts derived from bone marrow mesenchymal stem cells served as the control group. The rat dorsal root ganglion neurons promoted the proliferation of bone marrow mesenchymal stem cell-derived osteoblasts at 3 and 5 days of co-culture, as observed by fluorescence microscopy. The levels of mRNAs for osteogenic differentiation-related factors (including alkaline phosphatase, osteocalcin, osteopontin and bone morphogenetic protein 2) in the co-culture group were higher than those in the control group, as detected by real-time quantitative PCR. Our findings indicate that dorsal root ganglion neurons promote the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells, which provides a theoretical basis for in vitro experiments aimed at constructing tissue-engineered bone.

Zhang, S., Q. Xiao, et al. "Olfactory Dysfunction and Neurotransmitter Disturbance in Olfactory Bulb of Transgenic Mice Expressing Human A53T Mutant alpha-Synuclein." PLoS One **10**(3): e0119928.

Parkinson disease is a multi-system neurodegenerative disease characterized by both motor and non-motor symptoms. Hyposmia is one of the early non-motor symptoms occurring in more than 90% of Parkinson disease cases, which can precede motor symptoms even several years. Up to now, the relationship between hyposmia and Parkinson disease remains elusive. Lack of proper animal models of hyposmia restricts the investigation. In this study we assessed olfactory function in Prp-A53T-alpha-synuclein transgenic (alphaSynA53T) mice which had been reported to show age-dependent motor impairments and intracytoplasmic inclusions. We also examined cholinergic and dopaminergic systems in olfactory bulb of alphaSynA53T mice by

immunofluorescent staining, enzyme linked immunosorbent assay and western blot. We found that compared to wild type littermates, alphaSynA53T mice at 6 months or older displayed a deficit of odor discrimination and odor detection. No significant changes were found in olfactory memory and odor habituation. Furthermore compared to wildtype littermates, in olfactory bulb of alphaSynA53T mice at 10 months old we detected a marked decrease of cholinergic neurons in mitral cell layer and a decrease of acetylcholinesterase activity, while dopaminergic neurons were found increased in glomerular layer, accompanied with an increase of tyrosine hydroxylase protein. Our studies indicate that alphaSynA53T mice have olfactory dysfunction before motor deficits occur, and the cholinergic and dopaminergic disturbance might be responsible for the Parkinson disease-related olfactory dysfunction.

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