Chapter 2

Extrinsic and Intrinsic Factors Modulating Proliferation and Self-renewal of Multipotential CNS Progenitors and Adult Neural Stem Cells of the Subventricular Zone

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Introduction

Regulation of cell number in germinal zones of the nervous system is dependent on the interaction of extracellular signals with the "intrinsic" properties of the germinal cells that may vary depending on the developing stage of the organism. During early embryonic development, proliferation of cells occurs along the lumen of the developing neural tube, in an area defined as "the ventricular zone". At this stage, cells proliferate very fast and characteristically give rise to identical daughter cells, via a process identified as "symmetric cell division" that allows for expansion of the primordial structures (Fig. 2.1A). As the organism develops, the need for "rapid expansion" decreases and new structures begin to form while still allowing for growth of the organism. Therefore, by mid-gestation, a second germinal zone arises, the subventricular zone (SVZ) and cells in this area acquire a modality of cell division characterized by the generation of two different daughter cells ("asymmetric cell division"): One with the ability to self-renew and the other one with the ability to differentiate into a specific lineage (Temple, 2001). In adult SVZ, the maintenance of homeostasis induces stem cells and multipotential progenitors to divide asymmetrically, unless a need for rapid expansion (e.g. repair after injury) induces the cells to shift to a symmetric modality of division (Fig. 2.1B).

Changes in the levels of the extracellular signals, alterations of their receptors or modification of the intracellular signaling molecules regulating proliferation during embryonic development, may result in abnormalities of

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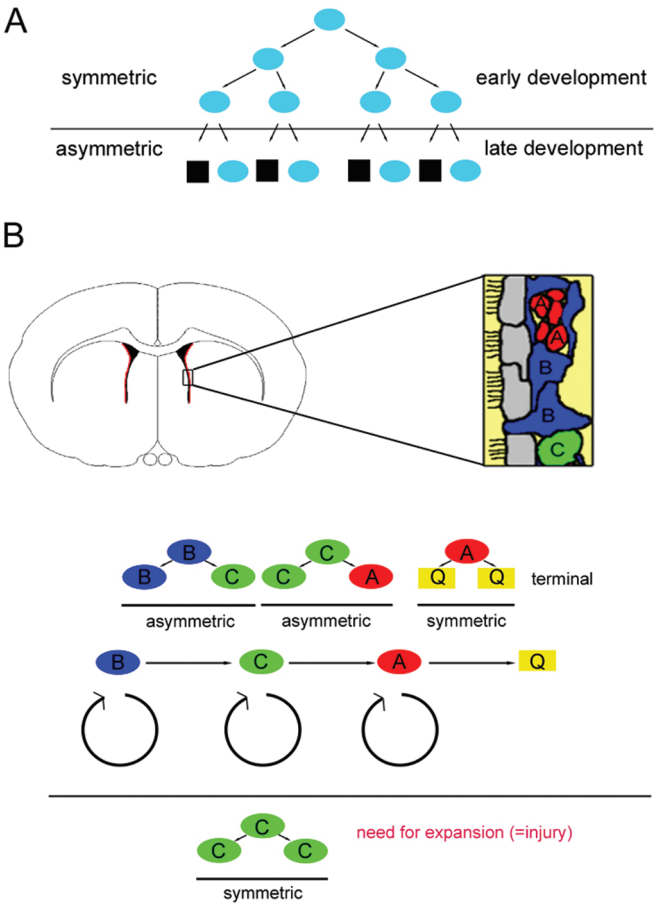

FIGURE 2.1. **Schematic representation of the distinct modalities of cell division**. During development (A), the expansion of brain structures is first guaranteed by the rapid and symmetric non-terminal cell division. As new cell types are generated, the pattern of cell division becomes asymmetric. In the adult animal (B) it is likely that stem cells (B cells) in the remaining germinal zones such as the SVZ undergo asymmetric cell division to maintain a specific number of mother and daughter cells. "Multipotent progenitors (C cells) undergo a similar pattern of asymmetric cell division and generate A cells and oligodendrocyte progenitors (not shown), with the ability to divide following a symmetric division where both daughter cells exit from the cell cycle (Q) and differentiate. Note that upon injury, the need for expansion of the progenitor population leads to symmetric division and expansion of C cells that generate both neurons and oligodendrocytes."

brain structures. Changes or modifications of extracellular or intracellular signals in adult neural stem cells, in contrast, may not affect the histoarchitecture of the brain, but affect the number of multipotential progenitors available for repair after injury. If proliferation is defective, a smaller number of cells will be available for repair, conversely, if proliferation proceeds uncontrolled, larger number of cells may result in hyperplastic foci and eventually lead to neoplastic transformation.

Since the responsiveness of neural stem cells and multipotential progenitors to extracellular signals is a dynamic process dependent on the developmental stage and on the regional localization of the cells, it becomes important to recognize that conclusions based on studies on embryonic stem cells may not be translated directly to adult neural stem cells. These temporally and developmentally restricted profiles of responsiveness to mitogenic and anti-mitogenic signals are determined by several parameters, including the bioavailability of extracellular signals, the presence of specific receptors, cross-talks among distinct signaling pathways and modulation of cell cycle regulatory molecules. All of these events can be affected or determined by specific genetic traits, expression of transcription factors and epigenetic modifications of chromatin components resulting in differences of gene expression that modulate the "context-specific" responsiveness of a stem cell.

It is worth mentioning that although the steady-state number of neural stem cells at any given stage of development is the result of the equilibrium between proliferation, differentiation, migration and survival of these cells, this chapter will focus only on the experimental evidence on extracellular factors and intracellular molecules affecting proliferation of neural stem cells and multipotent progenitors. This has been a very challenging task and although we have attempted to include several studies in this area, the overwhelming body of available literature has hindered our attempts to be exhaustive.

Extracellular Factors Affecting Proliferation

Basic Fibroblast Growth Factor (bFGF)

The Fibroblast Growth Factor (FGF) family includes a large number of ligands and receptors initiating signaling cascades that are critical for the early development of the organism (Burke *et al.*, 1998; Klint and Claesson-Welsh, 1999; Reuss and von Bohlen und Halbach, 2003). Of the different members of the FGF family of ligands, for instance, FGF8 is primarily involved in patterning of the midbrain and anterior forebrain (Mason *et al.*, 2000), FGF3 is important for the development of the ear (Represa *et al.*, 1991) and FGF2 is important for proliferation of neural stem cells and neurogenesis both in vitro (Reynolds and Weiss, 1992; Vescovi *et al.*, 1993; Vaccarino *et al.*, 1995; Kuhn *et al.*, 1997) and in vivo (Craig *et al.*, 1996; Tao *et al.*, 1996; Kuhn

et al., 1997; Wagner *et al*., 1999). FGF2 (or bFGF) is expressed in the rodent brain at mid-gestation, from E11.5 to E17.5 in mice and from E13.5 to E19.5 in rats (Vaccarino *et al*., 1999b; Raballo *et al*., 2000), during a period coincident with active neurogenesis (Bayer and Altman, 1991; Caviness *et al*., 1995). Targeted deletion of *Fgf2* in mice results in a 50% reduction in the number of cortical neurons (Vaccarino *et al*., 1999b), thus suggesting a critical role for this ligand in neurogenesis.

The expression of the bFGF receptor, FGFR1 in the ventricular zone (Fig. 2.2), is observed at E8.5-9.5 (Orr-Urtreger *et al*., 1991; Wanaka *et al*., 1991) and it progressively decreases as neuroblasts begin to exit from the cell cycle and start differentiating (Raballo *et al*., 2000). The phenotypic analysis of mutant mice with targeted deletions in the *FgfR1* or *FgfR2* receptors supports the idea that FGF signaling mediated by these two receptors, but not by FGFR3 and FGFR4, is critical for regulating proliferation and development of telencephalic structures (Yamaguchi *et al*., 1994; Deng *et al*., 1997; Partanen *et al*., 1998; Xu *et al*., 1998; Tropepe *et al*., 1999).

The role of FGF receptor signaling in proliferation of neural progenitors and stem cells is also supported by a separate line of investigation on the effect of FGF2 administration at distinct developmental stages (Qian *et al*., 1997; Kelly *et al*., 2003). High doses of FGF2 intracerebrally injected during embryogenesis (E14 in mice), result in massive enlargement of the ventricles and aberrant proliferation and differentiation (Ohmiya *et al*., 2001). However, low doses of recombinant FGF2 in rat embryos (Vaccarino *et al*., 1999a) or even in neonatal and adult rats (Tao *et al*., 1996; Wagner *et al*., 1999) enhance proliferation and neurogenesis.

Epidermal Growth Factor (EGF) Family

The epidermal growth factor (EGF) family of polypeptides includes EGF, transforming growth factor-alpha (TGF-alpha), heparin-binding EGF (HB-EGF) and related neuregulins. These polypeptides, produced by neurons and glial cells, play an important role in the development of the nervous system, by affecting proliferation, survival, migration and differentiation of neuronal and glial cells (Xian and Zhou, 1999). Neuregulins have been identified during the late embryonic development (Corfas *et al*., 1995), and their receptors ErbB2 and ErbB4 are expressed in the E12 embryo (Kornblum *et al*., 2000) as well as in embryonically derived neural stem cells (Calaora *et al*., 2001). Although neuregulin signaling especially via the ErbB4 receptor is critical for migration of adult neuroblasts and possibly survival and neurogenesis (Calaora *et al*., 2001; Anton *et al*., 2004), the available experimental evidence does not support a role of this EGF family member in proliferation. TGF alpha, in contrast, is a potent mitogen and also the predominant form of EGF ligand expressed in the developing brain and in adult SVZ (Kornblum *et al*., 1997). The importance of this ligand

in regulating proliferation of adult neural stem cells is supported by the phenotypic characterization of the TGF alpha null mice characterized by decreased number of mitosis exacerbated by senescence (Tropepe *et al*., 1997).

Expression of EGFR in vivo occurs during late embryogenesis (Fig. 2.2) in the developing SVZ and follows the expression of FGFR1 in ventricular zone cells (Burrows *et al*., 1997). Consistent with this temporal progression, cells isolated from embryonic mouse brain during early development (i.e. E10-E12) are FGFR1+, while those isolated at later developmental stages are both EGFR+ and FGFR1+ (Ciccolini and Svendsen 1998; Gritti *et al*., 1999; Lillien and Raphael 2000). This expression pattern is also consistent with the distinct growth factor requirements of early embryonic stem cells for FGF2 and of the late embryonic stem cells for EGF and FGF2 (Tropepe *et al*., 1999; Martens *et al*., 2000).

The concept of temporal responsiveness to distinct growth factors determined by the sequential expression pattern of distinct receptor subunits is also supported by a comparative phenotypic analysis of the *EgfR* and *FgfR* null mice. While the *FgfR1* null mice are early embryonic lethal (Deng *et al*., 1994; Yamaguchi *et al*., 1994), the phenotype of the *EgfR* null mice is characterized by reduced cortical size at E18 (Threadgill *et al*., 1995), and progressive neuronal degeneration during the postnatal period (Sibilia and Wagner, 1995; Sibilia *et al*., 1998).

Despite the similar role as mitogens, FGF2 and EGF have been differentially implicated as modulators of lineage restriction and neurogenesis. It has been proposed that the differential role played by these factors depends on the segregation of the mitogenic effect on distinct cellular populations: EGF preferentially targeting the quiescent stem cells and FGF targeting the more committed neuroblasts (Morshead and van der Kooy, 1992; Morshead *et al*., 1994). The co-expression of FGFR1 and EGFR within the same cell type at later stages of development, however, argues against this possibility (Gritti *et al*., 1999). An alternative explanation for the differential effect exerted by these two growth factors is the possibility that through the activation of distinct tyrosine kinase receptors, they may affect distinct intracellular signaling effectors, or the kinetics of activation of specific signaling molecules (Lax *et al*., 2002; Yamada *et al*., 2004).

The idea that FGF2 and EGF may differentially affect the behavior of multipotent neural progenitors is also based on the evidence that two weeks of intraventricular administration of EGF to adult mice result in decreased neurogenesis and increased generation of astrocytes, while administration of FGF2 results in enhanced generation of neurons (Kuhn *et al*., 1997). Similar data have been obtained by several other groups with the exception of a study, reporting similar effects of FGF2 or EGF treatment on adult neurogenesis (Craig *et al*., 1996). The in vivo ultrastructural identification of adult SVZ cells affected by EGF intraventricular infusion, for instance, clearly

demonstrated the ability of EGF to affect the modality of cell division of the transit amplifying C cell population from asymmetric to symmetric, and to restrict neuroblast formation (Doetsch *et al*., 2002a). Similarly, intrastriatal infusion of TGF alpha in an animal model of Parkinson's disease (Cooper and Isacson, 2004) induces the formation of clusters of $GFAP^{-}/nestin^{+}$ cells along the lateral wall of the ventricle, very likely representing an expansion of the transit amplifying C cells (Cooper and Isacson, 2004). Finally, in vitro studies in cultured neurospheres show increased astrocyte generation in response to EGF and enhanced neuronal differentiation in response to FGF2 (Whittemore *et al*., 1999; Jori *et al*., 2003). Together, these data identify EGF signaling as permissive for astrocytic but not neuronal differentiation and FGF signaling as permissive for the neurogenic fate in the adult SVZ.

Insulin-Like Growth Factor-1 (IGF1)

Insulin growth factor peptides 1 and 2 are members of a family of insulin-related peptides originally identified by their ability to stimulate growth of chondrocytes (Laron, 2001). IGF1 is secreted by many tissues and its function varies according to the site of secretion and the presence of its receptors. The expression of its receptors is highly conserved throughout evolution (Garofalo and Rosen, 1988). IGF1R, in particular, is expressed in the embryonic brain and co-localizes with the expression of FGFR and EGFR in cells of selective germinal zones (Bondy *et al*., 1990; Garcia-Segura *et al*., 1991; Kar *et al*., 1993). The phenotype of mice with targeted deletion in the *Igf1* gene or in the *Igf1R* gene is severely hypomorphic, with a clear decrease in brain size (Baker *et al*., 1993; Liu *et al*., 1993; Beck *et al*., 1995), thus suggesting IGF1R function as critical for brain development. Conversely, transgenic mice over-expressing IGF1 show a generalized increase in cell number and corresponding increase in brain size (Carson *et al*., 1993). The role of IGF1 in neurogenesis is still controversial. While in vitro studies on embryonic and adult stem cells suggest a role in neuronal differentiation of EGF-responsive stem cells (Arsenijevic and Weiss 1998; Arsenijevic *et al*., 2001), other reports underline its role as survival factor for FGF responsive stem cells (Drago *et al*., 1991) and studies on freshly isolated PSA-NCAM+ cells describe IGF1 as both survival and mitogenic factor for EGF responsive cells (Gage *et al*., 2003). Its function in oligodendrocytes and myelination is better characterized. In addition, it has been recently suggested that IGF1 also favors the commitment of adult neural stem cells towards the oligodendrocytic phenotype (Hsieh *et al*., 2004). More studies on the in vivo function of IGF1 will be necessary to decipher the multiple roles played by this factor in the adult SVZ.

Neurotrophins

The neurotrophin family is composed of several trophic factors including the originally discovered founding member nerve growth factor (NGF) (reviewed in Aloe, 2004), and the related brain-derived neurotrophic factor (BDNF), neurotrophin-3, -4 and -5 (NT-3, NT-4, NT-5) (Leibrock *et al*., 1989; Hohn *et al*., 1990; Maisonpierre *et al*., 1990; Berkemeier *et al*., 1991; Hallbook *et al*., 1991). Neurotrophin bind to two classes of receptors: tyrosine kinase receptors (Trk A, B and C) and a low affinity neurotrophin receptor called p75 that is structurally related to the TNFR superfamily (Barker, 2004). Each ligand binds with the highest affinity to a specific tyrosine kinase receptor (i.e. TrkA and NGF, TrkB and BDNF, TrkC and NT-3), while all the neurotrophins can bind to the low-affinity p75 (Chao, 2003). The complexity of the system is enhanced by the presence of alternatively spliced isoforms for TrkB and TrkC that may differ in case of the presence of specific catalytic domains (Huang and Reichardt, 2003; Teng and Hempstead, 2004).

In the adult SVZ p75 immunoreactivity is confined to proliferating cells. The majority of the $p75^+$ cells are identified also by EGFR immunoreactivity. Few $p75^+$ cells in the SVZ are also $nestin^+$, but the majority of them does not colabel with GFAP or PSA-NCAM (Giuliani *et al*., 2004), thus suggesting that p75 is mainly expressed in the fast-proliferating cell population. Interestingly, no TrkA receptor expression is detected in the periventricular region by in situ hybridization (Anderson *et al*., 1995) or immunohistochemistry (Giuliani *et al*., 2004; Fiore *et al*., 2005), while the full-length and truncated form of TrkB receptors are both present. Truncated TrkB is confined to the ependymal cell layer and to choroid plexus, while full length TrkB expression is more widespread (Anderson *et al*., 1995). Therefore, it is not surprising that BDNF is the primary neurotrophin-affecting neurogenesis in the adult SVZ (Kirschenbaum and Goldman, 1995). In vivo infusion of BDNF in the lateral ventricle of the rat adult brain enhances BrdU incorporation in the SVZ and is associated with an increased number of neurons migrating to the olfactory bulb (Zigova *et al*., 1998). Since the $BrdU^+$ cells are also $p75^+$ and $TrkB^-$ (Pencea *et al*., 2001), it is thought that the proliferative effect of BDNF is mediated by signaling through the low affinity p75 receptor in the fast proliferating cell population. The effect of BDNF on adult neurogenesis (i.e. the generation of neurons from the multipotential stem cells), in contrast, is a TrkB-dependent event, and is likely directed on $PSA\text{-}NCAM^+$ neuroblasts. In agreement with this model, treatment of embryonic and adult-derived neurospheres with neurotrophins affects differentiation, but not proliferation of $TrkB^+$ cells (Ahmed *et al*., 1995; Benoit *et al*., 2001). BDNF also acts as permissive factor for the maturation and survival of neuroblasts generated from the SVZ (Kirschenbaum and Goldman 1995). A recent study on the effect of BDNF on GABAergic interneurons derived from the SVZ has shown that the sequential activation of p75 and then TrkB signaling pathways is critical for the

development of the dendritic arbor (Gascon *et al*., 2005). Together, these studies support a p75-mediated effect in cell proliferation and a TrkB-mediated effect in neurogenesis of adult neural stem cells.

Ephrins

Ephrins are cell-surface-tethered ligands for Eph receptors, a family of tyrosine kinase receptors. The functional complex ephrin/Eph is involved in several processes, including the formation and guidance of growth cones from differentiating neurons and the induction and maturation of neuronal spines (Palmer and Klein, 2003). There are two subclasses of ephrin ligands: type A (ephrinA) are GPI-linked membrane proteins while type B (ephrinB) are transmembrane proteins (Orioli and Klein, 1997; O'Leary and Wilkinson, 1999). The ephrin family of receptors (Eph) can also be subdivided into class A (EphA) and B (EphB) on the basis of structural similarities in the extracellular domain and on their ability to preferentially bind to specific ligands. Type A ligands (ephrinA) bind to EphA receptors, and type B ligands (ephrinB) bind to EphB receptors, although the EphA4 receptor can bind to both types of ligands (Kullander and Klein, 2002) and ephrinA5 can also bind to the EphB2 receptor (Himanen *et al*., 2004; Pasquale, 2004). During development, this signaling system modulates attraction/repulsion, cell adhesion and cell migration (Klein, 2004). In addition, a possible direct or indirect role for ephrinB1 in neurogenesis is suggested by its expression in neuroepithelial cells in the VZ at the onset of neocortical neurogenesis and its persistence throughout the neurogenetic period (Stuckmann *et al*., 2001). It has been suggested that ephrinB1 plays a role in affecting the responsiveness of neuroepithelial cells to other cues and also to favor migration of newly generated neurons towards their targets.

In adult SVZ, both ephrin ligands (ephrin-B2,B3 and A5) and ephrin receptors (EphB1-B3, EphA4) are expressed in specific subpopulations of cells (Conover *et al*., 2000). Intraventricular infusion of ephrin B2 or of the EphB2 ectodomain dramatically disrupts neuroblast migration and increases proliferation in the SVZ, thus resulting in the formation of regions of localized hyperplasia (Conover *et al*., 2000).

Therefore, ephrins/Eph complexes act as environmental cues for migration processes, axonal pathfinding and topographic mapping during development, although they can also modulate proliferation and guided migration of neurons in the adult SVZ.

The Tgfbeta Family, Including Bone Morphogenetic Protein (BMP)

Transforming growth factor beta (TGFbeta) signaling controls several intracellular processes including proliferation, apoptosis, differentiation and

lineage specification. TFGbeta ligands bind to serine-threonin kinase receptors (type I and II) on the cell surface and the signal is mediated by a heterogeneous group of proteins called Smads (Shi and Massague, 2003).

The TGFbeta family of cytokines comprises two subfamilies, TGFbeta/Activin/Nodal subfamily and BMP (Bone Morphogenetic Protein)/GDF (Growth and Differentiation Factor)/MIS (Muellerian Inhibiting Substance) subfamily. TGFbeta cytokines are expressed in the CNS of the developing rodent (Flanders *et al*., 1991; Millan *et al*., 1991; Schmid *et al*., 1991) in regions where neuronal differentiation occurs. In fact, TGFbeta2 in vitro induces cell cycle exit and differentiation of precursor cells (Mahanthappa and Schwarting, 1993; Constam *et al*., 1994; Kane *et al*., 1996). The BMP family includes a group of dorsal morphogens whose effect is pleiotropic and ranges from the induction of a dorsal fate in cells of the developing neural tube (Shah *et al*., 1996; Liem *et al*., 1997; Panchision *et al*., 2001), to the suppression of differentiation and maintainance of self-renewal in embryonic stem cells (Ying *et al*., 2003), from the down-regulation of EGFR expression in embryonic progenitors (Lillien and Raphael, 2000), to the induction of apoptosis (Graham *et al*., 1996). In addition, BMP signaling has been implicated in neurogenesis (Liem *et al*., 1995; Reissmann *et al*., 1996; Li *et al*., 1998; Panchision and McKay, 2002) as well as in gliogenesis (Gross *et al*., 1996), and also to favor the commitment to the astrocytic lineage at the expenses of neurogenesis and oligodendrogliogenesis (Grinspan *et al*., 2000; See *et al*., 2004). The effect of BMPs on astrogliogenesis is dependent on cross-talks among distinct signaling pathways and involves the activation of critical signaling molecules, including SMADs and STATs (Nakashima *et al*., 1999a). Since SMADs are downstream of BMP signaling and STATs are downstream of LIF signaling, it is the interaction between these two signaling pathways that appears to be critical for astrogliogenesis. Intriguingly, however, an alternative pathway of activation of STATs by BMP receptor signaling (Rajan *et al*., 2003) has been suggested. According to this model, STAT activation is mediated by a serine-threonine kinase (called FRAP) that becomes activated upon binding of BMP4 to its receptor (Rajan *et al*., 2003).

Besides their role in development, BMPs favor astrogliogenesis also in the adult animal (Lim *et al*., 2000; Panchision *et al*., 2001). Indeed, BMP2 and 4 and cognate receptors are expressed in the adult SVZ where they favor the astrocytic phenotype of adult neural stem cells (Lim *et al*., 2000) and possibly modulate the cell cycle length of migrating neuroblasts (Coskun and Luskin, 2001). Noggin, a BMP antagonist expressed by the ependymal cells, promotes neurogenesis by counteracting the effect of the BMPs on astrogliogenesis (Lim *et al*., 2000).

Thus, the activation of the TGFbeta signaling modulates both the decision of a cell to exit from the cell cycle and the commitment to an astrocityc fate.

Ciliary Neurotrophic Factor (CNTF) and Leukemia Inhibitory Factor (LIF)

Ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF) are two neuroregulatory cytokines which play a major role in the developing nervous system. They both exhibit broad structural similarities (Bazan, 1991) and share signaling components (Gearing *et al*., 1991, 1992; Gearing and Bruce, 1992; Ip *et al*., 1992, 1993) among each other and with other members of the family, including interleukin-6, oncostatin or cardiotrophin 1. CNTF is widely expressed within the nervous system (Ip *et al*., 1993; Ip and Yancopoulos, 1996; Ip, 1998) and has been implicated in fate choice decision and survival of sensory, sympathetic, ciliary and motor neurons (Sleeman *et al*., 2000; Turnley and Bartlett 2000).

LIF and CNTF share a common receptor, gp130 (Davis *et al*., 1993; Ip and Yancopoulos, 1996; Nandurkar *et al*., 1996). Specificity of the signaling response is achieved by selective binding of the ligand with specific receptor components. LIF signaling requires dimerization of the LIF receptor subunit beta (LIFRbeta) with gp130; while CNTF requires trimerization of its cognate receptor subunit (CNTFRalpha) with LIFRbeta and gp130 (Fig. 2.2). CNTFRalpha is expressed in embryonic neural precursor cells (Ip *et al*., 1993; Lachyankar *et al*., 1997) and in neurons and astrocytes of the adult central nervous system (Ip *et al*., 1993; MacLennan *et al*., 1996; Lee *et al*., 1997a,b; Kirsch *et al*., 1998; Dallner *et al*., 2002), including the subventricular zone (Seniuk-Tatton *et al*., 1995).

In vitro studies on embryonic stem cells suggest a role for CNTF/LIF signaling in maintaining pluripotency (Conover *et al*., 1993) and preventing differentiation (Pennica *et al*., 1995) or even promoting survival (De Felici and Dolci, 1991; Pesce *et al*., 1993). The phenotype of the *CNTF* null mice, however is relatively normal and exhibits motor neuron losses only later in life, thus arguing against a major role played by this cytokine during development (Masu *et al*., 1993). The phenotypes of the *CNTFR* −/− (DeChiara *et al*., 1995), of the *LIFR* −/− (Li *et al*., 1995) or the *gp130* −/− (Nakashima *et al*., 1999a) mice, in contrast, are characterized by a profound motor neuron defect at birth, thus supporting the notion that CNTF is critical for survival and viability of motor neurons (Sendtner *et al*., 1994; Ip 1998). The neuroprotective effect of CNTF is also observed in vivo, as demonstrated by the intracerebral administration of this cytokine in animal models of Huntington's disease (Anderson *et al*., 1996; Emerich *et al*., 1996) and in injured dopaminergic neurons after transection of the nigrostriatal pathway (Hagg and Varon, 1993).

The detection of CNTF receptors during embryonic development and in adult neural germinal zones raises the possibility that CNTF/LIF family members play a role in regulating proliferation and fate choice of neural stem cells. Treatment of neural embryonic progenitors and stem cells with these cytokines suggests a critical role in astroglial differentiation (Bonni *et al*., 1997;

Rajan and McKay 1998; Park *et al*., 1999; Galli *et al*., 2000; Morrow *et al*., 2001). Signaling through STAT3, a transcription factor downstream of the LIF/gp130 receptor signaling pathway is critical for the expression of GFAP (Bonni *et al*., 1997) a fact also supported by the severly perturbed astrogliogenesis in *LIFR* −/− mice (Koblar *et al*., 1998). The role of STAT in astrocytic differentiation has been the subject of several studies. It has been shown that GFAP promoter activation requires the assembly of a complex including SMADs, STATs, the co-activator CBP and the histone acetyl-transferase p300 (Nakashima *et al*., 1999b). Over-expression of neurogenin, a neuronal-specific basic HLH factor, disrupts this "gliogenic" complex by sequestration of the CBP/p300 component from STATs and thus prevents GFAP promoter activation (Sun *et al*., 2001). The presence of histone acetyl transferase p300 in the transcriptional complex suggests that activation of the astrocytic program of differentiation necessitates changes in chromatin conformation. Besides acetylation of nucleosomal histones, the GFAP promoter is also regulated by a switch in the methylation of specific lysine residues on nucleosomal histones (Song and Ghosh, 2004). The "switch" from a silencing methylation on lysine 9 to an activating methylation on lysine 4 of histone H3 is affected by the presence of FGF2 and results in an open chromatin conformation in the promoter region, thus facilitating binding of transcriptional activators such as STATs and SMADs (Song and Ghosh 2004). CNTF signaling has also been implicated in oligodendrocytic maturation (Barres *et al*., 1996; Marmur *et al*., 1998) and neuronal differentiation (Ernsberger *et al*., 1989; Saadat *et al*., 1989; Ip *et al*., 1994; Rudge *et al*., 1996; Ezzeddine *et al*., 1997; Lachyankar *et al*., 1997). In the adult forebrain, signaling through the CNTFR/LIFR/gp130 complex is responsible for the maintenance of EGF-responsive neural stem cells (Fig. 2.3). CNTF treatment of SVZ-derived cells in vitro, increases self-renewal and expansion (Shimazaki *et al*., 2001) and in vivo, it enhances proliferation of the EGF-responsive population (Shimazaki *et al*., 2001; Chojnacki *et al*., 2003). The effect of CNTF/LIF signaling on proliferation and self-renewal can be explained in terms of receptor cross-talks. Proliferation could be consequent to the effect of CNTF on Notch1 signaling (Chojnacki *et al*., 2003), while self-renewal could be due to the effect of LIF on differentiation inhibitors, such as the Ids, downstream of BMP receptor signaling (Ying *et al*., 2003).

Notch1

Notch is a cell-surface receptor activated by contact with a member of the DSL family of ligands (Delta, Serrate, Lag2). Upon ligand activation, the Notch receptor is cleaved and its intracellular domain (Notch ICD) is released into the cytosol, translocates into the nucleus where it activates the transcription of CSL/CBF and induces the expression of HES genes that have been described as basic HLH transcription factors with the ability to

inhibit neuronal differentiation (Lindsell *et al*., 1996; Weinmaster, 2000). Therefore, Notch signaling during development has been linked to inhibition of differentiation (Artavanis-Tsakonas *et al*., 1995). Although the role of Notch in timing of cell fate specification and differentiation is supported by several studies (Yun *et al*., 2002), the persistence of Notch1 and Jagged 1 expression in the adult SVZ (Stump *et al*. 2002) suggests that these molecules may also modulate the behavior of pluripotential progenitors and adult stem cells. The depletion of neural stem cells in the *Notch1−/−* mice (Hitoshi *et al*., 2002) indicates a role for Notch in promoting self-renewal at the expenses of neurogenesis. However, transient Notch activation induced by administration of Notch ligand results in severe decrease of the neurogenic potential paralleled by increased gliogenesis (Morrison *et al*., 2000b). These apparently contradictory results can be reconciled by evoking the importance of spatial and temporal cues on the responsiveness of progenitor cells to Notch signaling. Indeed, expression of active Notch at midgestation inhibits proliferation and decreases the generation of neurons (Chambers *et al*., 2001). At later stages, however, Notch ICD promotes proliferation and gliogenesis (Gaiano *et al*., 2000; Chambers *et al*., 2001). Thus, similar to what was described for BMP and CNTF, the same signal can result in maintenance of stem-like cells or gliogenesis, depending on the cellular context.

Sonic Hedgehog

Sonic hedgehog (Shh), is a very well characterized morphogen expressed at high levels in cells of the ventral telencephalon at embryonic day 11.5 (E11.5) and maintained throughout development (Dahmane and Ruiz-i-Altaba 1999; Wallace 1999; Wechsler-Reya and Scott 1999). Shh has been implicated in several aspects of CNS development such as proliferation (Marti *et al*., 1995; Roelink *et al*., 1995; Chiang *et al*., 1996; Ericson *et al*., 1996) and cell fate determination (Zhu *et al*., 1999). It has alo been shown to exert opposing actions to BMP2 in embryonic cortical progenitors (Machold *et al*., 2003, Viti *et al*., 2003b). Mice, bearing conditional null alleles of both *Shh* and its receptor *Smoothened*, have a dramatic reduction in the number of neural progenitors in the SVZ, possibly resulting from reduced proliferation and increased apoptosis (Machold *et al*., 2003).

Recent studies on the adult SVZ in postnatal and adult mice have identified the Shh responsive SVZ cells as the $GFAP^{+}$ B cells and the EGF responsive transit amplifying progenitors C cells (Palma *et al*., 2005). The in vitro data in SVZ cultures treated with Shh do not support a direct effect of this molecule on proliferation, although they do suggest a synergistic effect with EGF (Palma *et al*., 2005). Similarly, the increased number of neurospheres formed by embryonic stem cells pre-treated with Shh and cultured in the presence of EGF has been ascribed to the up-regulation of EGFR level (Viti *et al*., 2003b). The lack of proliferation or differentiation in the adult SVZ after intrastriatal injection of a myristoylated form of Shh

(Charytoniuk *et al*., 2002) is consistent with the in vitro data. However, the decreased proliferation observed in the SVZ after administration of the Shh antagonist cyclopamine suggests a more complex role for this molecule (Palma *et al*., 2005). Although the role of Shh in survival of SVZ cells has not been addressed, it is likely to play a role in modulating the responsiveness of neural stem cells to other signaling molecules regulating cell number (Fig. 2.3).

Wnt

The behavior of cells in the developing nervous system is tightly regulated by the highly conserved family of Wnt signaling molecules. Wnt proteins can either be secreted or located at the cell surface and may interact with a family of cell surface receptors in the Frizzled family (Ikeya *et al*., 1997; Yoshikawa *et al*., 1997; Hall *et al*., 2000). Binding of the ligand to the

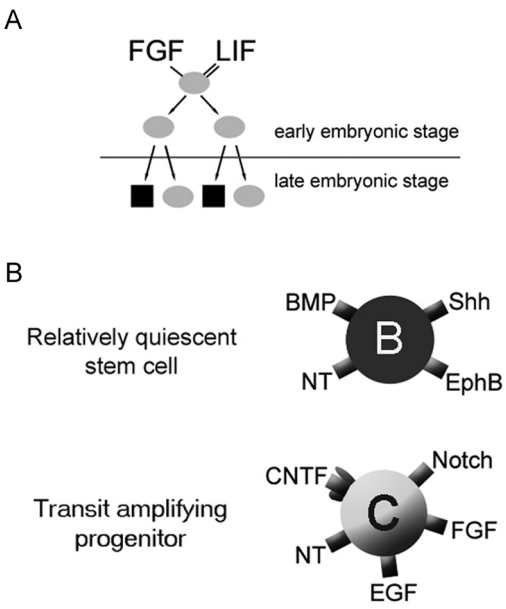

FIGURE 2.2. **Extracellular Receptors in embryonic and adult neural stem cells.** Schematic representation of the major subtypes of extracellular receptors observed during embryonic development (panel A) and in the adult SVZ (panel B). Note that during early embryonic development (upper cell in panel A), only FGF and LIF receptors are expressed, but at later stages cells become also responsive to BMPs, Shh and EGF (lower cell in panel A). In the adult SVZ (panel B), a differential pattern of receptor expression is observed. The relatively quiescent B cells are responsive to BMPs, Shh and neurotrophins ephrins, while the transit amplifying progenitors express the receptors for EGF, FGF, CNTF, and Notch (B).

receptor transduces a signal which involves inactivation of the GSK-3 kinase and the accumulation of the transcriptional regulator beta catenin. Of the several Wnt family members, analysis of the phenotype of mice with targeted deletions in specific genes has revealed the critical importance of Wnt1, Wnt3a and Wnt7a in the developing nervous system (Megason and McMahon, 2002). Cell proliferation is commonly regulated by Wnt signaling and expansion of the CNS fails in *Wnt1* mutants (reviewed in Logan and Nusse, 2004) Over-expression of Wnt7a in embryonic stem cells increases proliferation and self-renewal both in vivo and in vitro and further promotes maturation of cortical progenitors by inducing the expression of EGFR (Viti *et al*., 2003b).

Recently, the role of Wnt and its downstream-signaling molecule beta catenin has been explored in neural stem cells. Transgenic mice over-expressing beta catenin have grossly enlarged brains that could not be simply explained in terms of mitogenic effect or decreased apoptosis (Chenn and Walsh, 2002). Rather, it appears that beta catenin affects the decision of progenitors to exit from the cell cycle and this, in turn, results in loss of growth control (Chenn and Walsh, 2002; Zechner *et al*., 2003). However, in other cellular systems such as embryonic stem cells, beta catenin favors neurogenesis (Otero *et al*., 2004). This cell context role of β catenin has been linked to the presence of FGF2 (Israsena *et al*., 2004). In the presence of FGF2, beta catenin contributes to the maintenance of a proliferative state (Viti *et al*., 2003), while in the absence of FGF2, it enhances neuronal differentiation by forming transcriptionally active complexes on neurogenic promoters (Israsena *et al*., 2004; Otero *et al*., 2004; Logan and Nusse, 2004). A better understanding of the role of Wnt pathway in neural stem cell biology will be a very important and critical step for the design of stem cell-based therapies.

Hypoxia-Induced Growth Factors

Ischemia and cerebral injury stimulate neurogenesis in neuroproliferative regions of the adult brain, including SVZ and the hippocampal DG (Gould and Tanapat, 1997; Parent *et al*., 1997; Liu *et al*., 1998; Takagi *et al*., 1999; Gu *et al*., 2000; Magavi *et al*., 2000; Jin *et al*., 2001; Yoshimura *et al*., 2001; Zhang *et al*., 2001). Concomitantly to ischemic injuries, expression of some factors increases (Kawahara *et al*., 1999; Marti, 2004):

(a) Erythropoietin EPO

Erythropoietin (EPO) is a pleiotropic-inducible molecule produced by the kidney and whose function was first described as the regulator of red blood cell production (Carnot and Deflandre, 1906) by promoting erythrocyte survival in the bone marrow (Koury and Bondurant, 1990a; 1990b; Youssoufian *et al*., 1993; Fisher, 2003). EPO is also a key example of a gene that is regulated in an oxygen-dependent manner and, thus, its expression is

induced when the oxygen levels are reduced (Wenger, 2002). Recently, EPO and its receptor EPOR have also been detected in the developing CNS, thus suggesting a possible role in neural development (Buemi *et al*., 2002; Liu *et al*., 1994; Juul *et al*., 1998,1999). Indeed, mice with an *Epor* targeted deletion ($Epor^{-/-}$) (Lin *et al*., 1996), are characterized by the severe reduction in the number of neural progenitor cells and increased apoptosis (Yu *et al*., 2002).

The observation that embryonic precursors in the CNS proliferate and differentiate more in response to lowered oxygen (Morrison *et al*., 2000a; Studer *et al*., 2000) suggests that perhaps they could play a similar role in adult neural stem cells. In vitro studies on cultured neural stem cells are consistent with the idea that increased EPO gene expression results in increased adult neurogenesis (Shingo *et al*., 2001). Furthermore, intraventricular infusion of EPO in mice favors the migration of newly generated neurons to the olfactory bulb and the effect is blocked by anti-EPO antibodies (Shingo *et al*., 2001). Together these data suggest that EPO can negatively regulate proliferation of stem cells while favoring the differentiation towards the neuronal lineage.

(b) Vascular Endothelial Growth Factor VEGF

The vascular endothelial growth factor (VEGF) is a hypoxia-inducible secreted protein (Wenger, 2002) that regulates endothelial cell growth and differentiation and is also a survival factor for endothelial cells (Risau, 1997). The loss of a single allele in the mouse results in death during embryogenesis, due to vascular defects (Ferrara *et al*., 1996). In the nervous system, VEGF is expressed during development (Breier *et al*., 1992), and is related to the EPO-induced response to hypoxic insults in the brain as a target for the hypoxia inducible transcription factor (HIF-1) (Marti, 2004). VEGF has neurotrophic and neuroprotective effects on distinct types of neurons (Silverman *et al*., 1999; Sondell *et al*., 1999, 2000; Jin *et al*., 2000a, 2000b; ; Matsuzaki *et al*., 2001) and its receptor VEGFR2/flk-1 is expressed in neural progenitor cells (Yang and Cepko, 1996; Jin *et al*., 2002b), thus suggesting a possible role in neurogenesis. In the adult murine brain, administration of exogenous VEGF increases proliferation (Fig. 2.3) of neuronal precursors in the SVZ by modulating cell division rather than survival (Jin *et al*., 2002b). Finally, in cultures from the neonatal SVZ, treatment with FGF2 increases the expression of VEGFR2/flk-1, and in turn, treatment with VEGF enhances the chemotactic response of FGF2-stimulated progenitors, thus suggesting a synergistic effect of these two factors on migration (Zhang *et al*., 2003).

(c) Heparin-Binding HB-EGF

Heparin-binding EGF-like growth factor (HB-EGF) is a mitogenic and chemotactic glycoprotein that contains an EGF-like domain and acts

through several receptors, including ErbB1, ErbB4, and heparin sulfate proteoglycans. Although the targeted deletion of *HB-EGF* in mice affects mainly heart and skin development (Yamazaki *et al*., 2003), the expression in neurons and glial cells throughout the brain suggests a role in the CNS (Mishima *et al*., 1996; Hayase *et al*., 1998; Nakagawa *et al*., 1998). As for EPO and VEGF, the expression of HB-EGF in the brain is increased by ischemia and results in neuroprotection (Kawahara *et al*., 1999). In addition, HB-EGF enhances neurogenesis in vitro, in neonatal cerebellar cultures (Opanashuk and Hauser 1998) and embryonic mouse neurons exposed to hypoxic conditions (Jin *et al,*. 2002a). In vivo, intraventricular infusion HB-EGF enhances neurogenesis in the adult SVZ (Jin *et al*., 2002a) and restores neurogenesis to young adult levels when administered to aged mice in combination with FGF2 (Jin *et al*., 2003).

Extracellular Matrix and Cell–Cell Contact

It has been proposed that the maintenance of neural stem cells in the adult brain is favored by the presence of extracellular conditions creating a ''niche'' that favors the preservation of an undifferentiated and proliferative state (Doetsch, 2003; Alvarez-Buyilla and Lim, 2004). The concept of a ''niche'' including components of the extracellular matrix, is quite attractive and has also been described in the hematopoietic system (Mercier *et al*., 2002). Remarkably, several components identified in the extracellular matrix of the SVZ (Gates *et al*., 1995) have been proven effective in modulating the responsiveness to mitogens (i.e. FGF2, EGF) or to morphogens (i.e. Shh, Wnt, BMPs). For instance, ECM molecules such as Tenascin C and chondroitin sulfate proteoglycans, present in the late embryonic SVZ and persist in the adult brain (Garcion *et al*., 2004), modulate the sensitivity to other extracellular signals at several developmental stages. This effect could be due to indirect binding to other matrix components or to direct interaction with specific cell surface receptors. In the tenascin null mice the responsiveness of embryonic stem cells to FGF2 is dramatically reduced, while the sensitivity to BMP4 is increased (Garcion *et al*., 2004). Given the previously discussed antagonistic role of BMP and FGF2 on EGFR expression (Lillien and Raphael, 2000), it is not surprising that tenascin loss of function results in decreased proliferation of SVZ cells and delayed EGFR expression.

Another component of the ECM, the glycosaminoglycan heparin sulfate, has also been shown to promote the action of FGF2 in embryonically derived cells (Chipperfield *et al*., 2003), although it inhibits the response to this same factor in cells derived from the adult brain (Leventhal *et al*., 1999; Shen *et al*., 2004). These data corroborate and support the idea that the extracellular matrix is a critical component of the niche and that it may affect stem cell behavior by modulating the responsiveness to other extracellular cues and possibly affecting intracellular signals.

Another essential component of the neural stem cell niche is the vascular compartment. In the developing CNS, the embryonic neural stem cells in the VZ have been shown to produce vascular endothelial growth factor (VEGF) which is known to contribute to the neovascularization of the area. A more direct evidence that endothelial cells enhance proliferation and neurogenesis of embryonic and adult neural stem cells is provided by co-culture experiments (Leventhal *et al*., 1999). Explants of adult SVZ cultured in the presence of endothelial cells express higher levels of the neurotrophin BDNF (Shen *et al*., 2004). Time-lapse video recording of dividing clones of neural stem cells, grown in the presence of endothelial cells, indicates that co-culture conditions tend to favor the symmetric modality of cell division (Shen *et al*., 2004). Therefore, proliferation of the neural stem cells seems to be affected by a wide range of molecular signals, including the production of soluble factors (i.e. VEGF, BDNF), the cross talk with the wnt/beta catenin signaling pathway and/or with the Notch signaling pathway (Temple, 2001, Shen *et al*., 2004).

Neurotransmitters

(a) Dopamine

Dopamine is a neurotransmitter produced by neurons in the substantia nigra, ventral tegmental area and preoptic area. It is involved in numerous brain processes and contributes to integration of cortical information underlying motor, limbic and cognitive aspects of behavior (Nieoullon, 2002).

Besides its function as neuromodulator, dopamine also plays a role in neurogenesis during development. The D1 and D2-receptors are expressed in the striatal VZ and have been shown to play opposing roles in favoring (D2) or inhibiting (D1) cell cycle progression in the lateral ganglionic eminence (Jung and Bennett, 1996). The effect of D1-receptor activation is dominant over the effect of the D2 receptor and results in an overall reduction of cells entering S-phase (Ohtani *et al*., 2003). The role of D3 receptor signaling is not well established, although it is expressed in the proliferative neuroepithelium and persists postnatally in the subventricular zone (Diaz *et al*., 1997). Administration, either in vivo or in vitro of D3-receptor agonists, increases the proliferative rate of neural stem cells and the number of cells expressing neuronal markers (Pilon *et al*., 1994; Coronas *et al*., 2004; Van Kampen *et al*., 2004). This effect is mediated by MAPK activation, a pathway also activated by BDNF to affect neurogenesis (Zigova *et al*., 1998; Pencea *et al*., 2001). Given the dual relationship between dopamine receptor activation and BDNF expression (Guillin *et al*., 2001, 2003; Kuppers and Beyer, 2001; Sokoloff *et al*., 2002;), it is likely that they synergize in promoting neurogenesis.

(b) Serotonin (5-HT)

Serotonin (5-HT) is produced by neurons of the raphe nucleus in the brain stem and modulates sensorimotor control, cognition and mood (Struder and

Weicker, 2001b, 2001a). In addition to modulating synaptic function in the adult brain, 5-HT also controls important functions in brain development such as neurite outgrowth, cell survival and synaptogenesis (Gaspar *et al*., 2003).

The role of serotonin in neurogenesis is suggested by studies on the class of antidepressants called ''Serotonin Selective Re-uptake Inhibitors (SSRI)''. Stress is known to inhibit neurogenesis by elevating the levels of gluco-corticoids (Moghaddam *et al*., 1994; Stein-Behrens *et al*., 1994). SSRI anti-depressants reverse the effect of stress and increase proliferation and differentiation of newly formed cells into neurons in the hippocampus (Malberg *et al*., 2000; Santarelli *et al*., 2003). Since serotonin receptors (5-HT1A and HT2C) are expressed in the SVZ, it is not surprising that systemic administration of various agonists increases proliferation of cells in this brain region (Banasr *et al*., 2004). Intriguingly, like for dopamine, the effects of serotonin on neurogenesis seem to be related to BDNF signaling, thus suggesting that the effect of the distinct classes of neurotransmitters is possibly linked to the presence of neurotrophins (Mattson *et al*., 2004).

(c) Opioids

Opioid peptides are known to act as neurotransmitters or neuromodulators in the adult nervous system. They act through three cognate receptors: μ, δ, κ (Dhawan *et al*., 1996) that are also expressed in the SVZ (Zagon and McLaughlin, 1986; Stiene-Martin *et al*., 2001). Blockade of opioid receptors enhances cell proliferation, while their activation induces an anti-proliferative effect (Hauser *et al*., 1996). Although this effect was originally attributed to a fourth opioid receptor ζ (Zagon *et al*., 1991), it is likely that the opioid effect on neurogenesis is a μ-mediated effect since the μ receptor is widely expressed postnatally in neuroproliferative regions (Stiene-Martin *et al*., 2001).

Hormones

(a) Thyroid Hormone

T3 constitutes the active ligand of the thyroid hormone (TH). The expression of TH receptors in the brain varies according to the cell type, region and age as it clearly shows a spatial-temporal patterning during development (Bradley *et al*., 1992) and adulthood (Puymirat *et al*., 1991). Besides the well-established role of TH in maturation of oligodendrocytes (Baas *et al*., 1997; Baumann and Pham-Dinh, 2001), the presence of its receptors in the adult brain also led to investigate a possible effect in neurogenesis. Indeed, hypothyroid rats showed increased proliferation in the SVZ and olfactory bulb, while hyperthyroid rats showed reduced proliferation and increased tendency to differentiate into oligodendrocytes (Fernandez *et al*., 2004). Co-administration of thyroid hormone with retinoic acid results in a net increase of proliferation in SVZ and enhanced neurogenesis (Giardino *et al*., 2000).

(b) Estrogens

The role of sex steroids in neurogenesis has been suggested by the existence of a gender bias in hippocampal-dependent tasks (Roof *et al*., 1993; Frye *et al*., 2000; Conrad *et al*., 2003). At the cellular level, these differences are correlated with the proliferative effects of estrogens in the hippocampus (Tanapat *et al*., 1999, 2005). Estrogens can bind to two types of receptors, called alpha and beta. Both receptors have been detected in several brain regions throughout development (Shughrue *et al*., 1990). Both receptors are also present in the ventricular wall of the embryonic neural tube as well as in the adult brain (Brannvall *et al*., 2002), but the functional role of estrogens at distinct stages of development is quite distinct. While estrogen treatment potentiates the mitogenic effect of EGF in embryonic neural stem cells, it antagonizes the EGF effect in adult neural stem cells, by upregulating the cell cycle inhibitor p21Cip/Waf1 (Brannvall *et al*., 2002).

(c) Prolactin

Prolactin is a hormone that increases during pregnancy and at postpartum, signaling lactation. Prolactin stimulates the production of neuronal progenitors in the SVZ (Bridges and Grattan, 2003; Shingo *et al*., 2003). The increased neurogenesis results in the formation of new neurons in the olfactory bulb (Shingo *et al*., 2003), and is possibly related to the enhanced olfactory capability of the mother.

Others

(a) Amyloid Precursor Protein and Amyloid Peptide

The amyloid precursor protein (APP) is a type I transmembrane protein with unknown physiological functions. Its soluble-secreted form (sAPP), present in normal brain tissue (Palmert *et al*., 1989), has biological activities resembling a growth factor and increases the in vitro proliferation of embryonic neural stem cells (Ohsawa *et al*., 1999). The soluble sAPP binds to $EGFR^+$ cells in the adult SVZ and in vitro, EGF induces the secretion of soluble APP (sAPP) by SVZ-derived cells. Intriguingly, sAPP infusions into the lateral ventricle enhances proliferation of the EGF-responsive progenitors and increases the cell number (Caille *et al*., 2004). In pathological conditions such as Alzheimer's disease, however, neurons are exposed to the amyloid beta-peptide (Abeta), a self-aggregating neurotoxic protein. This peptide, in contrast to sAPP, has been shown to impair neurogenesis in the SVZ of adult mice and in human cortical neural precursor cells (Fig. 2.3). Amyloid beta peptide treatment suppresses both proliferation and differentiation of neural progenitors and induces apoptosis, associated with a disruption of calcium regulation. The cumulative result of these effects is a severe depletion of neurons possibly contributing to the olfactory and cognitive deficits observed in Alzheimer's disease (Haughey *et al*., 2002).

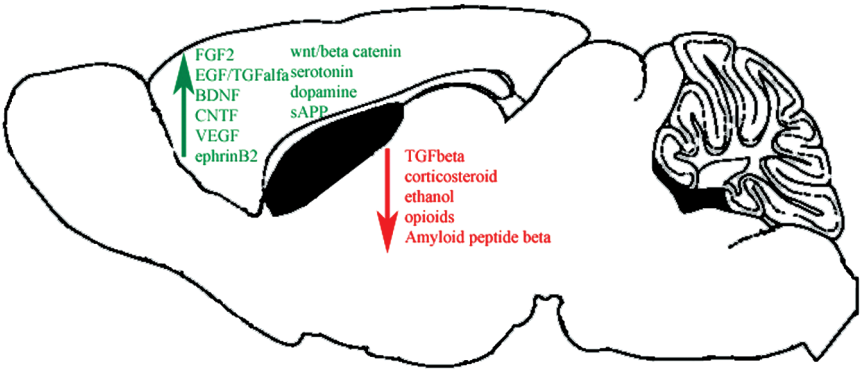

FIGURE 2.3. **Schematic view of a sagittal section of the adult brain.** In red are some of the extracellular signals that inhibit proliferation and favor the exit from the cell cycle. In green are the extracellular signals that promote proliferation and increase neurogenesis.

Intracellular Signals Affecting Proliferation

Although it is often assumed that experimental results obtained in stem cells isolated in the developing animal can be extrapolated to the behavior of stem cells in the mature CNS, a large number of studies support the concept of intrinsic differences in distinct neural stem cell populations, depending on their location and birthdate (Temple 2001). The existence of temporally regulated changes intrinsic to the cell is suggested by studies of in vitro time-lapse videos of isolated stem cells. These studies have shown that cells maintained in the same culture conditions can first give rise to neurons and then to glia (Qian *et al*., 1998, 2000).

These "intrinsic differences" may result from genetic differences and epigenetic modifications affecting the pattern of gene expression in a given cell population. Consistent with this interpretation, genetic profiling of embryonic and adult hematopoietic stem cells has identified a relatively small subset of commonly expressed genes and an even smaller number of genes shared with neural stem cells (Ivanova *et al*., 2002). Changes in gene expression may also result from differences in the extrinsic signaling pathways whose cross talk affects the length of the cell cycle (Tc) and/or the probability of progenitor cells to re-enter the cell cycle or become quiescent (Nowakowski *et al*., 2002). In this respect, it has been shown that cells in the embryonicVZ undergo a progressive increase in the length of Tc and that an increased proportion of these cells leaves the cell cycle with each cell division (Takahashi *et al*., 1996). Both these events are likely to be modulated by the expression levels of cell cycle regulatory molecules and other transcription

factors (Tarui *et al.*, 2005). Thus, progressive changes in the expression of cell cycle genes modify the cycle kinetics and the relative proportion of proliferating cells within each population, depending on the developmental stage and cellular context.

Studies on the cell cycle kinetics of progenitors/neural stem cells during embryonic development, for instance, have reported increased cell cycle length with increasing embryonic age (Fig. 2.4) and a switch of cell division from symmetric and rapid (Tc = ~17.6 hr) at E11, to asymmetric and slower (Tc = ~26.5) at E14 (Tropepe *et al.*, 1999). Differences in cell division persist in the adult forebrain subependyma (Fig. 2.4), and at least two distinct populations of proliferating cells have been identified (Morshead *et al.*, 1998). One population, the constitutively proliferating population, has a Tc of 12.7 hr (Morshead and van der Kooy, 1992) and corresponds to the transit amplifying progenitor population (Doetsch *et al.*, 2002a), also called the "C cell type" (Doetsch *et al.*, 1997). The other population has a much longer cell cycle duration (Tc~15 d or more) and corresponds to the quiescent cell population (Morshead *et al.*, 1994, 1998), of adult "stem cells" also called "B cell type" (Garcia-Verdugo *et al.*, 1998).

Lengthening of the cell cycle time is thought to be a function of an increase in the duration of G1 as the rest of the cell cycle parameters remain relatively

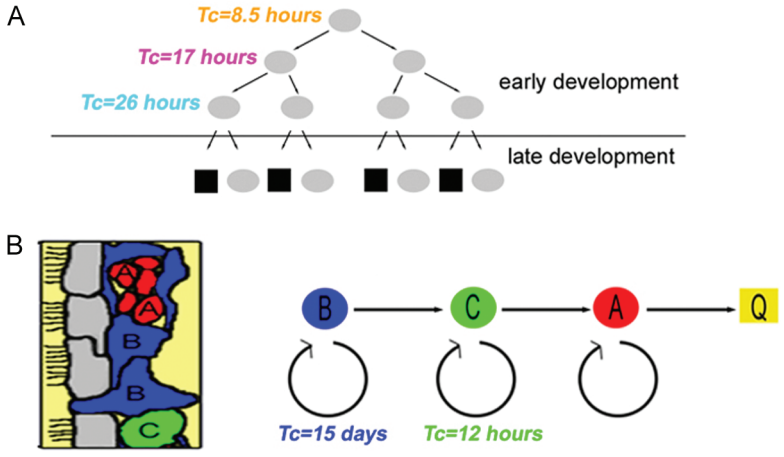

FIGURE 2.4. **Lengthening of the cell cycle duration in stem cells during development.** Note that during the early stages of development (A), the cell cycle duration (Tc) is very fast, possibly allowing for expansion. Around E11 the Tc is 17 hours and the modality of cell division primarily symmetric. As the organism develops and neurogenesis begins (E14) the cell cycle time increases to 26 hours and the modality of division becomes asymmetric. In the adult SVZ (B) two main cell types have been identified. The relatively quiescent B cells has a very long Tc (15 days) and has been proposed to be the precursor of the rapidly expanding population of C cells, characterized by a short cell cycle time (12 hrs) and the ability to give rise to neuroblasts and oligodendrocyte progenitors that become quiescent (Q).

constant over time (von Waechter and Jaensch, 1972; Caviness *et al*., 1995). Therefore, it is likely that the expression of cell cycle regulatory molecules in distinct cell populations accounts for differences in cell cycle kinetics. In agreement with this model, studies on cell cycle length in the neonatal rat brain (Schultze and Korr, 1981; Menezes *et al*., 1995; , 1998; Smith and Luskin, 1998) have indicated that differences in cell cycle kinetics between cells in the neonatal anterior SVZ (that have a fast cell cycle time) and the migratory cells in the RMS with a slower kinetics of cell division (Smith and Luskin, 1998), correlate with the levels of expression of the G1 inhibitor p19INK4d (Coskun and Luskin, 2001).

Indeed cell cycle length and the probability to exit from the cell cycle are both affected by cell cycle regulatory molecules and transcription factors whose expression can be modulated by genetic factors, epigeneticmodifications of chromatin and by the integration of extracellular signals.

Cell Cycle Regulatory Molecules

In order to discuss intracellular mechanisms of proliferation of CNS progenitors and neural stem cells, it becomes critical to introduce the molecules regulating the progression from G1 into the S phase of the cell cycle. Progression through G1 is regulated by the ordered synthesis, assembly and activation of distinct cyclin-CDK enzymatic complexes (Dyson, 1998; Nevins, 2001). Two main enzymatic activities have been described: CDK4, acting in early-mid G1; and CDK2, acting in late G1, very close to the entry into the S replicative phase (Sherr, 1994; Sherr and Roberts, 1999). These two activities differ in terms of substrate specificity and modality of regulation. CDK4, for instance, is positively regulated by cyclin D and is inhibited by members of the INK4 (**IN**hibitors of CD**K4**) family. CDK2, in contrast, is positively regulated by cyclin E and negatively regulated by the Kips (**K**inase **I**nhibitory **P**roteins). The main substrates of cyclinD/CDK4/6 complexes are proteins of the Rb family (including pRb, p107 and p130). INK4 proteins prevent their phosphorylation, thus allowing them to sequester E2F and blocking the transcription of E2F-responsive genes that are responsible for driving the cell into S-phase (Kastan *et al*., 1992). Besides the role of Rb as growth-inhibitory pathway, another important cell cycle checkpoint acting at the G1 phase is mediated by the p53 tumor-suppressor gene (Paggi *et al*., 1996; Mundle and Saberwal, 2003). We shall now review literature pertinent to the expression patterns of these cell cycle regulatory molecules in the central nervous system, with a special emphasis on their possible functional role in the SVZ.

(a) Rb Family

The Retinoblastoma gene family is composed of three members of closely related proteins characterized by a ‘‘pocket’’ domain pRb, p107

and p130/Rb2 (Brehm *et al*., 1998; Luo *et al*., 1998; Magnaghi-Jaulin *et al*., 1998). These molecules play a critical role in eukaryotic cell cycle progression as negative regulators of proliferation. The retinoblastoma gene product pRb, in its hypophosphorylated state, binds to members of the E2F family of transcription factors, converting them to active transcriptional repressors, by recruiting histone deacetylases (Dyson, 1998). Phosphorylated pRb in contrast, is unable to bind to E2F, the repression is relieved and results in the transcription of genes involved in DNA-replication (Fig.2.5) and nucleotide biosynthesis (Beijersbergen *et al*., 1994; Ginsberg *et al*., 1994). Distinct members of the Rb family show association with specific members of the E2F family and pRb preferentially binds to E2F-1, -2 and -3 while p107 and p130 preferentially bind to E2F-4 and -5 (Lees *et al*., 1992; Li *et al*., 1993). In addition, p107 and p130 can also bind to cyclin/CDK2 complexes (Gill *et al*., 1998; Callaghan *et al*., 1999; Ferguson and Slack, 2001).

The expression profile of the ''pocket proteins'' in the brain has a characteristic cellular and temporal pattern. While pRb is found in both dividing precursor cells and postmitotic neurons during embryogenesis, p107 expression is restricted to the ventricular zone and is rapidly down-regulated at the onset of differentiation (Jiang *et al*., 1997; Yoshikawa 2000). P130 is expressed mainly in post-mitotic differentiated cells (Clarke *et al*., 1992; Jacks *et al*., 1992; Lee *et al*., 1994). Consistent with the temporal pattern of expression, targeted deletions in the *Rb* locus result in embryonic lethality (Cobrinik *et al*., 1996; Lee *et al*., 1996), while mice with deletions in *p107 or p130* develop normally (Vanderluit *et al*., 2004). The expression pattern of

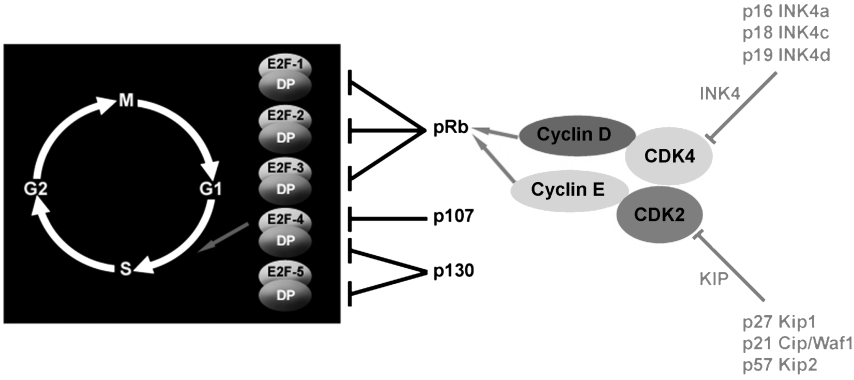

FIGURE 2.5. **Molecular control of cell cycle entry.** The G1/S transition of the cell cycle is regulated by the enzymatic activity of cyclin/CDK complexes. The resulting increased phosphorylation of the tumor suppressor gene pRb (or other members of the pocket protein family) induces the release of transcription factors of the family E2F/DP and allows the transcription of genes involved in S phase entry. The main inhibitors (INK4 and KIP family members) and activators (cyclin D and E) of the cyclin/CDK complexes active at the G1/S transition are shown.

p107 persists in the adult SVZ, where it is expressed in small clusters of cells around the ventricular wall (Vanderluit *et al*., 2004). Mice lacking p107 exhibit increased proliferation of the fast proliferating population, but also increased self-renewal of neural stem cells, as indicated by the ability of cells derived from the SVZ of p107 null mice, to generate a larger number of secondary neurospheres than wild type mice (Vanderluit *et al*., 2004).

(b) INK4 Family Members

INK4 proteins inhibit S-phase entry by preventing the formation of active cyclin D/CDK4 holoenzymes, due to the formation of binary complexes between the INK inhibitor and the catalytic subunit CDK4 (Quelle *et al*., 1995, 1997).

The *Ink4* locus is composed of several genes identified as *Ink4*a, *Ink4b*, *Ink4c* and *Ink4d*. While each of the *Ink4 b-d* genes encodes for one protein named on the basis of the molecular weight p15INK4b, p18INK4c, p19INK4d, the *Ink4a* locus is unusual because its second exon contributes coding sequences to two distinct reading frames resulting in two proteins: p16INK4a and p19ARF (Zindy *et al*., 1997).

In developing mouse embryos, only p18INK4c and p19INK4d have been identified (Zindy *et al*., 1997). P18INK4c is preferentially localized in neurons as they exited from the cell cycle (Zindy *et al*., 1999), whereas p19INK4d is mainly detected in post-mitotic neurons and expressed at high levels in the adult brain (Zindy *et al*., 1999), often together with p27Kip1 (vanLookeren-Campagne and Gill, 1998). In the neonatal rat SVZ, p19INK4d levels are low in proliferating cells at the anterior border of the SVZ and progressively increase in the migratory cells of the rostral migratory stream (Luskin and Coskun, 2002), thus suggesting that this molecule plays a critical role in the induction of cell cycle exit once the migrating cells have reached their final destination (Zindy *et al*., 1999). Consistent with this interpretation, studies on mice with targeted deletion of two major cell cycle inhibitors, p18INK4c and p27Kip1 continue to proliferate even after the migratory period (Zindy *et al*., 1997).

The results regarding the expression of p16INK4a and its possible role in cell cycle regulation of developing CNS are more controversial. While Northern and Western Blot analysis of extracts from developing mouse embryos (van Lookeren Campagne and Gill 1998) have not detected any p16INK4a signal in the brain, different results have been obtained in the developing rat, where p16INK4a is expressed at high levels in the proliferating cells of the VZ from E16 to E20 (Zindy *et al*., 1997). Although p16Ink4a expression is apparently down-regulated in the rat brain also, there appears to be a general consensus on the increasing levels of this protein with increasing age of the animal (Zindy *et al*., 1997). It is important to mention, however, that p16INK4a can be easily detected in vitro, in dissociated primary cultures, thus suggesting that the stress of culturing

could induce the expression of molecules that may not be present in an in vivo context (Jacobs *et al*., 1999a, 1999b). As previously mentioned, the p16INK4a represents the alpha transcript of the *Ink4a* locus and represents an inhibitor of cyclin D/CDK complexes acting on pRb-E2F complexes. The other transcript of the same *Ink4a* locus is p19ARF (beta transcript) and it originates from a promoter some 15 kb upstream of the alpha transcript resulting in a different reading frame of exon 2 than the alpha transcript (see Fig. 2.6).

As a consequence, the beta transcript encodes a protein that has no sequence homology with p16INK4a and that activates p53 rather than the pRb pathway (Fig. 2.6). Given the importance of the *Ink4a* locus in the transcription of regulatory components for two growth-inhibitory pathways, Rb and p53, it becomes easier to understand the high incidence of deletions or inactivations observed in this locus in patients with brain tumors.

The INK4a proteins have not been detected in the developing SVZ, although presumably their expression increases with age. Given the importance of these molecules as modulators of the cell cycle, it becomes critical to understand the mechanisms regulating their expression. In this respect, it has been shown that a member of the polycomb family of chromatin modifiers called Bmi is expressed in the adult SVZ and acts as a potent repressor of the *Ink4a* locus (Molofsky *et al*., 2003). Mice with targeted deletions in the Bmi gene have a significant decrease in proliferation of neonatal and adult SVZ cells together with a 20 fold induction of p16INK4a gene product and a 3 fold increase of p19ARF (Molofsky *et al*., 2003). Besides proliferation, the increased levels of p16INK4a also modulate the ability of the stem cells to self-renew, thus supporting the importance of the Ink4 locus as tumor suppressor.

Remarkably, however, spontaneous glial tumors are not observed in the *Ink4a/Arf* null mutants. Even though both GFAP+ astrocytes and nestin+ cells in these mice have the characteristics of "immortal" cells (Holland *et al*., 1998a), they still require the delivery of a constitutively active form of the

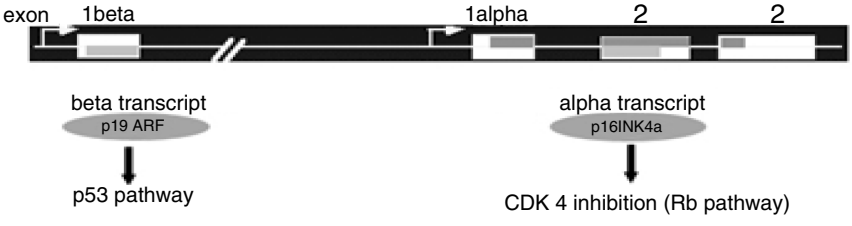

FIGURE 2.6. **The INK4a locus**. The INK4a locus can generate two transcripts: p19 ARF that regulates p53 function and p16INK4a, that modulates the activity of CDK4 and therefore regulates the Rb pathway.

EGFR (Bachoo *et al*., 2002) or of the activated forms of Ras or Akt (Uhrbom *et al*. 2002; Kamijo *et al*., 1997) for neoplastic transformation. Finally, it is worth mentioning that mice with selective deletion of p19ARF, with intact p16INK4a, develop spontaneous gliomas (Sherr and Roberts 1995), thus arguing that p19ARF rather than p16INK4a is involved in the neoplastic transformation of SVZ cells.

(c) Kip Family Members

Inhibitors of the Kip family can bind CDK4/cylinD complexes, although with lower affinity than the INK4 proteins, but this event does not result in efficient functional inhibition of enzymatic activity (Polyak *et al*., 1994; Toyoshima and Hunter, 1994; Sherr and Roberts, 1999). The ability of the Kips to inhibit S-phase entry is mediated by the formation of ternary complexes with cyclin A or E and CDK2 (Russo *et al*., 1996). The inhibitory effect of the Kip molecules on cyclin/CDK complexes is two-fold: they prevent substrate binding and rearrange the amino-terminal lobe of CDK2; thus blocking ATP binding (Russo *et al*., 1996) Three Kip inhibitors have been identified: p27Kip1 (Matsuoka *et al*., 1995), p21Cip1/Waf1 and p57Kip2 (Sherr and Roberts 1999). The p57Kip2 inhibitor is found in the VZ and SVZ of the developing rat brain at E16 and E18, and higher levels of expression are observed in post-mitotic cells at E20 (van Lookeren Campagne and Gill, 1998). The p21Cip/Waf1 inhibitor is also detected at E16 and E18, but its expression is confined to the ependymal layer of the ventricle and the choroid plexus and dramatically decreases to undetectable levels in the adult brain (van Lookeren Campagne and Gill, 1998). In agreement with this expression pattern *p21Cip1*−/− mice do not show any change in the proliferative ability of cells in the developing or mature brain in physiological conditions (Qiu *et al*., 2004).

Of the three members of the Kip family, p27Kip1 is undoubtedly the most interesting. Its expression is detected in proliferating cells of the VZ at mid-gestation (van Lookeren Campagne and Gill, 1998) and its levels progressively increase with increasing numbers of cell divisions (Delalle *et al*., 1999). Given the characteristic pattern of expression during the embryonic neurogenetic period, it has been suggested that p27Kip1 accumulation is part of the mechanism regulating progressive lengthening of the cell cycle and/or increased probability of cell cycle exit (Tarui *et al*., 2005). Studies on p27Kip1 −/− mice, however, have shown that the length of the cell cycle (Tc) of cortical embryonic progenitors is not affected by p27Kip1 loss of function (Goto *et al*., 2004), although there is a definite increase in the probability of the cells to re-enter the cell cycle, and thus an increase of the proliferating population.

The expression of p27Kip1, however, persists in cells of the adult SVZ and in the rostral migratory stream, thus suggesting a role for this molecule also in the regulation of the proliferating population in the adult brain (van Lookeren

Campagne and Gill, 1998). Mice with targeted deletions in the first exon of p27Kip1 show a selective increase in the number of transit amplifying progenitors concomitant with a reduction in the number of neuroblasts and no change in the number of stem cells (Doetsch *et al.*, 2002b). This indicates that cell cycle regulation of SVZ adult progenitors is remarkably cell-type specific with p27Kip1 being a key regulator of cell division in transit amplifying progenitors, but not of the slow proliferating stem cells (Doetsch *et al.*, 2002b). In vitro studies on neurospheres cultured from the neonatal SVZ support this interpretation. The levels of p27Kip1 are low in proliferating neurospheres, they increase during the early stages of differentiation and decrease again with time, in culture, thus indicating a possible role for this protein in regulating the cell cycle of immature, but not stem cells or the more mature neuroblasts (Jori *et al.*, 2003). Together, these data suggest that distinct molecular pathways may be activated in physiological and pathological conditions in order to modulate the number of neural stem cells (Fig. 2.7).

(d) p53 Pathway

The tumor-suppressor gene p53 is an important checkpoint for mammalian cells in the G1 phase of the cell cycle. Upon genotoxic stress, irradiation, DNA damage, oxidative stress or glucose deprivation, this molecule activates a transcriptional response resulting in either exit from the cell cycle (possibly mediated by up-regulation of p21Cip1/Waf1) or apoptosis. In the developing brain, however, p53 expression is most abundant in proliferating

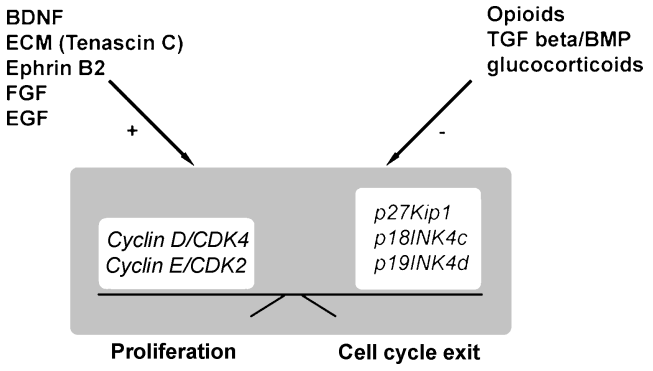

FIGURE 2.7. **Schematic representation of extracellular signals and intracellular molecules regulating the decision of a cell in the G1 phase of the cell cycle.** Although it is not clear whether mitogenic and anti-mitogenic signals affect the same cellular effector molecules in SVZ cells, it is likely that activation of active cyclin/CDK complexes result in proliferation, while their inhibition by Kip and INK family members may result in cell cycle exit.

cell populations of the embryonic and postnatal rat brain, and is not observed in regions undergoing spontaneous apoptosis (Donehower *et al.*, 1992). At E14, its levels are very high in proliferating cells of the ventricular zone, while from E16 to E20, it is also expressed in the SVZ and the cortical plate. The expression of p53 decreases postnatally, but it remains quite high in the postnatal rostral migratory stream and in the subventricular zone, where it persists together with p27Kip1 (van Lookeren Campagne and Gill, 1998). Interestingly, the pattern of expression of p21Cip1/Waf1, one of the downstream transcriptional targets of p53, is quite different, indicating that the role of p53 in cell cycle regulation of adult neural stem cells is independent of p21Cip/Waf1 expression. Despite the high levels of p53 detected in the VZ and SVZ of the developing rat brain, *p53* null mice develop normally, and do not display any major defects in brain histoarchitecture (Donehower *et al.*, 1992). Intriguingly, however, they do display increased susceptibility to the development of glial tumors after transplacental exposure to mutagens (Leonard *et al.*, 2001). Current studies in our laboratory support the hypothesis that the increased susceptibility of these mice to brain tumors is secondary to a specific role of this molecule in modulating the number of adult neural stem cells in vivo (SGP and PCB unpublished).

In vitro, the levels of the cell cycle regulator p53 are quite low in proliferating neurospheres generated from neonatal rats and maintained in EGF and its transcript levels are significantly higher in cells differentiated after mitogen withdrawal (Nakamura *et al.*, 2000; Jori *et al.*, 2003). Higher p53 levels correlate with increased apoptotic index in vitro after 3-7 days in culture. Increased protein levels, however, are observed only after 21 days in differentiating conditions, and correlate with the detection of high levels of neuronal and glial markers, thus suggesting a dual role for this molecule in apoptosis and in differentiation or lineage commitment of neural stem cells.

Other Intracellular Signaling Molecules

Emx2

Emx2 and the related gene *Emx1* are the vertebrate homologues of the *Drosophila* gene *Empty spiracles (ems)* involved in cephalic development (Mallamaci *et al.*, 1998). The distinct expression pattern during late embryonic development with Emx2 expression restricted to the VZ, and Emx1 strongly expressed in the subplate and cortical plate (Gulisano *et al.*, 1996), suggests that these two transcription factors play distinct roles in the developing nervous system. Emx2 is involved in proliferation and migration while Emx1 seems to affect neurogenesis (Yoshida *et al.*, 1997). *Emx1* null mice, however, do not have the corpus callosum and show only subtle defects in cerebral cortex (Pellegrini *et al.*, 1996), while *Emx2* null mice display major alterations of the brain histoarchitecture (Mallamaci *et al.*, 2000; Tole *et al.*, 2000). Recent studies on *Emx2* null mice have shown significant enlargement of the proliferative ventricular and subventricular zones (Galli *et al.*, 2002),

thus suggesting that this molecule acts as a negative regulator of proliferation of neural precursors and adult neural stem cells. Emx2 is expressed in vivo in the adult SVZ (Gangemi *et al*., 2001; Galli *et al*., 2002) and in the rostral migratory stream, and in vitro in multipotent neural precursors (Galli *et al*., 2002). Its expression is significantly decreased when these stem cells differentiate into neurons and glia (Gangemi *et al*., 2001; Galli *et al*., 2002). Gain-of-function studies by over-expressing Emx2 decrease the proliferative rate of cells while retaining their differentiative potential (Gangemi *et al*., 2001; Galli *et al*., 2002). Based on these in vivo and in vitro studies, it can be concluded that *Emx2* acts as a negative regulator of proliferation of adult neural stem cells.

Vax 1

The homeobox *Vax1* is a homologue of *Emx2* and is also strongly expressed in the embryonic and adult SVZ and in the RMS (Soria *et al*., 2004). In the absence of *Vax1*, embryonic precursor cells proliferate 100 times more than wild-type controls, in vitro. In addition, the SVZ of Vax1 null mice shows signs of hyperplasia and disorganization (Soria *et al*., 2004). Together, these data suggested that, like Emx2, the transcription factor Vax1 is an important regulator of proliferation of SVZ cells.

PTEN

PTEN is a lipid phosphatase originally cloned as a tumor suppressor for glioma (Li *et al*., 1997; Tamura *et al*., 1998; Datta *et al*., 1999). PTEN is a phosphatidylinositol (PIP) phosphatase, responsible for the dephosphorylation of PIP3, thus antagonizing the role of the survival kinases PI3K and Akt and rendering the cells more susceptible to apoptosis (Groszer *et al*., 2001). In addition, PTEN is responsible for the dephosphorylation of the focal adhesion kinase FAK, resulting in the inhibition of cell migration (Groszer *et al*., 2001). In the adult brain, PTEN is expressed mainly in neurons and is found both in the nucleus and cytoplasm of cells in the olfactory bulb, in the SVZ and in large projection neurons. Given the importance of this signaling molecule in regulating multiple pathways, several groups have generated conditional knockout mice using the Cre-lox system. The first to be reported is the PTEN deleted by Cre expression in nestin+ cells (Backman *et al*., 2001; Kwon *et al*., 2001). These mice show increased proliferation and decreased apoptosis of cells lining the ventricular walls with a dramatic brain enlargement and death immediately after birth (Li *et al*., 2003). Very different is the phenotype of mice where PTEN is deleted in cells expressing Cre from the GFAP promoter (Recht *et al*., 2003; Berger *et al*., 2004). In this case, no change in proliferation or apoptosis has been reported, although the mice displayed an abnormal organization of the cerebellum. These data clearly indicate that the effect of PTEN is cell-context dependent and is affected by the intracellular and extracellular milieu, possibly due to the cross-talk with distinct signaling pathways that are active in different cells at different times.

Conclusions

Although stem cell therapy has been proposed for therapeutic strategies aimed at repairing functions, it is important to realize that as yet, relatively little is known about the behavior of embryonic and adult stem cells in terms of responsiveness to extracellular cues and intracellular signaling molecules.

The challenge that awaits ahead is to define possible differences in intracellular signaling molecules between embryonic and adult derived neural stem cells that may underlie the distinctive responsiveness of these different cell types to external signals. A better understanding of the mechanisms regulating proliferation and differentiation of multipotent progenitors into differentiated neurons, astrocyte and oligodendrocytes is, therefore, essential for developing a realistic frame of therapeutic intervention while preventing undesirable - and yet possible-neoplastic transformation of adult neural stem cells.

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Table 1.

Extracellular factor	Effect	Reference
FGF2	↑ proliferation	(Wagner *et al*., 1999)
	↑ neurogenesis	(Wagner *et al*., 1999)
EGF	↑ proliferation	(Kuhn *et al*., 1997)
	↓ neurogenesis	(Doetsch *et al*., 2002)
TGFa	↑ proliferation	(Cooper and Isacson 2004)
	↑ migration	
IGF-1	↑ proliferation	(Arsenijevic *et al*., 2001)
	↑ neurogenesis	(Arsenijevic and Weiss 1998)
	↑ survival	(Gago *et al*., 2003)
BDNF	↑ proliferation (p75)	(Zigova *et al*., 1998)
	↑ neurogenesis (TrkB)	(Pencea *et al*., 2001)
	↑ survival	(Kirschenbaum and Goldman 1995)
EPO	↑ neurogenesis	(Shingo *et al*., 2001)
VEGF	↑ proliferation	(Jin *et al*., 2002b)
	↑ migration	(Zhang *et al*., 2003)
HB-EGF	↑ neurogenesis	(Jin *et al*., 2002a)
Ephrins	↑ proliferation	(Conover *et al*., 2000)
	↓ migration	
TNFa	↑ proliferation	(Wu *et al*., 2000)
BMP	↓ proliferation	(Coskun and Luskin, 2001)
	↑ self-renewal	(Ying *et al*., 2003)
	↑ gliogenesis	(Gross *et al*., 1996)
	↑ neurogenesis	(Li *et al*., 1998; Panchison *et al*., 2001)
Noggin	↑ neurogenesis	(Lim *et al*., 2000)
CNTF/LIF	↑ self-renewal	(Shimazaki *et al*., 2001)
	↑ gliogenesis	(Bonni *et al*., 1997; Rajian *et al*., 1998)
	↑ neurogenesis	(Emsley and Hagg 2003)
Shh	↑ proliferation	(Charytoniuk *et al*., 2002; Palma *et al*., 2005)
Wnt (β catenin)	+FGF2 proliferation	↑ (Viti *et al*., 2003; Israsena *et al*., 2004)
	−FGF2 neurogenesis	↑ (Israsena *et al*., 2004; Otero *et al*., 2004)
Notch	variable	(Chambers *et al*., 2001)
Tenascin C	↑ proliferation	(Garcion *et al*., 2004)
Serotonin	↑ proliferation	(Banasr *et al*., 2004)
	↑ neurogenesis	
Dopamine	↑ proliferation (Baker *et al*., 2004)	(Coronas *et al*., 2004)
	↑ neurogenesis	(Van Kampen *et al*., 2004)
Opioids	↓ proliferation	(Stiene-Martin *et al*., 2001)
Others		
	sAPP ↑ proliferation	(Ohsawa *et al*., 1999)
	Abeta ↓ proliferation	(Haughey *et al*., 2002)
	↓ migration	
	↑ apoptosis	

**shh* enhanced the mitogenic effect of EGF

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