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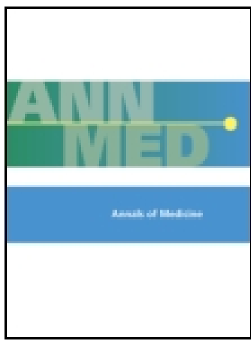

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SPECIAL SECTION ON STEM CELLS: REVIEW ARTICLE

New neurons in old brains

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Abstract
The brain was traditionally viewed as a static organ, without turnover of neurons or significant capacity for self-repair after insults. Research in the last years has established that neurons are renewed in certain areas throughout life. The prospect of stimulation of endogenous neurogenesis as well as cell transplantation has raised hope for new therapies for neurological diseases.

Key words: *Adult neurogenesis, cell transplantation, neural repair, neural stem cells, progenitor*

Adult neurogenesis

The initial exploration of the developing brain and spinal cord more than a century ago unraveled many features of the dramatic expansion and the precise organization of the central nervous system. The explosive growth during embryogenesis is in stark contrast to the relative stability after birth. The leading scientists at that time, most notably Cajal, His and Koelliker, found that the structure of the brain stayed fixed from soon after birth, and concluded that neurogenesis does not take place in the adult brain.

Altman and colleagues suggested in the 1960s, contrary to the dogma posed by the founding fathers of neuroscience, that neurons were added in the olfactory bulb and the hippocampus of adult rodents (1). The question remained, however, whether the newborn cells were *bona fide* neurons or may represent glial cells. A decade later, electron microscopical studies demonstrated that newborn cells in the adult brain have the ultrastructural characteristics of neurons with dendrites and synapses (2). At about this time, Nottebohm and colleagues established in a series of elegant studies that neurons are continuously replaced in the brains of songbirds and that this is important for the annual change in song pattern (3). Nevertheless, the concept of adult neurogenesis in mammals remained controversial. It was not until the 1990s, with the introduction of novel techniques and the unequivocal demonstration of adult-born neurons by many laboratories that this concept gained full acceptance. In addition to the firmly established neurogenesis in the adult hippocampus and olfactory bulb (4), it remains controversial whether neurons are added also in other regions such as the cortex (5–7), amygdala (8), the CA1 region of the hippocampus (9) and the substantia nigra (10–13).

It may, with hindsight, appear surprising that the dogma of no adult neurogenesis lasted so long, not least since we now know that rather substantial numbers of neurons are added in certain regions in adulthood. One explanation of the controversy has been the scarcity of reliable methods for the detection of neurogenesis. The first method used was ^{3}H-thymidine, a labeled nucleotide analogue that incorporates into the DNA of dividing cells, and these newly born cells can be visualized by autoradiography. ^{3}H-thymidine is difficult to combine with molecular markers and the neuronal identity of the labeled cell was indicated by their morphology. About fifteen years ago the thymidine analogue 5-bromo-3'-deoxyuridine (BrdU) was introduced.

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BrdU is also incorporated in the DNA of the dividing cell and can be visualized with immunohistochemical techniques. This development together with the emergence of a rapidly growing panel of molecular markers for distinct cell types made it possible to securely identify the newborn cells. Although these technical developments have furthered the field substantially, they carry several inherent problems with risks of both false positive and negative results (14).

Although our understanding of neurogenesis in the adult brains of experimental animals has increased very substantially over last decade, we know very little about the situation in the human brain. Imaging studies have demonstrated changes in the volume of distinct brain areas in response to, for example, training of a certain task (15) and in major depression (16). There are, however, many potential explanations for a volume change, and it is not possible to draw conclusions regarding a potential correlation to neurogenesis. The technical developments that have aided the analyses in experimental animals have serious limitations when it comes to the study of humans. First, BrdU is toxic, which largely precludes its use in humans. Second, BrdU has to be given prospectively and the tissue then collected after the individual has died, which poses a significant logistical challenge. In a seminal study in 1998 Eriksson and colleagues for the first time demonstrated neurogenesis in the adult human hippocampus by BrdU labeling (17). Cellular markers of cell division, such as PCNA (proliferating cell nuclear antigen) or KI-67, are commonly used to detect cell divisions, but they do not provide information regarding the final fate of the newborn cell. The analysis of potential markers for immature neurons can be informative, but relies on the specificity of the marker. Using different markers, two recent studies reached opposite conclusions regarding whether neurogenesis takes places in the human olfactory bulb (18,19), indicating the uncertainty with this strategy. We have recently developed a novel method for studying cell turnover in humans (7). This method takes advantage of drastically altered atmospheric levels of ^{14}C produced by nuclear bomb tests during the Cold War. After the Test Ban Treaty in 1963, there has been no significant over ground nuclear bomb testing and the ^{14}C levels have decreased exponentially. As the atmospheric levels of ^{14}C are mirrored in the human body (20–22), the distinct levels of ^{14}C at different time points serves as a date mark in the DNA of cells. Therefore, the time of birth of a population of cells can be established retrospectively by the analysis of ^{14}C in genomic DNA (7).

Key messages

- The adult brain harbors neural stem cells, which continuously give rise to new neurons in discrete regions.
- Stimulation of neurogenesis, or transplantation of cells derived from stem cells, offer attractive avenues for nervous system repair.

Stem cells in the adult brain

The neurons generated in adulthood derive from stem or progenitor cells. Neural stem cells are immature cells that have the potential to generate the main cell types of the central nervous system: neurons, astrocytes and oligodendrocytes (23,24). Another key feature is their capacity to divide to give rise to new stem cells, i.e. self-renewal capacity, thus enabling the persistence and activity of the system over a long time. A progenitor cell may have less broad differentiation potential or limited self-renewal capacity (23,24).

The first evidence for the existence of stem cells in the adult mammalian brain came from *in vitro* cultures of adult brain cells (25,26). When cultured in the presence of epidermal growth factor (EGF), the vast majority of cells from the adult mouse brain died, but a small subset of immature cells thrived and proliferated to form spherical cell aggregates, denoted neurospheres (26). Many of these cells proved able to give rise to new clones of immature cells as well as neurons, astrocytes and oligodendrocytes, thus displaying self-renewal capacity and multipotency – the hallmark features of stem cells (25–27). The possibility to culture neural stem cells has been invaluable for their characterization and has been instrumental to the progress of the research field. Most of the studies have focused on rodents, but it is now also well established that there are cells in the human brain, which *in vitro* display self-renewal and multipotency (18,28,29).

Stem cells are notoriously difficult to identify due to their immature phenotype and lack of specific markers. The most common approach in the pursuit of neural stem cells has been the isolation of a subset of cells from the brain followed by *in vitro* culture and analysis of whether the assayed cells display self-renewal capacity and multipotency *in vitro*. This approach has the caveat that although a cell behaves as a stem cell *in vitro*, it cannot be concluded that it has similar properties *in vivo*. Indeed, there is evidence to suggest that many of the cells displaying neural stem cell properties *in vitro* act as more

restricted progenitor cells *in vivo* (30,31). Cells with *in vitro* neural stem cell properties can be isolated from many regions in the central nervous system, including the spinal cord (28,32,33). Most of these cells with *in vitro* stem cell properties may never give rise to neurons *in vivo*, and their physiological function is unclear.

The neurons that continuously are added to the hippocampus derive from local resident stem cells present in the subgranular zone of the dentate gyrus (24,34–36). The neurons that are added to the olfactory bulb derive from stem cells residing in the lateral wall of the lateral ventricles, from where they migrate along the rostral migratory stream to the olfactory bulb (37–39). Many studies have attempted to identify the stem cells in the lateral ventricle walls, but much of the data is contradictory (28,40–43). This is largely due to the lack of methods to identify stem cells and there is a need for the development of novel strategies for the visualization of the distinct steps in a cellular lineage *in vivo*.

Regulation and potential role of adult neurogenesis

The activity of tissue stem cells is not controlled strictly cell-autonomously, but to a large extent directed by systemic factors as well as local environmental cues in the so called stem cell niche (44–46). A striking example of the power of the local milieu is provided by the transplantation of neural stem cells from the spinal cord to the hippocampus, where the normally non-neurogenic spinal cord cells produce neurons of the appropriate site-specific hippocampal phenotype (47). Several genes, hormones and environmental factors that regulate neurogenesis in experimental animals, by modulating the proliferation of stem/progenitor cells or supporting the survival of newborn neurons, have been identified. Learning, enriched environment and physical activity stimulate the generation of adult born neurons in the hippocampus (48–50). Upon stress and ageing the level of glucocorticoids is raised, and high levels of adrenal steroids decrease the number of proliferating cells in the dentate gyrus (51–54). Stress early in life has furthermore been implicated in modulating the regulation of neurogenesis in adulthood (55).

The realization of continuous neurogenesis in the adult mammalian central nervous system poses the question what the role of this process may be in brain function and pathology. The first requirement for a new neuron to be able to exert function is that it can integrate into the mature brain and form appropriate connections. Several studies in the last few years have demonstrated that the new neurons integrate into the synaptic circuitry in the adult rodent hippocampus and olfactory bulb and respond to physiological stimuli (56–58). In order to establish the role of adult neurogenesis several groups have attempted to interfere with neurogenesis by killing proliferating stem or progenitor cells by irradiation or cytotoxic agents (59,60). This has resulted in indications that neurogenesis may be important for certain aspects of memory formation (59). Moreover, it was suggested that depression leads to reduced neurogenesis in the hippocampus, and that the behavioral effects of many antidepressants may be mediated by the stimulation of neurogenesis in the hippocampus (16). In support of this, the antidepressant effect of fluoxetine in animal models was blocked by irradiation-depleted neurogenesis (60). These different approaches to interfering with neurogenesis, however, all run the risk of affecting other processes, so that it remains difficult to delineate the role for adult neurogenesis. Novel approaches that selectively deplete adult-born neurons are critically needed.

Cell therapy for neurological disorders

The realization of the existence of neural stem cells and continuous neurogenesis in certain regions of the adult brain raises the prospect of new therapeutic strategies. There are two conceptually different routes for the use of stem cells for neural repair: cell transplantation and stimulated neurogenesis from endogenous stem or progenitor cells.

Several neurological diseases have been suggested to benefit from cell transplantation, but most progress has been made in Parkinson's disease. Patients have been transplanted with grafts of ventral midbrain tissue from aborted human fetuses containing dopaminergic neurons, the predominantly affected neuronal type in Parkinson's disease, with promising results (61). In some studies, the patients have benefited substantially from the grafts, whereas other studies have been less encouraging or the patients have suffered side effects, indicating a need to develop the strategy further. Even when optimized, there are, however, substantial hurdles for the use of fetal grafts in terms of clinical feasibility. Several aborted fetuses are used for each Parkinson's patient and the supply of fetuses is limited. Furthermore, ethical concerns largely preclude development and application in many countries. Stem cells could, in theory, be a source of an unlimited supply of neurons for transplantation (62). One could in this case consider several sources

of stem cells, and the most studied thus far in this context are embryonic stem (ES) cells and fetal neural stem cells. Studies in experimental animals using ES cells or fetal neural stem cells have lent support to the concept of stem cell-based cell replacement therapy for Parkinson's disease (62–64). Adult neural stem cells have the advantage that they are ethically uncontroversial and could be used autologously, circumventing the risk of immune rejection, but they have been less studied in this context.

The main challenge for the development of any stem cell-based cell therapy is the control of cell differentiation, i.e. to make sure that the desired cell type, and not all the other cells on the stem cell's repertoire, is generated. This is not only important in order to get clinical effect, but also to avoid the development of rapidly proliferating cell types and tumor formation. Much insight into the signals that govern the specification of distinct cell types can be gleaned from the studies of developmental biology, where enormous progress in the last decade has taught us much about how diverse cell types are generated. The recapitulation of developmental signals in the tissue culture dish has been used successfully to instruct ES cells to form specific neuronal subtypes (64–66).

Perhaps the most intuitive benefit of stem cell-based therapies for neural repair is the replacement of lost neurons. Neural stem cells may, however, mediate beneficial effects in indirect ways by affecting the resident cells (67). Transplanted neural stem cells can produce neurotrophic factors which may support the survival of neurons or have immunomodulatory effects (67,68). Moreover, stem cell transplantation in animal models of metabolic disorders suggests that the stem cells, or their progeny, can substantially reduce the accumulation of toxic products (69,70). Their capacity to spread substantially in the brain enables them to reduce the load of metabolic products throughout the tissue. All these different actions, which are not based on the replacement of lost cells, have been suggested as features that could be useful in therapies. It is also important to note that some of these properties may be disadvantageous under certain conditions. For example, stem cell transplantation to the injured spinal cord improves functional outcome in experimental animals, probably mainly through remyelinization and neurotrophic effects, but also promotes aberrant axonal sprouting associated with the development of allodynia (71). The aberrant axonal sprouting appears to be due to neurotrophic effects of the grafted cells, and can be circumvented by directed differentiation of the neural stem cells. For a recent comprehensive review on cell transplantation for neural repair the reader is referred to (62).

Neural repair by endogenous neural stem cells

When we now know that the brain retains the capacity to integrate new neurons, one may wonder why the recovery after neurological insults is so limited. Or is it so limited? The impediments after, for example, a stroke often gradually decrease over an extended time period. This is, to a large degree, most likely due to adaptation and compensation by the remaining cells, but neurogenesis could potentially, in part, contribute to some functional recovery. Several different types of central nervous system insults, including trauma, seizures and stroke evoke activation of endogenous stem/progenitor cells and production of neurons and/or glial cells in experimental animals (28,72–75). Nevertheless, recovery is in most cases incomplete. Indications of increased neurogenesis, such as more proliferative cells and/or more cells with immature neuronal phenotype have also been reported in less acute conditions such as Alzheimer's, Huntington's and Parkinson's disease (13,76,77). It is uncertain whether a potentially increased neurogenesis in neurodegenerative diseases may represent an attempt to compensate for the loss of neurons or a secondary consequence of the brain pathology.

An attractive alternative to cell transplantation is to induce resident stem or progenitor cells to produce new cells. This approach would have the advantage of potentially being non-invasive and using the patients own cells, without the need for immunosuppression. This may at a first glance appear very challenging, as there are several steps, including cell proliferation, differentiation and migration, which would need to work. However, it appears that the adult brain may retain many instructive signals, and several commonly used pharmaceuticals used in psychiatry actually stimulate neurogenesis, which may be partially responsible for their therapeutic effect (16).

Perhaps the least challenging approach to therapeutic neurogenesis is to enhance this process in the normally neurogenic regions. Characterization of the molecular pathways that normally control different steps in the generation of neurons in the adult brain have resulted in insights into how this process can be enhanced. Experiments in rodents have demonstrated that affecting several different steps, such as supplying mitogenic (78–80) or neurotrophic factors (81,82) or blocking a pathway inhibiting progenitor proliferation (83), can all result in increased neurogenesis.

A dramatic indication that such an approach may indeed be beneficial in neurological pathology was first provided by Nakatomi et al. They suggested that the delivery of the mitogens EGF and fibroblast growth factor (FGF) promoted the proliferation of stem/progenitors by the lateral ventricle resulting in neuronal replacement and functional recovery after stroke (80). Importantly, the neuronal replacement appeared to include regions where neurogenesis does not occur at appreciable levels under normal conditions. Studies by Macklis and colleagues have also provided support for the addition of neurons to normally non-neurogenic regions, in this case in the cerebral cortex, in response to insults (84,85).

Conclusions

Our view of the adult brain has changed with the realization of the presence of endogenous stem cells and continuous neurogenesis in certain regions. Many important questions remain, such as a precise understanding of the cellular pedigree in the stem cell lineage, the extent and distribution of neurogenesis in the adult human brain, the functional role of adult-born neurons and whether the promise of stem cells and neurogenesis can be captured in therapies for neurological diseases. The coming decade promises to be very exciting and will likely provide answers to several of these questions.

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