PROSPECTS
Journal of Cellular Biochemistry 112:1467–1474 (2011)

Journal of Cellular Biochemistry

Deviating From the Well Travelled Path: Precursor Cell Migration in the Pathological Adult Mammalian Brain

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ABSTRACT

The presence of both neural and glial precursor cells in the adult central nervous system (CNS) and the capacity of these cells to migrate through this mature structure to areas of pathological damage and injury raises hope for the development of new therapeutic strategies to treat brain injury and disease. Although at present time, the compensatory neurogenesis described after various types of brain pathologies appears to be modest, the development of a strategy promoting the directed mobilization and phenotypic induction of endogenous precursor cells to areas of neural cell loss remains of high interest. The development of such a strategy however is currently thwarted by a limited understanding of the process and factors influencing precursor cell migration. In this review, we will discuss the current knowledge around precursor cell migration in the pathological adult brain with particular focus on the response and fate of precursor sub-populations to neural cell loss and the role of the inflammatory system in mediating precursor cell migration. Through this discussion we will identify particular areas in which further detailed research is required in order to expand our current understanding and aid in the eventual development of a novel therapeutic application. J. Cell. Biochem. 112: 1467–1474, 2011.

KEY WORDS: NEUROLOGICAL DISEASE; BRAIN PATHOLOGY; ADULT NEUROGENESIS; NEURAL PRECURSOR CELLS; GLIAL PRECURSOR CELLS; CELL MIGRATION; SUBVENTRICULAR ZONE; INFLAMMATION; CYTOKINES; CHEMOKINES

The occurrence of neurogenesis, defined as the generation of new neurons, has become well established in the adult mammalian brain, including the human brain over the last two decades. Neurogenesis in the adult brain can be divided into four phases: (a) progenitor cell proliferation; (b) migration of progenitor cells toward a target area; (c) terminal differentiation into a specific phenotype; and (d) integration into established networks. Neural progenitor cells generate neurons throughout life in the mammalian forebrain subventricular zone (SVZ)–olfactory bulb (OB) pathway and the hippocampal dentate gyrus (for review see Whitman and Greer [2009]). While dentate granule cells are generated locally by proliferating progenitor cells in the subgranular zone (SGZ) of the dentate gyrus, progenitor cells generated in the SVZ migrate long distances to their final destination in the OB. Progenitor cells form neuroblasts which migrate from the SVZ to the OB via a unique form of tangential chain migration in a restricted forebrain pathway known as the rostral migratory stream (RMS). Migrating neuroblasts in the SVZ and RMS of adult rodents can be identified by their expression of characteristic markers such as the polysialylated form of neural cell adhesion molecule (PSA-NCAM), neuron-specific βIII-tubulin and doublecortin (Dcx). Once the neuroblasts reach the subependymal region of the OB, they disperse radially and differentiate into granule and periglomerular neurons.

In order to fully understand the process of adult neurogenesis, each of the four phases needs to be examined independently. A critical issue of neurogenesis, both during development and in adulthood, is the appropriate integration of different cell types to form mature neural cells. This means that precursor cells need to migrate from their places of birth to their final positions. Such a highly regulated process is mediated by a number of environmental cues-like substrates, chemoattractive/chemorepulsive factors, and detachment/stop signals. Although some of these factors have been identified, many remain to be discovered (for review see Cayre et al. [2009]). Precursor cell migration is most extensive in the developing and immature brain. In the adult brain, neural cell migration still continues, although in a more limited capacity with the most extensive region of migration observed in the SVZ-RMS-OB pathway. It is not yet clear why new neurons are not born in the place they need to reside. While the maintenance of stem cell niches in the adult brain may provide a potential source of cells for brain repair and cell replacement, these regions may be costly for the organism and may also require specific features that restrict the

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Received 15 February 2011; Accepted 17 February 2011 • DOI 10.1002/jcb.23086 • © 2011 Wiley-Liss, Inc.
Published online 24 February 2011 in Wiley Online Library (wileyonlinelibrary.com).

structures where they can persist. As a result, cells need to be able to migrate from these discrete niches to their final destination, in both normal and pathological conditions. While precursor cell migration may provide an additional level of control for cell positioning in the normal adult brain, it is as yet unclear whether this level of regulation extends to the injured or diseased adult brain. During pathological processes, such as in a variety of neurological diseases, brain reactivity occurs in spontaneous attempts at protection and/or repair. These processes result in a distinct profile of cell migration not observed in the normal adult brain, which appear to be mediated by an independent set of environmental cues.

In this review, we will discuss the current knowledge around precursor cell migration in the pathological adult brain with particular focus on the response and fate of precursor sub-populations to neural cell loss and the role of the inflammatory system in mediating precursor cell migration. Through this discussion, we will identify particular areas in which further detailed research is required.

PRECURSOR CELL MIGRATION IN THE PATHOLOGICAL BRAIN

Alteration in precursor cell migration following neural cell loss has been demonstrated in a number of disease and injury models, including seizure activity, focal ischemia, traumatic brain injury (TBI), and excitotoxic lesioning. From these studies it is apparent that while the migratory response of precursor cells is dependent on the size and location of neural cell loss, a common profile of precursor cell migration can be observed.

SEIZURES

Seizure activity in the adult rodent brain damages the hippocampus, causing the death of resident pyramidal cells. This results in an acute neurogenic response in the hippocampus which begins between 1 and 4 days following seizure induction (for review see Parent et al. [2002a]). In normal animals bromodeoxyuridine (BrdU) labeled cells are restricted to the SGZ of the hippocampus, whereas following seizure activity BrdU cells are found extensively in the hilus region of this hippocampus. This indicates aberrant migration of dividing cells following seizure activity. In addition to the neurogenic response observed in the hippocampus, precursor cells in the SVZ also respond to seizure activity in the adult rodent brain. Dcx expression is up-regulated at 7 and 14 days following seizure induction, but returns to normal levels by day 35 indicating this is also an acute response [Parent et al., 2006]. Migration of precursor cells to the OB is enhanced following seizures, with a significant increase in PSA-NCAM cells in the RMS at day 14, and BrdU labeled cells reaching the granule cell layer of the OB when labeled on day 14 following seizure induction [Parent et al., 2002b]. Importantly, a large number of cells are found adjacent to the RMS instead of within its realms (most prominent at 14 days following seizure induction), indicating that seizure activity induces aberrant migration of SVZ precursor cells into surrounding regions of the brain [Parent et al., 2002a, 2002b].

TRAUMATIC BRAIN INJURY

The most frequently used experimental models of TBI include the controlled cortical impact and lateral fluid percussion models. Controlled cortical impact injury results in damage to the cortex and also the CA1, CA3, hilus, and dentate gyrus regions of the hippocampus. In both injury models there is an acute neurogenic response with an increase in hippocampal progenitor cell proliferation observed from 24 h to 1–2 weeks following TBI [Dash et al., 2001; Chirumamilla et al., 2002; Emery et al., 2005]. Newly generated neurons in the dentate gyrus integrate into the existing hippocampal circuitry following TBI, potentially resulting in cognitive recovery [Sun et al., 2005]. Adult SVZ neurogenesis has also been investigated in the controlled cortical impact model of TBI [Goings et al., 2002; Ramaswamy et al., 2005]. In these studies, SVZ progenitor cell proliferation was observed to be either reduced [Goings et al., 2002], or exhibit a delayed increase in proliferation [Ramaswamy et al., 2005] following TBI. In the lateral fluid percussion model, an increase in SVZ progenitor cell incorporation of BrdU was observed between 2 and 8 days post-injury [Chirumamilla et al., 2002]. Interestingly, precursor cell migration within the SVZ-RMS-OB pathway, as demonstrated by PSA-NCAM expression, was not enhanced until 25–35 days post-TBI [Goings et al., 2002]. Retroviral labeling of SVZ progenitor cells and examination of the location of labeled cells at 4 days and 3 weeks in adult mice determined that very few cells migrated into the cerebral cortex in the normal brain, whereas a large number migrated into the lesioned area following cortical impact [Goings et al., 2004]. Migration of precursor cells into the lesioned cortex appeared to be at the expense of migration to the OB; in control animals approximately half of the labeled SVZ cells were found in the OB, whereas only a quarter of labeled cells migrated there following cortical injury [Goings et al., 2004].

FOCAL ISCHEMIA

Stroke involves an interruption in blood supply to the brain, termed as ischemia, and results in the death of neural cells and corresponding loss of brain function. Focal ischemia is generated through the blockage of blood vessels which supply specific regions of the brain, and is commonly modeled by the occurrence of transient middle cerebral artery occlusion (MCAo) which results in damage to the cortex and striatum. Focal ischemia results in an immediate and significant increase in both hippocampal and SVZ progenitor cell proliferation for up to 14 days post-ischemia. In addition, SVZ precursor cells have been observed to migrate into the lesioned striatum (for review see Ohab and Carmichael [2008]). Studies examining the temporal profile of SVZ precursor recruitment into the lesioned parenchyma in rodent models of focal stroke have found evidence reflecting both short- and long-term migration of progenitor cells into the damaged striatum [Jin et al., 2003; Carmichael, 2006; Thored et al., 2006]. A study examining the MCAo model of focal stroke provided evidence that Dcx cells are present in the striatum as early as 24 h following injury [Jin et al., 2003]. The origin of neuroblasts that appeared in the striatum was explored further by labeling SVZ cells with DiI, a lipophilic dye which is incorporated into lipid membranes on cells. Injection of DiI into the lateral ventricle in an attempt to label SVZ progenitor cells

resulted in DiI being observed in the adjacent striatum over 24–72 h after ischemia [Jin et al., 2003]. However, due to the nature of DiI being able to diffuse through tissue into both dividing and non-dividing cells, these results have to be viewed with some skepticism. Another study used BrdU labeling between 1 and 3 days following MCAo and did not find a significant number of BrdU/Dcx double labeled cells in the striatum at day 3, but a maximal number was found at day 5 post-stroke [Carmichael, 2006]. This suggests recruitment of SVZ precursor cells at very early stages post-stroke. In addition, an investigation by Thored et al. [2006] using a temporal profile of BrdU labeling detailed evidence that neuronal replacement in the damaged striatum from SVZ progenitor cells continues up to 2 months following focal stroke. However, as BrdU labels all proliferating cells in the brain at the time of administration, it cannot be determined with absolute certainty that these Dcx cells originated from the SVZ, and may therefore represent the presence of in situ progenitor cells. To more appropriately address the origin of migrating precursor cells in the MCAo lesioned striatum Yamashita et al. [2006] injected a Cre-encoding plasmid into the lateral ventricles of transgenic mice carrying a floxed green fluorescent protein (GFP) gene. This allowed both the migration and fate of labeled precursor cells to be examined. Yamashita et al. [2006] demonstrated that GFP-labeled cells originating in the SVZ generated neuroblasts that migrated toward the MCAo lesioned striatum. GFP+ neuroblasts in the striatum formed elongated chain-like cell aggregates similar to those in the normal SVZ, and these chains were observed to be closely associated with thin astrocytic processes and blood vessels. Furthermore, long-term tracing of GFP-labeled cells with a Cre-loxP system revealed that the SVZ-derived neuroblasts differentiated into mature neurons in the striatum, in which they expressed neuronal-specific nuclear protein and formed synapses with neighboring striatal cells [Yamashita et al., 2006].

Changes in neurogenesis are also observed in a more discrete model of focal ischemia which involves the selective damage of cortical tissue (for review see Ohab et al. [2006]). Following cortical stroke, hippocampal neurogenesis was augmented with increases in BrdU immunoreactivity and the formation of new neurons in the granule cell layer. At day 5 and 7, but not day 3 following stroke, there was a significant increase in Dcx positive cells in the infracted cortex [Ohab et al., 2006]. The lack of BrdU labeling in the infarcted cortex after direct injection of BrdU into the cortex suggests that these Dcx cells were likely to have arisen from SVZ progenitor cells. Furthermore, viral vector labeling of SVZ progenitor cells with GFP resulted in the appearance of GFP/Dcx co-labeled cells in the infarcted cortex at 7 days indicating that the cells originated from the SVZ [Ohab et al., 2006]. This cortical migration may also occur at the expense of normal OB migration, as the number of cells reaching the OB is nearly halved following cortical stroke despite an increase in the number of BrdU positive cells in the SVZ and RMS [Ohab et al., 2006].

EXCITOTOXIC BRAIN INJURY

Striatal injection of QA generates the selective loss of the GABAergic medium spiny neurons in the striatum. This results in a significant increase in progenitor cell proliferation at days 1–14 following QA lesioning [Collin et al., 2005; Tattersfield et al., 2004]. In addition, both expansion of the RMS and aberrant migration of SVZ Dcx+ precursor cells into the lesioned striatum have been demonstrated following QA-induced striatum cell loss [Tattersfield et al., 2004; Collin et al., 2005; Gordon et al., 2007]. In order to elucidate the temporal profile of precursor cell migration in response to QA-induced striatal cell loss, Gordon et al. [2007] used retroviral tracing to label SVZ precursor cells and track their migratory profile. This study demonstrated that SVZ precursor cell migration was significantly enhanced in the RMS of QA lesioned animals immediately following, and up to 30 days following QA-induced striatal cell loss. This was in contrast to the findings reported by Goings et al. [2004] in the TBI model, and demonstrated that recruitment of SVZ precursor cells into the QA lesioned striatum was not at the expense of OB migration. In addition, Gordon et al. [2007] identified that SVZ precursor cell migration into the QA lesioned striatum was transient, with precursor cell recruitment predominantly observed by cells labeled either 2 days prior or up to 3 days following QA lesioning. Interestingly, a change in the morphology of the recruited SVZ-derived precursor cells was observed over time. SVZ-derived progenitor cells labeled either 2 days prior, or on the day of QA lesioning predominantly exhibited a bipolar morphology and expressed Dcx. In contrast, the majority of progenitor cells labeled from the day of QA lesioning up to 3 days following lesioning displayed a multipolar morphology and did not express Dcx [Gordon et al., 2007]. This study indicates that striatal cell loss induces an expansion of the SVZ progenitor cell population, in which a sub-population of SVZ precursor cells are responsive to recruitment into the lesioned area. In addition, the novel observation of a temporal change in the morphological profile of precursor cells recruited into the QA lesioned striatum is of great interest, and warrants further investigation. This alteration in precursor cell morphology may be in response to changes in environmental cues present in the lesioned striatum.

UNDERSTANDING THE TEMPORAL PROFILE OF PRECURSOR CELL MIGRATION AND THE INVOLVEMENT OF GLIAL PRECURSOR CELLS IN THE PATHOLOGICAL BRAIN

The studies discussed above demonstrate that while the migratory response of precursor cells is dependent on the size and location of neural cell loss, a common profile of precursor cell migration can be observed. It becomes apparent that, in contrast to our previous understanding, precursor cell migration into an area of neural damage is not continuous but is limited, potentially in response to the temporal profile of chemoattractant factors expressed in the area of neural cell loss. To date relatively few studies have investigated the temporal profile of precursor cell migration into areas of neural cell loss. In order to fully understand precursor cell migration in response to brain pathology, additional temporal profile studies need to be done in a range of disease or injury models. This will allow us to identify key commonalities in precursor cell migration within the pathological brain. Previous studies have also predominantly focused on the migration of Dcx+ precursor cells. This may only provide us with information of a sub-population of the precursor cells migrating in response to neural cell loss, and hence significantly limited our full understanding of precursor cell migration in the pathological brain. This is best demonstrated by

the results obtained by Gordon et al. [2007] in which a population of multipolar Dcx negative were observed to be recruited into the QA lesioned striatum, in addition to recruitment of bipolar Dcx+ precursor cells. While the phenotype of these multipolar precursor cells remains to be elucidated, it can be supposed that these cells express NG2 and/or Olig2, markers of oligodendrocyte precursor cells (OPCs). In agreement with the observations made by Gordon et al. [2007], the presence of multipolar Olig2+ precursor cells were observed by Buffo et al. [2005] following a cortical stab wound injury. NG2 expression identifies a heterogeneous population of cells in the adult central nervous system (CNS), including OPCs (for review see Nishiyama et al. [2009]). The expression of NG2 on OPCs is involved in the migration of these cells through interactions with integrins and chondroitin sulphate glycosaminoglycan (for review see Karram et al. [2005]). In the brain, NG2+ precursor cells have been observed to respond by increased proliferation and migration to a range of pathological conditions; this is most prominent in conditions of demyelination or hypomyelination, though has also been reported in a variety of non-demyelinating inflammatory CNS pathologies (for review see McTigue and Tripathi [2008]). Specific signals have been identified that regulate the migration of OPCs during development, however very little is known about the signals that induce OPC migration in response to neural cell loss. While further studies are warranted to characterize the mechanisms by which OPCs respond to both demyelinating and non-demyelinating conditions, it is apparent that OPCs are able to respond to a range of molecules involved in CNS function and repair. It is of importance that the role of all precursor subtypes are investigated in the pathological brain, as the majority of previous studies have ignored the important role that glial precursor cells may play in response to neural cell loss. The response of both neuronal and glial precursor cells will best be determined using techniques such as retroviral tracing and cell fate mapping without the use of specific neural promoters, as this will allow examination of both neuronal and glial precursor populations and ensure a complete view of the regenerative response of precursor cells to neural cell loss.

It would be of great interest to determine the mechanisms regulating the induction of both neuronal and glial precursor recruitment into the pathological brain. One question which arises from the results of Gordon et al. [2007] is whether a change in precursor cell phenotype occurs in response to a pathological insult to the CNS, or alternatively whether different sub-populations of precursor cells are recruited dependent on the environmental cues being temporally expressed. It is becoming clear that both the developing and adult SVZ are comprised of a heterogeneous mixture of cells from different lineages [Merkle et al., 2007]. Phenotypic specification may occur within the SVZ or even after emigration from the SVZ. In vivo, instructive or permissive factors enable some precursor cells to migrate into the parenchyma while others remain within the SVZ. A change from a predominantly neuronal to a glial precursor phenotype may indicate an alteration in the bipotency of precursor cells over time, with an increase in the presence of Mash1/Olig2 precursor cells and a reduction in Mash1/Dlx2 or Mash1/Ngn2 precursor cells. Alternatively, the bipotency of precursor cells present in the SVZ may not change, but neuronal or glial precursor populations may be differentially effected by a temporal change in factors expressed in the damaged region [Seidenfaden et al., 2006]. Studies examining the temporal expression of proneural and glial transcription factors in SVZ precursor cells in response to neural cell loss need to be undertaken in order to address these questions. These observations also need to be combined with studies investigating the profile of chemoattractant expression in areas of pathological damage.

One final question that currently exists is what role glial precursor cells are playing following recruitment into a site of neural damage. While the majority of NG2+ or Olig2+ precursor cells are destined to form oligodendrocytes, NG2+ cells may generate other glia, such as astrocytes or neurons in specific brain regions [Kondo and Raff, 2000; Belachew et al., 2003; Guo et al., 2010], however neurogenesis from NG2+ cells could not be confirmed by other studies [Dimou et al., 2008; Kang et al., 2010]. Two potential roles recruited glial precursors may have are either myelination of new axons/remyelination of damaged axons or alternatively, the replacement of oligodendrocytes lost as a result of pathological damage. Recent work by Gotz et al. (reviewed in Robel et al. [2011]) have raised the question as to whether glial precursor cells can be "reprogrammed" to generate neuronal precursors, and enhance neuronal replacement. This is an exciting new advance which may allow novel alternatives to exogenous sources of neurons for therapeutic intervention. However, this approach may need to be treated with caution until it becomes more evident as to the role glial precursor cells play in the regeneration of areas of neural cell loss.

THE EXPRESSION OF CHEMOATTRACTANT FACTORS IN THE PATHOLOGICAL BRAIN

A fundamental issue concerning precursor cell migration in the adult brain is to understand the extracellular cues and mechanisms that allow the persistence of normal migratory pathways, as well as the recruitment of precursor cells into area of neural damage. Increasing evidence indicates the involvement of developmental signals that are maintained in restricted regions of the adult brain, including factors such as extracellular matrix molecules, Eph–Ephrin interactions, neuregulins, and a range of chemoattractant and chemorepulsive molecules (for review see Cayre et al. [2009]). In addition, several mechanisms and migratory tracks have been proposed for the guidance of migrating precursor cells toward regions of neural damage. These include migration along: (1) myelinated fiber tracks; (2) radial processes; and (3) blood vessels (for review see Cayre et al. [2009]). Besides these mechanisms, inflammation-induced chemoattraction plays a major role in precursor cell migration following neural cell loss and for the remainder of this review we will focus on the role of neuroinflammation, in particular cytokine and chemokine expression in regulating precursor cell migration in the pathological brain.

Upon insult or infection, the brain exhibits a profound innate response, characterized predominantly by robust activation of microglia (resident macrophages of the CNS). Activated microglia play a dual role, scavenging the damaged and dying neurons as well as initiating a prompt local inflammatory reaction. The inflammatory response involves production of proinflammatory cytokines

and chemokines, as well as various reactive nitrogen and oxygen species. Cytokines released by microglia subsequently activate resident astrocytes, which again release cytokines. Peripheral macrophages are recruited into the brain by chemotaxis in response to a superfamily of cytokines called chemokines. Chemokines are small, secreted proteins that play crucial roles in leukocyte migration under normal conditions as well as during neuroinflammatory responses. Following damage to the adult brain, a range of cytokines and chemokines have been shown to be up-regulated in the region of neural cell death, including GRO-α, IL-8, IP-10, MCP-1, MCP-2, MIP-1α, RANTES, SDF-1α, and TNF-α [McManus et al., 1998; Das and Basu, 2008; Gordon et al., 2009; Whitney et al., 2009]. In addition, chemokine receptors are widely expressed in neural precursor cells, including CXCR1, CXCR2, CXCR4, CXCR7, CCR1, CCR2, CCR3, and CCR5 [Ji et al., 2004; Tran et al., 2004; Gordon et al., 2009]. The expression of chemokine receptors on neural precursor cells signifies the crucial roles played by chemokines in guiding precursor cell migration and the influence these factors have in the recovery process in the damaged or injured CNS.

While a number of cytokines and chemokines involved in the inflammatory process have been demonstrated to play a role in directing precursor cell migration (summarized Table I), MCP-1 and SDF-1α and their receptors have been the most widely examined and clearly regulate the directed migration of endogenous neural precursor cells from the SVZ to the damaged striatum following either ischemic or excitotoxic neural cell loss [Imitola et al., 2004; Belmadani et al., 2006; Robin et al., 2006; Yan et al., 2006; Gordon et al., 2009]. The SDF-1α receptors CXCR4 and CXCR7 are highly expressed on neural precursor cells. SDF-1α expression is highly up-regulated in reactive astrocytes, microglia, and endothelial cells in ischemic striatum during several weeks after focal ischemic injury [Thored et al., 2006] and has been shown to induce the migration of precursor cells in vitro [Peng et al., 2004] and in vivo to areas of hypoxic-ischemic-induced inflammation via CXCR4 signaling pathways [Imitola et al., 2004; Robin et al., 2006]. The chemokine MCP-1 is also up-regulated in response to inflammation and induces the migration of neural precursor cells. The MCP-1 receptor CCR2 is expressed by neural precursor cells and MCP-1 recruits precursor cells to the site of brain inflammation by binding to CCR2 and inducing their migration [Widera et al., 2004; Belmadani et al., 2006; Gordon et al., 2009].

Overall, these studies clearly indicate that neuroinflammation and the resulting expression of cytokines and chemokines play a major role in directing the migration of precursor cells in the pathological brain. However, inflammatory cues involved in directing the migration of precursor cells can also contribute to decreased survival of these migrating cells, creating juxtaposition between regeneration and ongoing cell loss and highlighting the complexity of the neuroinflammatory environment: on one hand it is useful for attracting precursor cells to the appropriate region for neural replacement, but on the other hand it prevents efficient cell replacement by affecting the survival abilities of the migrating precursor cells. The opposing properties of neuroinflammation therefore complicates the development of therapeutic strategies involving the use of cytokines or chemokines.

Several interesting questions still exist in regards to the role cytokines and chemokines play in regulating compensatory adult neurogenesis. To date, most of the investigations into the role of cytokines and chemokines in regulating adult neurogenesis have focused on precursor cell migration. Very few studies have examined the effect of individual cytokines and chemokines on the differentiation of adult neural precursor cells. Accumulating evidence suggests that pro-inflammatory cytokines have a negative effect on neuronal differentiation, while anti-inflammatory cytokines exert a beneficial effect. Of the few studies that have been undertaken, Liu et al. [2008] provided evidence that either over-expression or inhibition of CXCR4 on SVZ-derived neural progenitor cells had no effect on differentiation, suggesting that SDF-1α/CXCR4 primarily regulates adult neural precursor motility but not differentiation. In contrast to this, Patel et al. [2010] recently demonstrated that CXCR4 promotes the differentiation of OPCs in a mouse model of demyelination. Liu et al. [2007] also examined the effect of MCP-1 on neural differentiation and established that MCP-1 promoted neuronal differentiation of SVZ-derived NPCs, suggesting that in addition to its role in cell motility, MCP-1 plays an important role in neuronal differentiation.

Based on our current limited knowledge, it is important that additional studies are undertaken to specifically examine the effect of cytokines and chemokines on the differentiation of adult neural and glial precursor cells. As discussed in the previous section, different sub-populations of precursor cells may be recruited dependent on the specific cytokines and/or chemokines being expressed. The expression of specific cytokines and/or chemokines

TABLE I. Cytokines and Chemokines Involved in Regulating Neural Precursor Cell Migration

Cytokine	Receptor in vitro	Receptor in vivo	Chemoattractant in vitro	Chemoattractant in vivo
GRO-α	Gordon et al. [2009]; Tran et al. [2004]	Gordon et al. [2009]; Tran et al. [2007]	Gordon et al. [2009]	
IL-8	Tran et al. [2004]		Beech et al. [2007]	
IP-10		Tran et al. [2007]	Tran et al. [2007]	
MCP-1	Gordon et al. [2009]; Tran et al. [2004]; Widera et al. [2004]; Yan et al. [2007]	Gordon et al. [2009]; Tran et al. [2007]; Yan et al. [2007]	Belmadani et al. [2006]; Gordon et al. [2009]; Tran et al. [2004]; Widera et al. [2004]; Yan et al. [2007]	Yan et al. [2007]
MCP-2		Tran et al. [2007]	Tran et al. [2007]	
MIP-1α	Gordon et al. [2009]; Tran et al. [2004]	Gordon et al. [2009]	Gordon et al. [2009]	
RANTES		Tran et al. [2007]	Tran et al. [2007]	
SDF-1α	Ji et al. [2004]; Tran et al. [2004]	Tran et al. [2007]	Tran et al. [2004]	Thored et al. [2006]
TNF-α	Ben-Hur et al. [2003]			Heldmann et al. [2005]

may induce phenotypic specification either within the SVZ or even after emigration from the SVZ. Studies need to be undertaken in order to elucidate the effect of specific cytokines, chemokines and their receptors on proneural and glial transcription factor expression and phenotypic differentiation of adult precursor cells. This can be achieved both in vitro and in vivo through the use of gene over-expression and knockdown techniques. It is also apparent that there is redundancy present in the response of adult precursor cells to cytokine and chemokine expression, with adult SVZ-derived precursor cells shown to express up to seven different cytokine and chemokine receptors. This further demonstrates the key role these factors play in neural regeneration. However, it remains to be answered whether there is an over-riding ''dominant'' cytokine/chemokine which acts to direct precursor cell recruitment in response to neuroinflammation, or whether a synergistic or additive effect of multiple cytokine/chemokines is required for a complete migratory response. In response to this, Gordon et al. [2009] demonstrated that the chemokines MCP-1, MIP-1α, and GROα acted in a partial additive manner on SVZ-derived neural precursor cells using an in vitro Boyden chamber assay. However, further studies examining the presence of a ''dominant'' cytokine or chemokine and the requirement for receptor redundancy will greatly enhance our understanding of the role cytokines and chemokines play in regulating adult precursor cell migration. Such studies will also assist in identifying whether up-regulation of multiple cytokines and chemokines are required in order to ensure the migration of a heterogeneous population of both neural and glial precursor cells. The final question remaining is why we observe only a sub-population of precursor cells being redirected from the SVZ-RMS pathway to areas of neural damage. This may reflect the timing of cytokine or chemokine receptor expression in SVZ-derived neural precursor cells, which influences their ability to respond as they proceed through the SVZ-RMS. Alternatively, it may reflect the production of anti-inflammatory cytokines by adult NPCs [Pluchino et al., 2005], which in turn may suppress their migration. In support of this, Guan et al. [2008] demonstrated that treatment of SVZ-derived neural progenitor cells with IL-4 and IL-10 up-regulated the expression of the chemokine receptors CXCR4 and CCR5 on neural precursor cells, leading to significantly higher chemotaxis to the ligands of the respective receptors than untreated cells. This demonstrates the need to undertake detailed molecular and cellular studies to fully elucidate the complexity by which cytokine and chemokines regulate precursor cell migration.

CONCLUSIONS

The presence of neural and glial precursor cells in the adult CNS and the capacity of these cells to migrate through this mature structure to areas of pathological damage and injury raises hope for the development of new therapeutic strategies. Unfortunately, the mobilization and recruitment of endogenous neural and glial precursor cells that occurs spontaneously after brain injury, or in neurodegenerative pathologies leads to very low rates of cell replacement. Identifying mechanisms by which endogenous precursor cell recruitment and survival can be enhanced may provide an opportunity for significant cell replacement in areas of neural cell loss. However, in order to achieve this we need to fully understand the mechanisms by which endogenous precursor cells undergo migration in the pathological brain, and in particular the response and involvement of specific precursor sub-populations. It is also apparent that acute inflammation is a key factor in promoting precursor cell migration to areas of pathology through the expression of cytokines and/or chemokines. However, we still know very little in regards to the complexity associated with the expression of multiple cytokines, chemokines and their receptors on precursor cell migration and phenotypic specification. The ability to manipulate cytokine and/or chemokine expression to enhance precursor cell migration for therapeutic application is a very exciting possibility, but will only be realized through further collaborative research between neuroscientists and immunologists. A detailed understanding of the process and factors influencing precursor cell migration would thus equip us with the knowledge to enhance adult neurogenesis, as per the need of the system, as well as unravel the mysteries behind the limited regenerative capacities of precursor cells in the pathological brain.

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