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Views & Comments

Adult Mammalian Neurogenesis: Hopes and Challenges in the Repair of Spinal Cord Injury

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Adult endogenous neurogenesis was first defined as the generation of neurons and glia cells in the central nervous system (CNS); it was subsequently referred to as the activation of endogenous neural stem cells, and ultimately limited to the generation of new neurons [1]. The research team led by Xiaoguang Li enriched this concept in 2015: Endogenous neural stem cells in the adult CNS can be activated, recruited, and migrated to the injured area, where these stem cells further differentiate into mature neurons. The new neurons may form a functional neural circuit with host neurons, resulting in function recovery [2]. The main body of endogenous neurogenesis is neural stem cells, they can be self-renewable and multipotent, means that they can replicate and can produce different mature cell types. Neural stem cells in the central canal and/or its subregion of the spinal cord are activated. Most of them proliferate and differentiate into astrocytes (which are involved in scar formation) and a small number of oligodendrocytes, with almost no new neurons [3].

Evidence has shown that adult neurogenesis exists in the forebrain, ependymal cells, and surrounding area in all mammals, including human beings. At least two sites in the forebrain exhibit constant neurogenesis: the subventricular zone (SVZ) and the dentate gyrus (DG) subgranular zone (SGZ). SVZ-origin neural stem cells can continually proliferate *in vivo* and migrate in a chain along the rostral migratory stream to the olfactory bulb, where these cells further differentiate into granular neurons and parabulbar neurons of the olfactory bulb, and subsequently integrate into the olfactory bulb circuits. After proliferation, SGZ-origin neural stem cells migrate for a short distance to the DG subgranular zone and differentiate into DG subgranular neurons. Ependymal cells are the ciliated cells arranged in the ventricle and central ventricle systems of the spinal cord. They push forward the cerebrospinal fluid, while serving as a barrier for the brain and spinal parenchyma. In the intact spinal cord, ependymal cells seldom divide; however, in *in vitro* culture, ependymal cells vigorously divide and generate astrocytes, oligodendroglia, and neurons, thus demonstrating their multipotency [2].

Mammalian hippocampus injury causes abnormality of spatial cognition and learning memory. Li's team implanted a bioactive material scaffold into the injured area of the adult mammalian brain (i.e., the hippocampus CA1 area and top cortex), which activated the endogenous neural stem cells and recruited them to migrate to the injured area and differentiate into neurons at a high percentage. These new neurons established functional synaptic connections with host neurons, thereby reconstructing the functional neural circuit and consequently alleviating cognitive impairment [4]. After implanting a neurotrophin (NT)-3-chitosan tube (whose controlled release of NT-3 was as long as 14 weeks) into the spinal cord injured area (where a 5 mm thoracic cord was completely removed), Li's research team observed that the NT-3-chitosan tube improved the microenvironment of the injured area and activated endogenous neurogenesis. That is, it activated and recruited endogenous neural stem cells in the spinal cord and induced these cells to migrate to the injured area and differentiate into functional neurons. This then established functional synaptic connections together with the host spinal cord, ultimately facilitating the recovery of the motor and sensory functions of the bilateral paraplegic hind limbs to some degree [5]. Moreover, weighted gene correlation network analysis (WGCNA) of the transcriptome indicated that, after spinal cord injury, the NT-3-chitosan tube facilitated neurogenesis and angiogenesis, while alleviating the inflammatory reaction [6]. In 2018, Li and colleagues used bioactive materials to induce the long-distance regeneration of the corticospinal tract (CST) in higher primates (i.e., rhesus monkeys). Under the support of the bioactive material, the CST traversed the injured area, which was 10 mm long, and reentered the distal host spinal cord, thus enabling the long-term and stable restoration of the sensory and motor functions of paraplegic limbs [7]. Due to the high similarity among the neuroanatomical structures and physiological functions of rhesus monkeys and humans, the aforementioned research results have brought hope to the clinical treatment of spinal cord injury. In September 2018, Prof. W. Dalton Dietrich, the director of the Miami Paraplegic Treatment Program, spoke highly of this work: "The fact that these studies were done in a large animal model in which the spinal cord anatomy closely mimics the human makes these results extremely important in terms of clinical significance and potential translation to the clinic" [8].

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Compared with the rodent brain, whether or not neurogenesis existed in the adult human brain and the extent and function of adult neurogenesis are still controversial. In 1998, brain samples collected from five cancer patients were histologically examined. The results revealed that neurogenesis did in fact exist in the adult human brain as it did in the rodent brain, and that it was concentrated in the SVZ and hippocampus. This was the first report on neurogenesis in the human brain [9]. After that, a series of reports were published to demonstrate the existence of neurogenesis in adult humans. The researchers used ^{14}C to label the large amount of neurogenesis observed in the human hippocampus; they found that the degree of neurogenesis decreased with age, and that there was no significant difference in terms of neurogenesis percentage between the adult hippocampus of humans and that of rodents [10]. Sorrells et al. [11] notably demonstrated in 2018 that the amounts of neurogenesis in the brain of rhesus monkeys and humans both dramatically decreased over age, with almost no neurogenesis being observed in the adult hippocampus. Several weeks later, Boldrini et al. [12] provided evidence of constant neurogenesis in the human brain. They detected neural stem cells in the hippocampus DG of normal adult bodies and observed no obvious change in neural stem cells and mature neurons with age. In 2019, Tobin et al. [13] reported that neurogenesis in the hippocampus was retained in the brain of aged and Alzheimer's disease patients and might correlate with cognitive functions. Soon afterwards, 18 neuroscientists jointly analyzed the possible reasons for these significantly different results, including the time from sample collection after autopsy to liquid fixation, stationary liquid type, and the selection and quantification of biomarkers [14]. Today, given the rapid technological development that has occurred, researchers can make full use of new techniques to detect neurogenesis, such as more complete cell phenotypes, potential analyses, and differentiation tracks. For example, we can use single-cell ribonucleic acid (RNA) sequencing, lineage tracing, and RNA interference to provide more accurate information and stronger evidence for adult neurogenesis. This may help to reveal physiological and pathological changes under different conditions, which would make great contributions to clinical treatment.

After CNS injury, lack of blood supply, serious inflammatory reactions, and neurogenesis prohibition, factors such as inflammatory cytokines accumulation, immunocytes activation and infiltration, and excitotoxicity significantly impede the generation of new neurons from neural stem cells, as well as the subsequent reconstruction of the neural circuit in the injured area. Meanwhile, the hostile microenvironment impels neural stem cells to differentiate into astrocytes and finally form glia scars. Under these circumstances, neuron regeneration becomes impossible. Only by better modifying the microenvironment of the injured area can we attempt to solve the problem. After years of enormous efforts, Li's team has presented the "incubation theory of adult endogenous stem cells" for mammals [2]. They use in-house-developed bioactive materials that are capable of long-term neurotrophic factor release to improve the microenvironment in the injured area of the CNS (analogous to soil) and to activate and migrate neural stem cells (analogous to seeds) to the injured area, where these cells further differentiate into mature neurons and join the host neurons to establish a functional circuit, thus realizing functional recovery to some degree.

Since the first discovery of adult neurogenesis by Altman and Das in 1965 [15], the hot debate on the limitation of primate neurogenesis [16], and the description of adult songbird neurogenesis by Fernando Nottebohm's team in the 1980s, great progress has been achieved in this field, and sufficient evidence has demonstrated the existence of adult neurogenesis in the human brain. Nevertheless, many problems remain unsolved. For example, how can we precisely regulate the occurrence of adult mammalian neurogenesis to reconstruct functional synaptic balance, while avoiding neuron malfunctions? In addition, special attention should be paid to species difference. As Sorrells et al. [11] warned, a simple equivalent translation from animal experiments to human clinics will put people at risk.

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