Neurogenesis and Gliogenesis in Nervous System Plasticity and Repair

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Abstract

The brain constantly changes to store memories and adapt to new conditions. One type of plasticity that has gained increasing interest during the last years is the generation of new cells. The generation of both new neurons and glial cells contributes to neural plasticity and to some neural repair. There are substantial differences between mammalian species with regard to the extent of and mechanisms behind cell exchange in neural plasticity. Both neurogenesis and gliogenesis have several specific features in humans, which may contribute to the unique plasticity of the human brain.

Contents

INTRODUCTION

The central nervous system combines exceptional stability, allowing for storage of memories for many decades, with plasticity, enabling adaptation and the continuous formation of new memories. There is little exchange of cells in the adult nervous system compared with many tissues, and it appears intuitive that it would be difficult to exchange neurons while, for example, retaining memories. That intuition probably contributed to the long-standing dogma that the adult brain is very static, that all neurons are generated during fetal life, and that new neurons cannot be generated postnatally.

Today we know that new neurons are continually generated in the adult brain of all studied mammals. However, adult neurogenesis appears strictly localized to discrete regions of the brain, and most neurons are never exchanged. Functional studies in experimental animals have demonstrated that adult-born neurons convey specific types of neural plasticity.

It has been increasingly appreciated over the last few years that glial cells modulate neuronal function. Oligodendrocytes influence neuronal conductance by forming insulating myelin sheets, which increase the speed of neural processing. The thickness of myelin is dynamically modulated in response to experience, and the generation of new oligodendrocytes is required in the mouse brain to learn certain new tasks.

The current review aims to provide an overview of cell generation in the adult central nervous system (**Figure 1**). Emerging concepts and outstanding questions are discussed.

HOW CAN A NEW BRAIN CELL BE RECOGNIZED?

It was not until the 1960s that it was first suggested that new neurons are added in the adult brain (Altman & Das 1965), and this concept did not become broadly accepted until several decades later. Our knowledge of cell generation, especially in humans, is still limited. Neurons are postmitotic, and the lack of mitotic neuronal figures is likely to have contributed to the early conclusion that there is no postnatal neurogenesis in mammals. Moreover, oligodendrocytes are postmitotic cells, without the possibility of duplicating, and both of these cell types derive from progenitor cells in the adult brain.

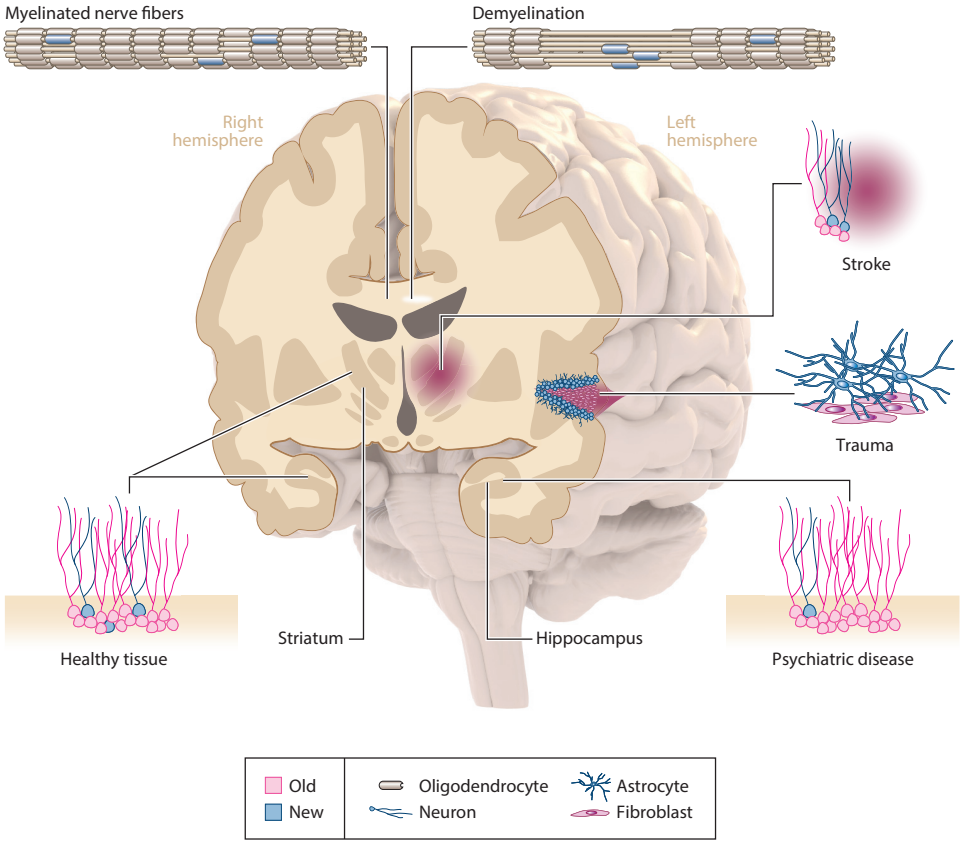

Figure 1

New cells in old brains. (*Right hemisphere*) In the healthy brain, new neurons are added in the hippocampus and striatum, and new oligodendrocytes form myelin sheets to insulate nerve fibers. (*Left hemisphere*) The generation of neurons and nonneuronal cells may change in pathology, such as reduced hippocampal neurogenesis in depression; generation of new oligodendrocytes in response to demyelination in, for example, multiple sclerosis; and scar formation after injury.

Cell generation is often studied by the detection of molecular markers of mitosis, such as, for example, PCNA, Ki-67, or phospho-histone3. This type of analysis can give a snapshot of the mitotic activity in a tissue and can be useful in comparing cell proliferation during different conditions. However, it is not possible to infer the future fate of a cell, such as whether the progeny will survive and integrate in the tissue and, if so, what the phenotype of the mature cell will be.

Detection of cells with a molecular profile consistent with being a precursor cell, such as a neuroblast (an immature neuron), can lend some support for the generation of new cells. However, many precursor cells die and never become fully mature and functional cells (Kuhn 2015), precluding firm conclusions as to cell renewal on the basis of precursor markers. Moreover, few markers are completely specific to precursor cells, but such markers are often shared by some mature cells.

Firm evidence for the generation of new cells can be obtained by prospective marking of dividing cells and analysis of the progeny. The general principle is to administer a compound that is stably integrated into DNA, as DNA is a molecule with little atomic exchange, whereas all

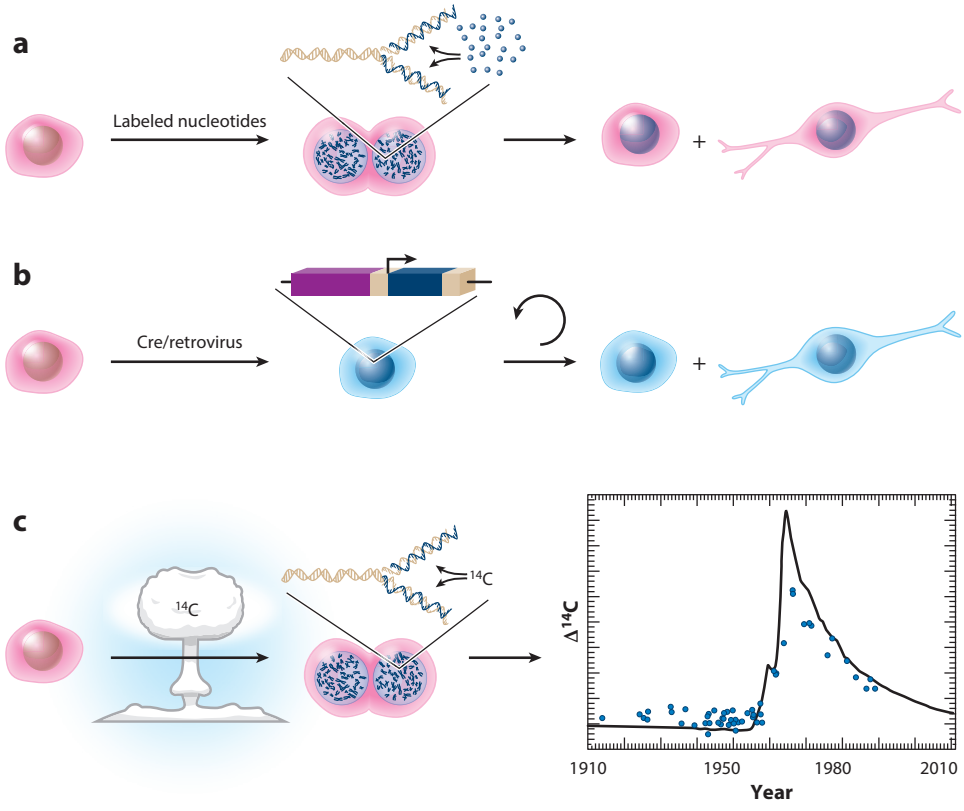

Figure 2

How to recognize a new cell: schematic illustration of different strategies to identify newborn cells. (*a*) Administration of labeled nucleotides results in their integration into genomic DNA in cells undergoing DNA replication in mitosis. Labeled nucleotides can be visualized with antibodies to identify newly generated cells. (*b*) Viral or transgenic strategies can be used to introduce a stable genetic label to trace the progeny of a cell of interest. (*c*) Nuclear bomb tests during the Cold War resulted in a large increase in the atmospheric concentration of ^{14}C. ^{14}C enters the human body through the food chain, resulting in the atmospheric concentrations being mirrored in the body. When a cell replicates its genomic DNA in mitosis, it integrates ^{14}C with a concentration corresponding to that in the atmosphere at that time. The ^{14}C concentration in genomic DNA can be measured by accelerator mass spectrometry and can be used to infer when cells were born.

other molecules in a cell are probably in constant flux. Prospective marking is commonly done by administering labeled nucleotide analogs such as ^{3}H-thymidine, BrdU, or EDU, which are stably integrated into the DNA of dividing cells and inherited by their progeny (**Figure 2*a***). These labels can then be detected in tissue sections and combined with cell type–specific markers to trace the generation of new neurons. Prospective labeling strategies dominate the analysis of cell generation in experimental animals, but they are not without caveats. For example, DNA repair may result in the integration of labeled nucleotides, falsely giving the impression that a cell is newborn. Moreover, labeled nucleotides can be toxic at higher doses or if delivered during longer time periods and, in that way, interfere with the studied process and result in an underestimation of cell generation.

Dividing cells can be stably marked by retroviral infection, which integrates only in the DNA of mitotic cells, where the virus can be detected by the expression of a reporter gene or a sequence barcode (**Figure 2*b***). An additional way to identify newborn cells is by transgenic fate-mapping strategies. The most common way to do this is to induce the stable and heritable expression of a reporter gene in a stem/progenitor cell population, specified by a certain promoter (**Figure 2*b***). This strategy does not directly detect mitotic activity but rather indicates that a cell type with one phenotype has given rise to another cell type.

Prospective labeling strategies are not easily applicable in humans, as labeled nucleotides may be toxic, and taking biopsies of, for example, the brain in healthy volunteers is not possible. Due to these limitations, studies of cell turnover in humans lag far behind those in experimental animals, and the situation in humans has often been inferred from results in experimental animals, most often rodents. In a few situations, cancer patients have received labeled nucleotides for diagnostic staging purposes or for radiosensitization, and postmortem tissue has been used for the analysis of cell generation in the adult human brain (Bhardwaj et al. 2006, Eriksson et al. 1998, Ernst et al. 2014, Yeung et al. 2014).

Another way to study cell generation in humans is by retrospective ^{14}C birth dating. This strategy takes advantage of the enormous increase in atmospheric ^{14}C caused by nuclear bomb tests during the Cold War. ^{14}C enters the food chain, resulting in the atmospheric concentration being mirrored in the human body at any given time. Since the Cold War, there have been no major overground nuclear bomb tests, and the levels of ^{14}C have decreased exponentially. For this reason, there have been distinct levels of this isotope in different years over the last decades, creating, in cells, a date mark in their DNA that indicates when they were born (**Figure 2*c***). ^{14}C can be measured in genomic DNA of cells such as those in human postmortem tissues and can provide detailed information about cell turnover dynamics (Spalding et al. 2005).

THE ORIGIN OF NEW CELLS IN THE ADULT BRAIN

The main cell types of the adult central nervous system—neurons, astrocytes, oligodendrocytes, and microglia—have distinct origins and turnover dynamics. Microglia derive from the hematopoietic lineage, whereas neurons, astrocytes, and oligodendrocytes derive from the neuroectoderm.

New neurons are continuously produced from neural stem or progenitor cells in two distinct niches in the adult brain of most mammals. In the hippocampal dentate gyrus, new neurons are produced locally in the subgranular zone (Kempermann et al. 2015). In many species, new neurons destined for the olfactory bulb are born in the subventricular zone lining the lateral ventricle and migrate for some distance along what is termed the rostral migratory stream to their target area (Lledo et al. 2008).

The neurogenic cells in the subgranular and subventricular zones derive from radial glial cells during fetal development and share morphology and markers with astrocytes (Kriegstein & Alvarez-Buylla 2009). In vitro, the neurogenic cells of the adult brain cells display the stem cell properties of multipotency and self-renewal. However, in vivo they often act as unipotent cells, giving rise to only one distinct subset of neurons (Lledo et al. 2008). It has also been questioned whether these cells self-renew efficiently in vivo, and it has been suggested that lack of self-renewal results in depletion with age (Calzolari et al. 2015, Encinas et al. 2011). However, elegant fate-mapping experiments have provided evidence for both self-renewal and multipotency in vivo in the mouse dentate gyrus (Bonaguidi et al. 2011). The neurogenic astrocytes in the subventricular zone and subgranular zone niches appear distinct from other astrocytes, which do not give rise to neurons under physiological conditions. However, in certain pathological situations such as experimental stroke, astrocytes in the brain parenchyma, outside the regular stem/progenitor cell

niches, can enter a neurogenic program and give rise to new neurons (Magnusson et al. 2014). It is unclear to what degree the neurogenic potential of astrocytes is regulated cell autonomously, i.e., whether neurogenic potential is intrinsically different in different astrocytes or whether neurogenic potential is regulated by the environment in a non-cell-autonomous fashion.

A long-standing debate is whether all neural stem cells are astrocytes or whether other cells also have similar properties. Ependymal cells with motile cilia that line the ventricular system share many features with astrocytes. Spinal cord ependymal cells have neural stem cell properties in vitro, but they rarely proliferate and do not give rise to any nonependymal cells under physiological conditions (Barnabé-Heider et al. 2010, Johansson et al. 1999, Meletis et al. 2008, Pfenninger et al. 2011). However, in response to injury, spinal cord ependymal cells proliferate vigorously and give rise to both scar-forming astrocytes and remyelinating oligodendrocytes (Barnabé-Heider et al. 2010, Johansson et al. 1999, Meletis et al. 2008). Different studies have suggested that forebrain ependymal cells are postmitotic, that they continuously give rise to olfactory bulb neurons in rodents, or that they are quiescent and can give rise to progeny after injury or growth factor infusion (Carlén et al. 2009, Coskun et al. 2008, Johansson et al. 1999, Luo et al. 2015).

Oligodendrocyte progenitor cells (also often referred to as NG2 cells because these cells express the marker NG2) continuously give rise to new oligodendrocytes (Bergles & Richardson 2016). Oligodendrocyte progenitor cells constitute the main proliferative cell type in the mouse central nervous system and account for approximately 80% of the mitotic activity in the adult spinal cord (Barnabé-Heider et al. 2010). One point of debate is whether oligodendrocyte progenitor cells can generate additional cell types in addition to mature oligodendrocytes, which are their dominant progeny (Bergles & Richardson 2016).

There is very little generation of new astrocytes in the brain parenchyma. New astrocytes appear to derive from proliferating mature astrocytes. Astrocytes are well known to have an important influence on neural transmission (Khakh & Sofroniew 2015) but astrocyte turnover does not have a known function in neural plasticity.

Microglia derive from an early branch of the hematopoietic lineage in the yolk sac and populate the nervous system in early fetal life, after which they are a self-sustaining population (Ginhoux et al. 2010, Schulz et al. 2012). Under physiological conditions, the microglial population is likely maintained mainly by self-duplication by mature microglia, and there appears to be no contribution from the hematopoietic system (Ajami et al. 2007, Mildner et al. 2007). A recent study suggested that there are resident microglial progenitor cells in the central nervous system that can rapidly reconstitute microglia after experimental depletion (Elmore et al. 2014). After injury, monocytes from the blood often invade the central nervous system. Their functions are very similar to those of microglia, and the two cell types share most markers and are difficult to distinguish.

NEUROGENESIS IS RESTRICTED TO DISCRETE BRAIN AREAS, AND MOST NEURONS ARE NEVER EXCHANGED POSTNATALLY

In the 1960s the presence of ^{3}H-thymidine–labeled cells with neuronal morphology in the adult rat dentate gyrus and olfactory bulb was reported (Altman & Das 1965). However, the lack of specific molecular markers for neurons and the strong dogma that there was no postnatal neurogenesis precluded these findings from being broadly accepted. Not until the mid-1990s—with the advent of novel ways to label newborn cells, such as BrdU and retroviruses, and the emergence of immunohistochemical markers—did the continuous neurogenesis in the dentate gyrus and olfactory bulb of rodents become widely recognized.

The new neurons in both the dentate gyrus and the olfactory bulb are interneurons. They become functionally integrated through synaptic contacts with the preexisting neurons (Carlén et al. 2002, van Praag et al. 2002). New neurons generated in the adult brain have specific electrophysiological properties the first few weeks after their birth; they are hyperexcitable in an otherwise mainly inhibitory environment, which substantially impacts the circuitry (Toni & Schinder 2015). Gain- and loss-of-function experiments have demonstrated that the new neurons contribute to pattern separation: the ability to separate similar perceptions into distinct memories (Clelland et al. 2009, Nakashiba et al. 2012, Sahay et al. 2011).

In parallel with the increasing knowledge of neurogenesis in the hippocampus and olfactory bulb, there has been a constant flow of publications reporting adult neurogenesis in other areas of the brain. For many areas there are single or few reports. Some regions, especially the neocortex, have been intensively studied. There is no consensus that in healthy adult rodents adult neurogenesis takes place in regions other than the hippocampus and the olfactory bulb, the areas most intensively studied. Studying neurogenesis has many pitfalls, and many of the studies have likely arrived at incorrect conclusions. However, excluding low-level neurogenesis in certain areas is difficult, and this will continue to be an active area of exploration.

ADULT NEUROGENESIS IN HUMANS

Neurogenic niches and neurogenesis have been studied in detail in mainly the adult mouse brain, but much less is known about the human brain. In humans, there are cells with neuroblast markers and morphology in the subventricular and subgranular zones; these areas likely serve as neurogenic niches. The numbers of such cells decline rapidly in the first few postnatal months, with very similar dynamics in the two niches; after this period and throughout life, much lower numbers are detectable (Göritz & Frisén 2012, Knoth et al. 2010, Sanai et al. 2011, Wang et al. 2011).

Eriksson et al. (1998) reported in a seminal paper the first evidence for neurogenesis in adult humans. They analyzed the postmortem brains of subjects with head-neck cancer who had received BrdU for diagnostic purposes, and they found BrdU-labeled neurons in the dentate gyrus. Retrospective birth dating by measuring ^{14}C in genomic DNA of flow cytometry–isolated neuronal nuclei from the human postmortem brain has allowed for the characterization of the distribution and extent of adult neurogenesis in adult humans (Ernst & Frisén 2015).

Hippocampal neurogenesis is mostly similar in mice and humans: It is restricted to the dentate gyrus, the rate drops rapidly the first months after birth, and the exchange rate in adulthood is comparable in the two species (Bergmann et al. 2015, Ernst & Frisén 2015, Spalding et al. 2013). One difference between the species is that in humans the vast majority of dentate gyrus neurons are subject to exchange (Spalding et al. 2013), whereas in mice it is restricted to a subpopulation, constituting approximately 10% of the dentate gyrus neurons (Imayoshi et al. 2008, Ninkovic et al. 2007). Both in rodents and in humans there is a rather precipitous decline in dentate gyrus neuroblast generation during the first few postnatal months, after which the rate of neurogenesis declines much more slowly. As rodents become adults during the period of rapidly declining neurogenesis, there is a substantial difference in adult hippocampal neurogenesis between young and old adult rodents (Ben Abdallah et al. 2010). This is, however, not the case in humans, as most of the decline in hippocampal neurogenesis has taken place much earlier, and the decline in neurogenesis during adulthood is modest (Spalding et al. 2013).

Comparing neurogenesis between species is challenging, as, for example, the number of hippocampal neurons varies dramatically. The best way to make interspecies comparisons may be to assess the number of new versus old neurons (Kempermann 2012). This approach reveals that a middle-aged (1-year-old) mouse and a middle-aged (40-year-old) human have comparable rates

of neurogenesis (Bergmann et al. 2015). It is difficult to study the function of adult-born neurons in humans, but the similar rates suggest that this process may have similar functions in humans and mice.

The largest numbers of neurons are added to the olfactory bulb in rodents, and olfactory bulb neurogenesis is readily detectable in nonhuman primates. The trajectory of the rostral migratory stream, the migratory path for neuroblasts en route from the subventricular zone to the olfactory bulb, and the number of migratory cells were debated for some time (Curtis et al. 2007, Sanai et al. 2011, Wang et al. 2011). No adult olfactory bulb neurogenesis could be detected by carbon dating, setting the upper limit to maximally 1% of olfactory bulb neurons being exchanged over 100 years (Bergmann et al. 2012).

In humans, there is instead substantial neurogenesis in the striatum. A subpopulation of interneurons, mainly expressing the marker calretinin, is exchanged at a rate of 2.7% per year in adulthood (Ernst et al. 2014). The subventricular zone niche may provide this adjacent structure with new neurons, but the origin of the new striatal neurons in humans is difficult to assess. The switch from olfactory bulb to striatal neurogenesis follows the relatively pronounced reduction in relative olfactory bulb size and concomitant enlargement of the striatum during evolution (Ernst & Frisén 2015). There appears to be no striatal neurogenesis in mice, whereas it has been reported at low levels in rats, rabbits, and nonhuman primates (Arvidsson et al. 2002, Bedard et al. 2002, Dayer et al. 2005, Luzzati et al. 2006).

ADULT NEUROGENESIS IN PATHOLOGY AND NEURAL REPAIR

The currently known neuronal populations that are subject to exchange in adult humans—populations in the hippocampus and striatum—constitute <1% of the neurons in the brain. Other plasticity mechanisms of course dominate, but adult neurogenesis may convey certain specific plasticity qualities in humans as well, and perturbations of this process may be related to some pathological conditions.

The only pathology in which neurogenesis has been found to be altered in humans thus far is Huntington's disease. In this hereditary neurodegenerative disease, there is a substantial loss of postnatally born striatal neurons (Ernst et al. 2014). It is not known whether this is due to the disease inhibiting the generation of new neurons or whether neurogenesis is unaffected, but the newborn neurons are vulnerable to the pathology. In addition to the subpopulation of striatal interneurons that are exchanged throughout life, the much larger population of striatal projection neurons are gradually depleted in Huntington's disease, and this gradual decrease most likely causes most of the symptoms.

Several indications implicate reduced hippocampal neurogenesis in major depression. There is a reduced number of proliferating cells and neuroblasts in patients with major depression (Kang et al. 2016). Moreover, one of only a few common factors for different antidepressants is that they promote hippocampal neurogenesis in experimental animals. Furthermore, this increased neurogenesis is required for some of the antidepressant effects seen in animal models (Kang et al. 2016).

Experimental stroke affecting the striatum results in a strong neurogenic response, which represents the clearest example that adult neurogenesis may contribute to some neural repair. There is an increased generation of neuroblasts in the adjacent subventricular zone, and many of them migrate into the affected striatum (Arvidsson et al. 2002). Moreover, some resident astrocytes in the striatum activate a neurogenic program in response to stroke and generate neuroblasts and mature neurons (Magnusson et al. 2014). This activation of a latent neurogenic program in resident astrocytes is triggered by reduced Notch signaling (**Figure 3**). Experimentally blocking Notch signaling in striatal astrocytes in healthy mice without stroke is sufficient to initiate neurogenesis by resident

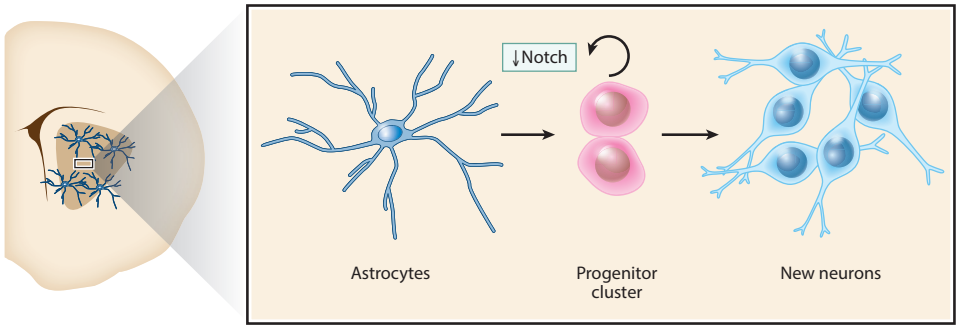

Figure 3

Recruitment of resident astrocytes to the neurogenic lineage. Astrocytes in the parenchyma of the striatum can enter a neurogenic program and give rise to new neurons in response to stroke or experimentally blocked Notch signaling.

parenchymal astrocytes in the striatum (Magnusson et al. 2014). The new neurons generated in response to stroke may contribute to some repair and regained function. However, the number of new neurons is small, and stroke is typically associated with permanent functional deficits.

OLIGODENDROCYTE EXCHANGE AND DYNAMIC MYELINATION REGULATE NEURAL PLASTICITY AND RECOVERY FROM DISEASE

The main glial cells in the central nervous system—astrocytes, oligodendrocytes, and microglia—influence neural plasticity and repair in different ways. Astrocytes contribute by being a source of new neurons, as discussed above, by modulating neural transmission and by making up a large part of the scar tissue that forms at injuries. Oligodendrocytes are exchanged at a high rate in mice, and microglia continuously monitor the immune status of the brain and can be rapidly expanded on demand.

A large proportion of the axons in the central nervous system are wrapped by myelin, multilayered sheets of specialized cell membrane from oligodendrocytes. Myelin insulates axons and dramatically increases the speed of signal propagation. Myelin and its interaction with oligodendrocytes also offer metabolic support for axons, and protracted loss of myelin results in axonal degeneration, as is seen in progressive demyelinating diseases (Simons & Nave 2015).

There are few oligodendrocytes and little myelination before birth. In humans, the number of oligodendrocytes and the myelin volume in white matter expand rapidly postnatally and start to plateau at approximately 5 years of age (Yeung et al. 2014). In the gray matter, oligodendrocyte numbers and myelin volume increase much more slowly and likely continue to increase until the fourth decade of life (Yeung et al. 2014).

Importantly, myelination is not a static process. Myelin expansion in childhood is affected by external factors. For example, social isolation in mice and humans strongly decreases myelination, which correlates with poor cognitive performance later in life (Makinodan et al. 2012). Oligodendrocyte generation and myelination are promoted by neuronal activity, suggesting on-demand increased myelination for active neural circuits (Gibson et al. 2014). This may explain how social isolation may decrease myelination or training a certain skill can increase myelination of specific axonal tracts.

It has been increasingly appreciated in the last years that, even when developmental myelination is completed, myelination is a dynamic and constantly modulated process. Neuronal activity is

associated with generation of new oligodendrocytes and with increased myelination in the employed brain regions in rodents (Gibson et al. 2014), and inhibiting the generation of new oligodendrocytes leads to impaired learning (McKenzie et al. 2014). Interestingly, MRI studies in humans have demonstrated an increase in the volume of brain areas in both white matter and gray matter as a task is learned (Zatorre et al. 2012). For example, individuals exposed to a training paradigm for juggling balls had an approximately 5% increase in the volume of an actively engaged brain area in just 6 weeks, in contrast to individuals in a control group who did not undergo the training program and did not have any volume increase (Scholz et al. 2009). Although it is difficult to use imaging to separate the contribution of myelin increase from that of other factors, such as axon thickening or increased vascularization, it is likely that myelination is dynamically modulated in humans learning new skills.

In rodents there is a high rate of continuous exchange of oligodendrocytes (Barnabé-Heider et al. 2010, Dimou et al. 2008, Rivers et al. 2008, Young et al. 2013). Experiments in mice have demonstrated that generation of new oligodendrocytes in the adult mouse brain is required for learning certain tasks (Gibson et al. 2014, McKenzie et al. 2014), suggesting that myelination is modulated by exchanging the myelinating cells. It is not known whether preexisting oligodendrocytes can alter the thickness of preexisting myelin sheets to modulate myelination.

The exchange dynamics of oligodendrocytes in humans is very different than in mice. Only approximately 1 in 300 oligodendrocytes is exchanged per year in adult human white matter, which is a rate at least 100-fold lower than what is seen in adult mice (Yeung et al. 2014). With this low generation rate, oligodendrocyte exchange cannot underlie the dynamic differences in white matter volume seen in, for example, training paradigms. Moreover, there is neither a correlation between the number of oligodendrocytes and myelin volume nor a correlation between generation rate and oligodendrocyte numbers in healthy humans (Yeung et al. 2014). Thus, the thickness of myelin sheets may be modulated in mature oligodendrocytes to regulate myelination, and it may constitute the main mechanism for myelin plasticity in humans. This could represent a more efficient way to modulate myelination, as exchange of oligodendrocytes would inevitably result in a transitory demyelination of axons, which likely would transiently impair function.

Demyelination, the loss of myelin sheets enwrapping axons, is a common component in many neurological diseases. In demyelinating diseases, of which multiple sclerosis is the most common, the loss of myelin is the primary cause of pathology. Remyelination can be efficient both in experimental animals, such as rodents, and in humans. However, with increasing duration of the disease and increasing age of the affected subject, the process becomes less efficient, eventually leading to permanent functional impairment in cases of chronic disease.

In rodents, new remyelinating oligodendrocytes are generated from resident oligodendrocyte progenitor cells, which proliferate in response to demyelination. Preexisting oligodendrocytes do not seem to contribute to remyelination in mice (Crawford et al. 2016, Keirstead & Blakemore 1997). It is difficult to know how informative mouse models of remyelination are for the situation in humans, given the very different kinetics of oligodendrocyte generation between species in the healthy situation and the difference between the pathology in humans and the experimental models used in animals. It will be important to assess the dynamics of remyelination in humans to understand how it can be therapeutically enhanced.

CENTRAL NERVOUS SYSTEM SCARRING BY GLIAL AND NONNEURAL CELLS

In lower vertebrates there is often complete regeneration of the tissue structure without scarring and with functional recovery after brain and spinal cord injuries. Lesions in the mammalian central

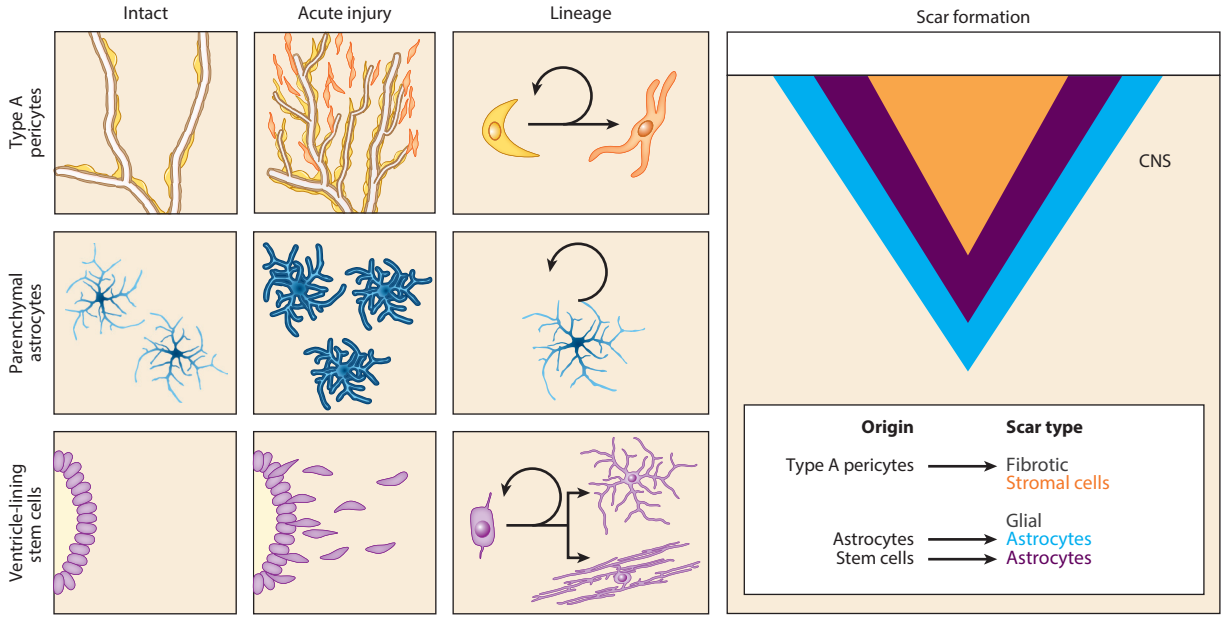

Figure 4

The origin of scar tissue in the injured central nervous system (CNS). Scar formation by resident astrocytes, stem cells, and pericytes. Resident astrocytes proliferate in response to injury and give rise to the perimeter of the scar tissue bordering the intact tissue. Stem cells lining the ventricular system—ependymal cells in the spinal cord and astrocytic stem cells in the subventricular zone—give rise to new astrocytes that contribute to the scar. Pericytes give rise to the central fibrotic component of the scar tissue that forms at a lesion.

nervous system are, in contrast, sealed by scar tissue, and there is typically permanent functional impairment. The scar tissue is often referred to as the glial scar, as it contains abundant reactive astrocytes. There is, however, also a sizeable fibrotic component of the scar, which has been much less studied to date. The functional impact of the scar tissue on regeneration has been a subject of debate for more than a century. Severed axons typically fail to regrow through the scar tissue, and there is abundant evidence that reactive astrocytes can inhibit axonal growth (Fawcett 2006, Okada et al. 2006, Silver et al. 2015).

The astrocytes that make up much of the scar tissue derive from two different sources (**Figure 4**). They derive both from preexisting resident astrocytes, which become reactive and self-duplicate in response to injury, and from neural stem/progenitor cells lining the ventricular system (Barnabé-Heider et al. 2010, Faiz et al. 2015, Johansson et al. 1999, Meletis et al. 2008). In the spinal cord, ependymal cells have neural stem cell properties (Barnabé-Heider et al. 2010, Johansson et al. 1999, Meletis et al. 2008, Pfenninger et al. 2011). They rarely proliferate under homeostatic conditions and do not give rise to nonependymal progeny. However, after spinal cord injury, their proliferation is dramatically increased, and they give rise to scar-forming astrocytes as well as to a small population of remyelinating oligodendrocytes (Barnabé-Heider et al. 2010, Johansson et al. 1999, Meletis et al. 2008). Ependymal cells constitute the main source of new astrocytes forming the scar tissue in the injured spinal cord and make up the part of the glial scar closest to the lesion, with resident astrocytes giving rise to the more peripheral part of the scar (Barnabé-Heider et al. 2010) (**Figure 4**).

Ependymal cell–derived astrocytes are necessary to regain tissue integrity, and when this process is experimentally inhibited, the lesions grow deeper over time, resulting in the severance of

additional axonal tracts (Sabelström et al. 2013). Moreover, ependymal cell–derived astrocytes constitute a rich source of neurotrophic factors, and there is increased neuronal loss when the generation of astrocytes by ependymal cells is blocked (Sabelström et al. 2013). Although less studied, the process of scar formation appears rather similar in the brain, where the glial scar is composed both of locally proliferating resident astrocytes and of astrocytes that are generated by subventricular zone stem/progenitor cells and that migrate to the lesion (Faiz et al. 2015).

The origin of the fibrotic component of the scar tissue was until recently unclear. In the injured spinal cord, it derives from a small subset of pericytes (Göritz et al. 2011). They proliferate vigorously after injury, and the daughter cells leave the blood vessel wall and differentiate into fibroblasts or myofibroblasts, which deposit the abundant extracellular matrix of the scar (Göritz et al. 2011) (**Figure 4**). These cells outnumber the reactive astrocytes in the scar after a spinal cord injury. The fibrotic component forms the most central part of the scar tissue and seals the lesion, and in the absence of this component, the injury fails to seal, resulting in open tissue defects (Göritz et al. 2011).

Thus, the scar tissue appears to have both positive and negative effects. Blocking the production of new astrocytes that form scar tissue in the injured spinal cord results in expansion of the lesion and increased neuronal loss. It will be important to study the role of the different components of the scar tissue to identify processes that may be attractive to therapeutically target in order to promote regeneration.

CONCLUSIONS

Although there is much less cell exchange in the central nervous system than in most tissues, even limited cell turnover at critical points in a network can have a substantial influence. In this way, exchanging a small number of neurons in the dentate gyrus of the hippocampus affects cognitive functions and modulation of oligodendrocyte generation, and myelination in actively employed neural circuits is important for learning in mouse models.

Studies indicate that cell generation in the adult brain may be affected in certain diseases and that modulation of these processes may be attractive therapeutic targets. It is important, however, to consider species differences in studies of cell turnover. It is becoming increasingly clear that there are rather dramatic differences between rodents and humans both in the distribution of adult neurogenesis, with a switch from olfactory bulb to striatal neurogenesis, and in the generation dynamics of oligodendrocytes and myelin modulation. Such differences are especially relevant when one is considering the role of cell turnover in disease or developing new therapeutic paradigms, as mouse models may not always be informative for the human situation.

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