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Endogenous neurogenesis in adult mammals after spinal cord injury

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During the whole life cycle of mammals, new neurons are constantly regenerated in the subgranular zone of the dentate gyrus and in the subventricular zone of the lateral ventricles. Thanks to emerging methodologies, great progress has been made in the characterization of spinal cord endogenous neural stem cells (ependymal cells) and identification of their role in adult spinal cord development. As recently evidenced, both the intrinsic and extrinsic molecular mechanisms of ependymal cells control the sequential steps of the adult spinal cord neurogenesis. This review introduces the concept of adult endogenous neurogenesis, the reaction of ependymal cells after adult spinal cord injury (SCI), the heterogeneity and markers of ependymal cells, the factors that regulate ependymal cells, and the niches that impact the activation or differentiation of ependymal cells.

adult endogenous neurogenesis, neural stem cells, ependymal cells, spinal cord injury, adult mammals, regeneration

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INTRODUCTION

The spinal cord injury (SCI) of adult mammals destroys the original anatomic architecture, which consequently leads to cell death; meanwhile, inflammation, demyelination and gliacyte proliferation in response to the SCI jointly trigger the secondary damage. Under these circumstances, the functional loss beneath the injury interface is almost inevitable (Karnezis et al., 2004; Silver and Miller, 2004; Thuret et al., 2006). The major causes of SCI involve traffic accidents, falls, sports, and job-related injuries. The annual SCI incidence is 280–316 per million in the western Europe (Lee et al., 2014), and approximately 54 cases per million population in the U.S. or approximately 17,000 new cases each year (The National Spinal Cord Injury Statistical Center, 2016). SCI usually occurs in the most active years of a person, and makes the patient suffer from the damage of motor and sensory functions, neuropathic pain, spasticity, etc. (Westgren and Levi, 1998). Also notably, the economic expense of SCI therapy is huge. Based on the traumatic patients' age and anatomic segment, each SCI patient has to pay on average $340,000–$1 million for his/her first-year therapy (The National Spinal Cord Injury Statistical Center, 2016).

No intervention/repair approach for the SCI of adult mammals is available in both academic and medical field until now (Bunge, 2008; Lu et al., 2004; Thuret et al., 2006). During the past few decades, endogenous multipotent neural stem cells have been discovered in the specialized regions of the adult central nervous system (CNS), and some advances have been achieved in the treatment of CNS injury and neurodegenerative diseases by activating the endogenous neural stem cells (NSCs) *in vivo* (Agrawal and Schaffer, 2005; Conti and Cattaneo, 2008). These endogenous NSCs are capable of constantly differentiating into neurons (Horner et al.,

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2000; Shihabuddin, 2008; Weiss et al., 1996), which then participate in the formation of new circuits and eventually lead to partial functional recovery after neurological damage (Yamashita et al., 2006). These studies, however, generally concentrated on the activation and recruitment of brain endogenous NSCs; almost no reports concern the activation of spinal cord endogenous NSCs for traumatic/disease treatment and finally functional recovery. What is the identity of endogenous NSCs in the adult spinal cord? How do they react to traumas? Clear answers to these questions will help develop new therapeutic strategies. For example, *in situ* regulation of endogenous NSCs after SCI is considered a feasible and attractive idea.

The underlying molecular mechanism of neurogenesis is not yet clear; however, scientists have evidenced that the ependymal cells lining the adult central canal are multipotent and take the role of endogenous NSCs using genetic fate mapping (Barnabé-Heider et al., 2010; Meletis et al., 2008). This review outlines the concept of adult endogenous neurogenesis, the reaction of ependymal cells after spinal cord injury, the heterogeneity and markers of ependymal cells, the factors that regulate the activity of the ependymal cells, and the niches that impact the activation or differentiation of ependymal cells.

WHAT IS ADULT ENDOGENOUS NEUROGENESIS? WHO ARE ENDOGENOUS NEURAL STEM CELLS IN THE ADULT SPINAL CORD?

Adult endogenous neurogenesis originally referred to generate cells (neurons and glia) of the central nervous system. It was later regarded as the activation of endogenous NSCs, and then confined to the generation of new neurons (Caviness et al., 1995; Kriegstein and Alvarez-Buylla, 2009; Nowakowski et al., 2002; Zupanc and Sîrbulescu, 2011). In 2015, the research team led by Prof. Li re-supplemented adult endogenous neurogenesis as follows: the endogenous NSCs in the adult CNS can be activated and recruited to the lesion/disease area, where they sequentially differentiate into mature neurons and form functional neural circuits together with host tissue, ultimately resulting in functional recovery (Duan et al., 2015; Yang et al., 2015). 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. Update, NSCs have been observed in various CNS areas, such as the subgranular zone in the dentate gyrus, the subventricular zone of the lateral ventricles, and the ependymal cell of the central canal (Coskun et al., 2008; Gage, 2000; Gross, 2000). When adult CNS damaged or disease, endogenous NSCs may be activated to proliferate and differentiate, but at a low percentage and in uncontrollable differentiation directions, which at last fails in spontanous recovery of CNS injury or disease. There exist three distinct dividing cell types in the intact adult mammalian spinal cord: oligodendrocyte progenitors (NG21/olig21, representing 80% of proliferating cells), astrocytes (GFAP1/Cx301/Sox91, representing <5% of proliferating cells), and ependymal cells (FoxJ11, representing <5%) (Barnabé-Heider et al., 2010; Horner et al., 2000; Meletis et al., 2008). Oligodendrocyte progenitor cells, the main dividing cell population in the intact adult spinal cord, can generate mature oligodendrocytes; after SCI, they increase the dividing rate and produce a large amount of re-myelinated oligodendrocytes (Barnabé-Heider et al., 2010). In the intact spinal cord, astrocytes divide sporadically to maintain their cell population; after SCI, they proliferate and divide correspondingly, forming the border of glia scar (Barnabé-Heider et al., 2010; Lee-Liu et al., 2013). Astrocytes and oligodendrocyte progenitor cells are both capable of self-renewal, but they are not multipotent, that is, they cannot differentiate into multiple types mature cells, thus demonstrating that they are not stem cells (Burda and Sofroniew, 2014). Ependymal cells are ciliated cells lining the ventricular system of the spinal central canal. They are responsible for pushing cerebro-spinal fluid and forming a barrier in the brain and spinal cord parenchyma. In the intact spinal cord, ependymal cells seldom divide; in *in vitro* cell culture, they vigorously divide and produce astrocytes, oligodendrocytes, and neurons, evidencing their multipotency (Burda and Sofroniew, 2014). After SCI, ependymal cells start fast division and self-renewal and generate a large amount of astrocytes to participate in scar formation; meanwhile, they generate a small amount of oligodendrocytes capable of myelinating axons. Ependymal cells in the adult spinal cord, therefore, represent a potential NSC population (Burda and Sofroniew, 2014; Luo et al., 2015).

REACTION OF EPENDAMAL CELLS AFTER ADULT SCI

SCI can trigger the proliferation of ependymal cells and further their multilineage differentiation. In various SCI models, such as contusions, compressions, and partial sections with the central canal well preserved, injuries of different fashions and severities all lead to extensive proliferation of ependymal cells (Johansson et al., 1999; Lacroix et al., 2014; Meletis et al., 2008; Mothe and Tator, 2005;). This phenomenon has been observed similarly in the SCI models of both mice and rats, indicating that extensive proliferation of ependymal cells is a basic conservative reaction to damage (Lytle and Wrathall, 2007). The proliferation of ependymal cells after SCI causes a significant increase of NSC population (Barnabé-Heider et al., 2010). Several weeks after spinal cord contusions at mice low thoracic segments, active proliferative reaction was observed at the cervical cord far

from the lesion site, suggesting that injury will lead to a long-lasting and long-distance proliferative reaction (Lacroix et al., 2014). Of note, using the lineage-tracing technique, scientists recently highlighted the fate of the prelabeled progenitors of oligodendroglia, astrocytes and ependymal cells after SCI. They pointed out that, at the population level, ependymal cells are the only multipotent cell population after SCI (Barnabé-Heider et al., 2010, Lytle and Wrathall, 2007; Meletis et al., 2008). That is, after SCI, the ependymal cells of Foxj1^{+} give rise not only to a large amount of astrocytes constituting the core of glial scars but also to oligodendroglia scattered in the spinal cord white matter. However, we have no sufficient evidence to determine whether the astrocytes and oligodendroglia coming from the ependymal are derived from the same cloning origin or from different subpopulations of ependymal cells (Barnabé-Heider et al., 2010).

MORPHOLOGICAL HETEROGENEITY OF EPENDYMAL CELLS

In mice, most of ependymal cells originate from radial glial cells on day 14–16 of embryonic development (Spassky et al., 2005). One week postnatal, these cells begin to differentiate, in the appearance of cilia (Fu et al., 2003; Masahira et al., 2006; Spassky et al., 2005). The first sub-population of ependymal cells is derived from radial glial progenitor cells during embryogenesis (Fu et al., 2003). The second sub-population is formed during postnatal life. The second ependymogenesis occurs on postnatal day 8–15, which might be associated with the two thin bundles of processes on the radial glial cells that appear at the roof plate and the floor plate in the spinal cord (Moreels et al., 2005; Oudega and Marani, 1991; Sevc et al., 2009; Shibata et al., 1997). Taken together, the ependymal cells lining the central canal have latent heterogeneity.

MARKERS FOR EPENDYMAL CELLS OF THE ADULT SPINAL CORD

Nestin is the marker not only for the undifferentiated stem cells and progenitor cells in the SVZ zone of the whole forebrain, but also for the cells lining the central canal of the adult spinal cord (Frisén et al., 1995; Meletis et al., 2008). In the central canal, nestin is mainly expressed in the cellular sub-population at the dorsal pole of the ependymal zone. These nestin-positive cells possess long filaments that extend along the dorsal middle line, as well as some similar fibers that extend from the ventral pole or sometime from the lateral ependymal zone.

Glia fibrillary acidic protein (GFAP) is the marker for NSC and astrocytes in the forebrain (Doetsch et al., 1999). It can be detected in the dorsal pole of the central canal ependymal zone and subependymal astrocytes in close vicinity of the ependymal zone. Transcription factor Sox2 is the marker for NSC and progenitor cells in the SVZ zone of the forebrain, as well as for ependymal cells and some subependymal cells in the central canal of the adult spinal cord (Hamilton et al., 2009). Musashi1 and CD133/prominin are the markers not only for the progenitor cells in the forebrain but also for ependymal cells lining the central canal of the adult spinal cord (Morrison and Spradling, 2008). Vimentin and S100b are the markers for ependymal cells in the forebrain and also for ependymal cells lining the central canal of the adult spinal cord (Hamilton et al., 2009). However, NG2 (the marker for progenitor cells in the forebrain) and Olig2 (the transcription factor of oligodendroglia in the forebrain) are not expressed in the cells in the ependymal zone, but often expressed in the areas neighboring the ependymal zone. Mammalian achaete scute homolog 1 (Mash1) is associated with progenitor cells in the SVZ zone of the brain, but cannot be detected in the spinal cord.

POTENTIAL FACTORS AND NICHES FOR NEUROGENESIS REGULATION IN THE ADULT SPINAL CORD

Few reports concern the mechanism of the activation of adult spinal cord ependymal cells and the following neural differentiation. The clarification of this mechanism will help optimize the neurogenesis after SCI. The signals exposed to a short distance, such as Wnt, Notch and/or BMP ligand from niches may distinguish stem cells from differentiating progenitor cells (Barnabé-Heider et al., 2010). Stem cells can also be regulated by extrinsic remote signals to reflect nutrition, energy metabolism, oxygen content, hormonal status, and other physiological alterations. The ependymal cells in the adult spinal cord central canal can be regulated by both intracellular and extracellular factors, and thus have the NSC properties.

The therapeutic strategies via NSCs are challenged mainly by how to maintain NSC self-renewal and control their differentiation into specific type neural cells. According to recent research, apart from the intrinsic NSCs characteristics, the local microenvironment or niches, such as the neighboring cells, growth factors, cellular factors, and periodic signals, coordinately regulate the survival, proliferation and differentiation of NSCs (Doetsch, 2003; Fuchs et al., 2004; Hamilton et al., 2009; Morrison and Spradling, 2008; Walker et al., 2009). In the niches during adult neurogenesis, for instance, Wnts derived from astrocytes impact the differentiation of adult NSC into neurons *in vitro*, whereas Wnt signal augments the neurogenesis in the dentate gyrus *in vivo* (Lie et al., 2005). BMPs facilitate the differentiation of NSCs from

the SVZ and hippocampus into glia cells (Bonaguidi et al., 2005; Lie et al., 2005). Two types BMP antagonists, Noggin expressed in the ependymal cells (Lim et al., 2000) and neurogenesin-1 expressed in dentate granule cells and oligodendroglia (Ueki et al., 2003), prohibit NSCs from differentiating into glia cells and re-direct their differentiation into neurons (Duan et al., 2008). Notch and sonic hedgehog (Shh) from niches also play a key role in controlling adult neurogenesis (Alvarez-Buylla et al., 2002; Hagg, 2005). The activation of quiescent Shh signals in adult NSCs contributes greatly to the establishment and maintenance of adequate NSCs pools in the adult SVZ and SGZ (Ahn and Joyner, 2005; Balordi and Fishell, 2007; Han et al., 2008).

Niches of ependymal cells in the spinal cord are seldom addressed, and the ependymal zone of adult spinal cord remains undefined. Only several cell types have been reported to be specifically localized, with specifically expressed markers, as well as different morphologies and functions (Bruni and Reddy, 1987; Hamilton et al., 2009; Hugnot et al., 2012; Meletis et al., 2008). Hugnot et al. stated that, in humans and rodents, niches of the spinal cord have a subset of Dcx^+ and $Nkx\ 6.1^+$ neural cells that protrude processes into the central canal (Hugnot et al., 2012). In another sub-population of $GFAP^+$ cells, cells protrude radial processes into the spinal cord parenchyma. These $GFAP^+$ cells can be observed at the dorsal or ventral site of the subset of ependymal cells lining the central canal, and in the ependymal or subependymal zone (Hamilton et al., 2009).

Scientists have discovered that $GFAP^+$ cells in the spinal cord central canal region express the pathways of the following genes: Notch (Jagged, Hes1), Wnt (Wnt7a, Fzd3), BMP (DAN, BMP6) and Shh. Additionally, these $GFAP^+$ cells highly express Zeb1, Zinc finger homologous structure of the domain transcription factors of homeodomain and is considered a significant regulator of epithelial-mesenchymal transition. Zeb1 and Zeb2 are critical to the formation and amplification of neurospheres, and are also expressed in NSCs of adult spinal cord (Hugnot et al., 2012). A deep understanding of the underlying mechanism of the interaction between NSCs and their niches will decipher why stem cells have high neurogenesis capacity in some areas, while remaining quiescence in other areas (Duan et al., 2008; Hamilton et al., 2009).

The research team led by Li has successfully repaired the semi-sectioned thoracic spinal cord injury by implanting a self-developed biomaterial scaffold of chitosan plus collagen. In their experiment, axons were regenerated including the corticospinal tract, neuron-like cells were observed in the lesion area, and paraplegic rats gained behavioral and electrophysiological (SEP, MEP) recovery to some extent. These results suggest that this biomaterial tube could inhibit the infiltrations of scars into the lesion area and modify the local inflammatory microenvironment, consequently stimulating axons to regenerate, extend and traverse the lesion gap to enter the host spinal cord tissue at the caudal end (Li et al., 2009). In 2015, this team implanted a NT-3-chitosan tube loaded with NT-3, whose controlled release was up to 14 weeks, into a 5 mm gap caused by completely cutting and removing the adult rat thoracic cord. As a result, the NT-3-chitosan tube improved the microenvironment of the injured spinal cord area and activated endogenous neurogenesis. That is, to activate and recruit endogenous NSCs in the spinal cord, induce them to migrate to the lesion area, differentiate into functional neurons, and establish functional synaptic contact with the host spinal cord, ultimately leading to some restoration of motor and sensory functions of both paraplegic hindlimbs (Yang et al., 2015; De Filippis et al., 2015). Moreover, they analyzed WGCNA transcripts, and demonstrated that, after SCI, the NT-3-chitosan tube could facilitate neurogenesis and angiogenesis, while alleviating inflammatory reaction (Duan et al., 2015; De Filippis et al., 2015). Some problems, however, still remain to be solved, such as the origin of endogeneous NSCs, their markers, and the mechanism of differentiation into functional neurons. In the future research, they will use genetic fate mapping and lineage-tracing to study the origin/marker of endogenous stem cells of the spinal cord, their morphological characteristics and functions, and a series of molecular events after activation, the outcomes of which are expected to reveal the mechanism of enhancing the local microenvironment of the lesion area to facilitate adult spinal cord neurogenesis.

PERSPECTIVES

Transplantation of stem cells, as reported, may become a new strategy of SCI therapy. The transplanted cells, including NSCs, mesenchymal stem cells, olfactoryensheathing cells, schwan cells, activated macrophages, and multipotent cells recently induced, have found widespread applications in the SCI animal models and achieved great progress. All approaches, however, are not without flaws. For example, when NSCs are transplanted into the intact and injured adult rat spinal cord, they either remain undifferentiated or differentiate along the glial lineage (Silva et al., 2014). Currently, the in situ regulation of endogenous stem cells in the adult spinal cord is considered the most promising strategy to repair SCI and facilitate functional recovery. In lower vertebrates, the activation of ependymal cells can stimulate spinal cord regeneration and functional recovery (Guo et al., 2011). In essence, adult mammalian ependymal cells have quite limited regeneration capability. After SCI, most ependymal cells differentiate into glia-like cells and constitute the core of scar tissue, while a small number of ependymal cells differentiate into oligodendroglia, but none into neurons (Meletis et al., 2008). The main obstacle to regeneration after SCI is neuron loss and axon demyelination. Therefore, the great challenge of activating endogenous stem cells to

repair SCI is to facilitate the generation of new neurons to supplement lost neurons, in parallel with the generation of oligodendroglia to re-myelinate axons.

Taken together, ependymal cells by reprogramming will differentiate into the oligodendroglia lineage (Hofstetter et al., 2005) and neuron lineage (Gregorian et al., 2009), thus leading to reduced scar formation, neuron supplementation, and stimulated myelination. In consideration of the safety and stability of *in vivo* gene operation, this method needs to be repeatedly verified in nonhuman primates before clinical treatment.

After CNS injury, a single neural repair strategy can hardly work efficiently because of various disadvantageous factors that hinder neural repair. To solve the key problem of neuron regeneration, the team led by Li presented the Adult Endogenous NSCs Incubation Theory as below: local microenvironment of the CNS act as soil, and endogenous neural stem cells act as seeds, improvement of the local microenvironment-soil after CNS injury or disease enables the activation of endogenous neural stem cells-seeds, induction them differentiation into neurons and functional integration into the host circuit. In their experiment, modified and characterized biomaterials were adopted to constantly deliver neurotrophic factors to the lesion area and function as a supporting scaffold simultaneously, aiming to create a microenvironment in favor of regeneration. As a result, endogenous neurogenesis was started in the microenvironment created by the NT-3 chitosan scaffold. This not only challenges the traditional view that mature neurons cannot be regenerated, but also predicts the critical role of endogenous NSC incubation theory in the treatment of CNS injury.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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