Cellular Dedifferentiation and Regenerative Medicine

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Preface

Since we have published our discovery of the dedifferentiation of epithelial cells in *The Lancet* in 2001 [Xiaobing Fu et al. Dedifferentiation of epidermal cells to stem cells *in vivo*. Lancet 2001; 358: 1067–1068], this phenomenon aroused a great deal of our interest. As researchers of trauma and regenerative medicine, we realized cellular dedifferentiation has been deeply investigated by generations of scientists ranging from botany to zoology, which further kindled our interest in unveiling the relation between dedifferentiation and regeneration.

Through our intensive investigation and discovery, dedifferentiation is found to be an irreplaceable process in biological development and regeneration. The evidence is witnessed by scientists in numerous fields, such as plant, invertebrate, amphibian, and mammal. Scientometric and bibliometric analyses have demonstrated that cellular dedifferentiation attracts researchers all over the world, with accent on those in the USA and Western Europe. Several universities and organizations were quite productive in academic achievements on this issue, such as University College London; the University of California, Irvine; the University of Michigan; etc. Prolific scientists, for example, Prof. David M. Gardiner, Prof. Panagiotis A. Tsonis, Prof. Satoh Akira, etc., have represented their works on many publications.

Our group has made remarkable achievements on skin repair and sweat gland regeneration via the process of dedifferentiation. These achievements of sweat gland in vivo and in vitro regeneration appeared in the international field of regenerative medicine for the first time and have earned worldwide commendation as a milestone research. Besides, regeneration of other tissues by dedifferentiation has also obtained exceptional results. For example, Jopling Chris et al. discovered zebrafish heart regeneration by cardiomyocyte dedifferentiation [Jopling Chris et al. Zebrafish heart regeneration occurs by cardiomyocyte dedifferentiation and proliferation. Nature. 2010 Mar 25; 464(7288); 606–609], and Odelberg SJ et al. induced mammalian myotube dedifferentiation by Msx1 [Odelberg SJ, et al. Cell. 2000 Dec 22; 103(7):1099–1109].

In the light of these, I planned to sketch out the spectrum of cellular dedifferentiation to scientists, researchers, and physicians in 2015. We mapped out the theories,

concepts, discoveries, achievements, practices, and perspectives of this issue in the form of a monograph. First, I would like to acknowledge two of my PhD students, Andong Zhao and Tian Hu, who have accomplished significant work in data collection and compiling. I am also grateful for all the authors who have contributed their articles and reviews in the appendixes. Additionally, I would like to express my great gratitude toward all the scientists and researchers, for their permission, whose figures and tables in their publications were cited in this book. Although we have tried our best to get contact with them and ask for permission, there is still imperfection. Finally, I am also grateful for the research foundation support from the National Key Research Projects offered by Ministry of Science and Technology, China, and the publication aid and support by the press of Springer. The accomplishment of this monograph could never be carried out without the effects of all the people and units I appreciated.

Owing to the busy schedule and limits in knowledge, the book might be incomprehensive with flaws and limitations. We hope readers could point these out and would feel free to contact us, in order to make more contribution to the field of dedifferentiation in the future.

Beijing, China Xiaobing Fu

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Chapter 1
Central Nervous System and Dedifferentiation

Abstract Central nervous system serves as the leading organ controlling, manipulating, and involving into almost every aspects of human body's functions. Researches and neuroscientists have been trying to find out varieties of approaches to repair and restore the damaged or degenerated central nervous system. It is generally believed that there are hundreds of billions of neurons in our brain, and the quantity would not change after birth. The olfactory bulb and hippocampus are the only two regions that could undergo self-renewal during our lifetime. Neural stem cells could differentiate into neuronal restricted progenitors and glial restricted progenitors. Glial restricted progenitors could produce type I astrocytes, type II astrocytes, and oligodendrocytes. But the regenerative capacity of these stem cells is far insufficient. Dedifferentiation of certain types of cells that resided in the central nervous system has provided the opportunity for neural regeneration, since other approaches, such as transplantation or drugs, could hardly take effects. Specifically, astrocyte dedifferentiation was observed successfully both in vivo and vitro. Injury triggers the dedifferentiation in vivo, while astrocytes could be reprogrammed to dedifferentiated types in vitro. This review summarized the current understandings and researches on central nervous regeneration, astrocyte differentiation, and direct reprogramming of astrocytes. In order to achieve the goal of CNS regeneration, clarifying the molecular mechanisms of regulating dedifferentiation and redifferentiation in situ would lay the solid foundation for further researches.

Keywords Central nervous system • Neural stem cell • Astrocytes
Dedifferentiation • Regeneration • Brain injury • Spinal cord injury

1 Central Nervous Stem Regeneration, Stem Cell, and Dedifferentiation

1.1 Central Nervous System Injury and Regeneration

Central nervous system (CNS) comprises of the brain and spinal cord. Injuries and diseases of CNS, such as Parkinson's disease, multiple sclerosis, stroke, traumatic brain injury, and spinal cord injury (SCI), result in various functional deficits and

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abnormalities. At the cellular level, all of them lead to apoptotic and necrotic death of neurons. Therefore, replacing the lost neurons with new neurons is essential for CNS repair and regeneration. Unlike non-mammals that exhibit tremendous capacity to regenerate neurons from damaged CNS [1, 2], mammals have limited capacity to spontaneously regenerate the lost neurons. Mammalian CNS was considered as a tissue where new neurons could not be generated once development finished. However, this dogma has been challenged by studies showing that newborn neurons can be generated throughout life in a process called "adult neurogenesis."

1.1.1 Neural Stem Cells

Grown neurogenesis is the process of putting out novel neurons integrating into the existent circuits after early postnatal and fetal development. In mammalian brain, this action predominantly occurs in two portions of the forebrain, subventricular zone (SVZ) of lateral ventricles in telencephalon and subgranular zone (SGZ) of the dentate gyrus in the hippocampus [3]. As neural stem cells (NSCs) dwell in both zones, SGZ and SVZ are called neurogenic area. NSCs are cells of self-renewing multipotent in the adult and developing mammalian CNS. Throughout development, assorted specified precursors dividing a restricted number of times are produced by NSCs before they differentiate into glial cells or neurons terminally, such as oligodendrocytes and astrocytes. In adult mammalian CNS, resident NSCs in SVZ and SGZ maintain neurogenesis throughout adult life: adult NSCs bring about neuroblasts further differentiating into matured neurons integrating into local circuitry within the olfactory bulbs or dentate gyrus. Unlike developing NSCs, fully grown NSCs originate from radial glia or so-called radial glial cells converting into astrocytic-like NSCs in the postnatal brain. Radial glia stem from neuroepithelial cells at the early stage of neurogenesis and are the principal cell type in the underdeveloped brain, where they both serve as scaffolds and neural progenitors for newborn neurons migration. Thus, NSCs in the SVZ share many characteristics with astrocytes. The finding of NSCs and neurogenesis in the grown mammalian CNS modifies our apprehension of the plasticity and role of brain and stimulates passion for harnessing their regenerative possibility in novel treatments for disorders like depression, stroke, SCI, and Parkinson's disease. Native NSCs' therapeutic potentiality is unfortunately limited by the confinement of sturdy neurogenesis to SVZ and the grown SGZ. Furthermore, novel neurons could be generated by adult NSCs only under normal physiological circumstances in SGZ region and SVZ. For example, while NSCs that are separated from SGZ or SVZ are transplanted into the adult brain's ectopic areas, they differentiate into astrocytes and oligodendrocytes mostly [4]. It may be owing to adult NSCs that share some features of glial lineage or neurogenic local microenvironment that is favorable to neuronal differentiation of NSCs. This is further supported by NSCs from SGZ region of the dentate gyrus that can differentiate into olfactory bulb neurons when grafted to SVZ and NSCs isolated from a non-neurogenic region, such as the spinal cord, that can differentiate into neurons when transplanted into dentate gyrus [3]. Therefore, the fact that the

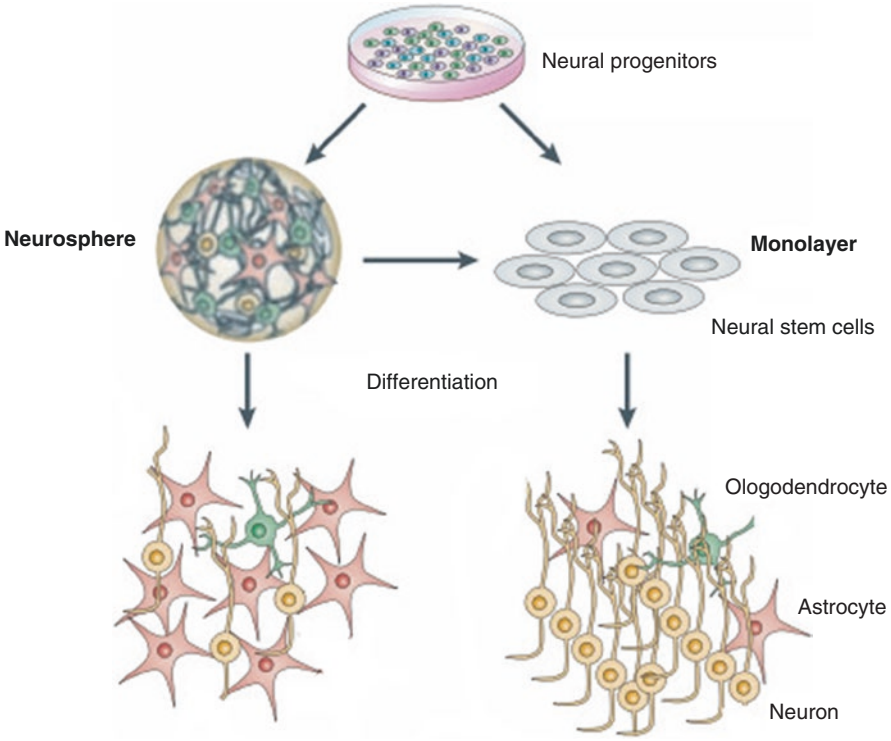

Fig. 1.1 Schematic diagram of neural progenitor differentiation

origin of adult NSCs and its neuronal differentiation are both restricted to the neurogenic niches in vivo largely limits the application of NSCs in various CNS diseases and injuries (Fig. 1.1).

1.1.2 Radial Glia

Radial glia, derived from neuroepithelium, is a ubiquitous glial cell type during the development of all vertebrate brains; they act as stem and progenitor cells that give rise to all neurons of mammalian CNS. However, radial glia represent more fate-restricted progenitors than NSCs, because radial glia are inclined to the generation of a single cell type, either astrocytes, oligodendrocytes, or neurons, rather than all of them like NSCs [5]. Stem cell properties not only are interestingly possessed by radial glia, astroglial properties are also exhibited. They express stem cell markers like the intermediate filament protein nestin and keep significant qualities of apical-basal polarity. They also have an ultrastructural distinctive of astroglial glycogen granules and express assorted molecules that are typical of astrocytes, such as astrocyte-specific glutamate transporter (GLAST), Ca^{2+}-binding protein S100β, glial fibrillary acidic protein (GFAP), vimentin, and brain lipid-binding protein (BLBP). More fate