Control of Cell Survival in Adult Mammalian Neurogenesis

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The fact that continuous proliferation of stem cells and progenitors, as well as the production of new neurons, occurs in the adult mammalian central nervous system (CNS) raises several basic questions concerning the number of neurons required in a particular system. Can we observe continued growth of brain regions that sustain neurogenesis? Or does an elimination mechanism exist to maintain a constant number of cells? If so, are old neurons replaced, or are the new neurons competing for limited network access among each other? What signals support their survival and integration and what factors are responsible for their elimination? This review will address these and other questions regarding regulatory mechanisms that control cell-death and cell-survival mechanisms during neurogenesis in the intact adult mammalian brain.

ARE NEUROGENIC BRAIN REGIONS EXPANDING DESPITE SPACE LIMITATIONS?

This question was addressed several decades ago following the first evidence for adult mammalian neurogenesis (Altman and Das 1965). Total neuronal cell counts of the olfactory bulb (OB) and dentate gyrus at different ages revealed that continued growth of the granule cell layers occurs in both regions throughout the adult life. From 1 month until 1 year of age, the number of dentate gyrus granule cells doubled in the rat (Bayer 1982; Bayer et al. 1982). A rise in total volume, as well as increased cell density, contributed to this phenomenon. In the rat OB, a linear growth of the granule cell layer was observed with age, as the number of olfactory granule cells doubled between 3 and 31 months of age (Kaplan et al. 1985).

Considering this substantial growth, we could postulate that new neurons are certainly added to the system. However, the estimated amount of new neurons generated in the adult brain is lower than extrapolated from acute labeling studies using bromodeoxyuridine (BrdU) or cell-cycle markers. This indicates that elimination mechanisms are also present in the neurogenic zone.

PROGRAMMED CELL DEATH IS A COMMON ELEMENT DURING ADULT NEUROGENESIS

During development, programmed cell death (herein also referred to as apoptosis) is involved in the optimal matching of a neuronal population with available synaptic targets (Buss et al. 2006). Programmed cell death has been shown

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to allow for the rapid elimination of neurons that have failed to make proper connections or to secure sufficient amounts of target-derived trophic factors (Oppenheim 1991). Apoptosis has been shown within the neurogenic zones of the postnatal and adult brain (Biebl et al. 2000; Dayer et al. 2003). Quantitatively, the highest number of dying cells was observed in the OB, followed by the rostral migratory stream (RMS), the subventricular zone (SVZ), and the dentate gyrus (Biebl et al. 2000). The location of apoptotic profiles indicated that apoptosis was intimately connected to the generation of new neurons (see Fig. 1).

A large majority of the apoptotic cells are immature (Seki 2002). In the dentate gyrus, the majority of cell death is detected in the subgranular zone (SGZ), the border between the

granule cell layer and hilus, in which dividing progenitors reside. Apoptotic profiles have been shown by colabeling with immature neuronal markers, such as doublecortin (DCX) (Kuhn et al. 2005). When monitoring cohorts of adult-born BrdU-labeled cells over time, a 30% to 70% reduction in the number of progenitors and young neurons was detected over a period of several months (Winner et al. 2002; Dayer et al. 2003). After this critical period, most adult-born neurons survive for the remainder of the animal's lifespan. For neurons generated during the postnatal period, even higher frequencies of elimination have been reported (Dayer et al. 2003; Kim et al. 2011), although developmentally produced neurons numerically dominate the dentate gyrus granule cell population during adulthood (Lagace et al.

Figure 1. Apoptotic cells can be visualized by terminal deoxynucleotidyl-mediated dUTP nick-end-labeling (TUNEL) in sections of the intact adult rodent brain. TUNEL-positive cells (green) can be frequently detected in (A) the subgranular zone (SGZ) of the dentate gyrus, (B) the subventricular zone (SVZ) of the lateral ventricle wall, (C) the rostral migratory stream (RMS), and (D) the granule cell layer of the olfactory bulb granule cell layer (OB-GCL). Red counterstain is propidium iodide (for more details, see Biebl et al. 2000; Cooper-Kuhn and Kuhn 2002; Kuhn et al. 2005). Scale bars, 15 μm (A–C); 50 μm (D).

2007; Muramatsu et al. 2007; Ninkovic et al. 2007).

INTRACELLULAR CELL-DEATH MECHANISMS

Numerous studies have reported survival-promoting activities and signals in adult neurogenesis. This assumption is often based on increased numbers of BrdU-labeled cells at later time points, albeit initially similar numbers of proliferating cells. However, proliferation and neuronal maturation of progenitor cells are closely intertwined with cell-death mechanisms, which makes it difficult to distinguish whether a net increase in neurogenesis is caused by a prolonged proliferative phase, a shift of multipotent progenitor cells toward increased neuronal lineage commitment, or decreased cell death. More definitive is the quantification of cell-death indicators, such as fragmented nuclei, pycnotic cells, terminal deoxynucleotidyl-mediated dUTP nick-end-labeling (TUNEL), activation of caspases, or expression of pro- and antiapoptotic proteins (Gould et al. 1991; Corotto et al. 1994; de Bilbao et al. 1999; Biebl et al. 2000).

Apoptosis is initiated by intracellular signaling pathways in response to cellular stress, which leads to activation of the cysteine-dependent aspartate proteases (caspases) followed by nuclear DNA fragmentation and cell death. Caspase-dependent apoptosis is thought to be a major contributor to cell death in the neurogenic niches. In vivo treatment with caspase inhibitors has been shown to increase the survival rate of newly generated neurons (Biebl et al. 2005; Gemma et al. 2007). Upstream of the caspase cascade, pro- and antiapoptotic signals are integrated by members of the Bcl-2 family. The major proapoptotic molecules, Bax and Bak, compromise the mitochondrial membrane integrity by forming channels that can release apoptogenic signals such as cytochrome *c*. The antiapoptotic proteins, Bcl-2 and Bcl-xL, protect the mitochondrial membrane by forming heterodimers with proapoptotic proteins, thus preventing the release of cytochrome *c* (Renault et al. 2013).

In adult neurogenesis, it appears that both pro- and antiapoptotic Bcl-2 family members are involved. Bax-deficient mice have a higher number of neuronal progenitor cells and a higher rate of neurogenesis in the dentate gyrus, as well as reduced cell death. The lack of apoptosis leads to an increased accumulation of granule cells and a larger dentate gyrus with age (Sun et al. 2004). Bax-deficient mice, as well as double-knockout mice for Bax and Bak, display a significantly larger pool of neural progenitor cells in the SVZ, which can serve as multipotent stem cells in vitro (Lindsten et al. 2003; Shi et al. 2005). Fewer apoptotic cells were also found in the OB of Bax knockout and Bax/Bak double-knockout mice; however, increased OB neurogenesis was less than expected because of decreased migration of SVZ progenitor cells via the rostral migratory stream (Lindsten et al. 2003; Kim et al. 2007). In the dentate gyrus of Bax-deficient mice, because of an absence of elimination, accumulating granule cells show somatic atrophy, reduced dendritic complexity, and synaptic connectivity, indicating that programmed cell death is required for normal hippocampal maturation (Sun et al. 2004; Kim et al. 2009). Induction of Bax expression in progenitor cells of the adult brain increased the number of granule cells in the dentate gyrus (Sahay et al. 2011). These mice show enhanced pattern separation, indicating that the rescued neurons contribute to improved hippocampal function.

Bcl-2 expression is also intimately linked to neurogenesis in the adult brain, with high levels in the SVZ and dentate gyrus (Bernier and Parent 1998; Bernier et al. 2000). Similar to Bax-deficiency, transgenic overexpression of Bcl-2 in neuronal cells results in increased hippocampal neurogenesis caused by reduced cell death of neuronal progenitor cells (Kuhn et al. 2005; Sasaki et al. 2006). The cAMP response element-binding (CREB) protein signaling pathway has also been reported to alter cell death of adult-born neurons (Jagasia et al. 2009; Herold et al. 2011). CREB signaling is responsible for maintaining the neuronal differentiation program of progenitor cells, which includes expression of survival-promoting factors (Zhang et al. 2009).

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EXTRACELLULAR SIGNALING

The survival-promoting effect of neurotrophic factors, hormones, and other extracellular signals is ultimately mediated by interference with apoptosis-inducing signaling pathways. Trophic factors, such as fibroblast growth factor (FGF)-2, brain-derived neurotrophic factor (BDNF), granulocyte colony-stimulating factor (G-CSF), and vascular endothelial growth factor (VEGF), can directly stimulate expression of antiapoptotic Bcl-2 family proteins (Fig. 2) (Bryckaert et al. 1999; Desire et al. 2000; Rios-Munoz et al. 2005; Cao et al. 2006; Solaroglu et al. 2006; Milosevic et al. 2007), thereby counteracting Bax and Bak functions and preventing caspase activation.

Neurotrophic Factors and Growth Factors

The neurotrophin family (nerve growth factor [NGF], BDNF, neurotrophin [NT]3, and NT4/5) is involved in the development and maintenance of a variety of neuronal cell types through multiple cell mechanisms. In the classical view, neurotrophins are released by target structures, acting as neurite-attracting molecules (Lewin and Barde 1996). On reaching the target, neurons soon become dependent on retrogradely transported neurotrophins for their survival (Oppenheim 1989). Target-independent roles of paracrine- and autocrine-released neurotrophins have also been described (Acheson and Lindsay 1996).

For adult neurogenesis, BDNF appears to play a central role in stimulating the differentiation and survival of newly generated neurons in the SVZ and the hippocampus (Zigova et al. 1998; Benraiss et al. 2001; Scharfman et al. 2005; Rossi et al. 2006). Paradoxically, central nervous system (CNS) depletion of BDNF in mice reportedly induced hippocampal cell proliferation without affecting cell survival or fate specification, suggesting a role in cell-cycle exit and maturation rather than cell death (Chan et al. 2008). Although it is less well studied, NGF was shown to promote neurogenesis following infusion into the lateral ventricle (Frielingsdorf et al. 2007). NT3 also appears to be involved,

because adult NT3-deficient mice show impaired granule cell differentiation in the dentate gyrus, despite normal proliferation (Shimazu et al. 2006).

FGF-2, produced and released by astrocytes (Gomez-Pinilla et al. 1992), is an important regulator of adult neurogenesis, and FGF-2 infusion leads to increased neurogenesis (Kuhn et al. 1997; Wagner et al. 1999) by stimulating proliferation. In contrast, FGF receptor 1-deficient mice show impaired neurogenesis in the adult hippocampus (Zhao et al. 2007). Interestingly, in mouse slice cultures, FGF-2 deficiency results in no deficiency in proliferation, but rather increased cell death (Werner et al. 2011).

Similarly, a variety of growth factors are known to affect adult neurogenic regions. A subset of these peptides, such as epidermal growth factor (EGF), transforming growth factor (TGF)- β 1, leukemia-inhibiting factor, and pigment epithelium-derived factor, act only on proliferation and self-renewal of stem cells (Craig et al. 1996; Kuhn et al. 1997; Jin et al. 2002; Buckwalter et al. 2006; Ramirez-Castillejo et al. 2006; Wachs et al. 2006). Although EGF expands the pool of radial glia-like neural stem cells on the expense of neurogenesis, betacellulin (BTC), a member of the EGF family, induces expansion of neuroblastoma–spinal cords (NSCs) and neuroblasts, and promotes neurogenesis in the OB and dentate gyrus (Kuhn et al. 1997; Gomez-Gavira et al. 2012; Lindberg et al. 2012a,b). Tumor necrosis factor α (TNF- α) signaling has both positive and negative effects on neurogenesis in vivo, because TNF receptor (TNFR)-1 and TNF- α -deficient animals have elevated baseline neurogenesis in the hippocampus, whereas absence of TNFR-2 decreases baseline neurogenesis (Chen and Palmer 2013). Other peptide factors, such as FGF-2, VEGF, and pituitary adenylate cyclase-activating polypeptide (PACAP) show both proliferative and neurotrophic activity (Zhu et al. 2003; Mercer et al. 2004; Schänzer et al. 2004; Ohta et al. 2006; Fournier et al. 2012). On the other hand, erythropoietin, G-CSF, and insulin-like growth factor (IGF)-1 have been shown to increase neurogenesis through their survival-promoting capacity

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Figure 2. A multitude of factors regulates adult neurogenesis by controlling proliferation, fate determination, and survival of cells. Trophic support is required at all stages during development, from stem cell to neuron, and depletion of the stem-cell pool or apoptotic cell death may significantly reduce the amount of new neurons. Neurotransmitter and synaptic influences are detected at early progenitor stages, indicating a strong influence of the preexisting network on neuronal maturation in the adult brain. EGF, Epidermal growth factor; LIF, leukemia inhibitory factor; TGF- β 1, transforming growth factor β 1; PEGF, platelet-derived endothelial cell growth factor; FGF-2, fibroblast growth factor 2; VEGF, vascular endothelial growth factor; NT3, neurotrophin 3; IGF-1, insulin-like growth factor 1; EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GABA, γ -aminobutyric acid; NO, nitric oxide.

(Åberg et al. 2000; Shingo et al. 2001; Schneider et al. 2005; Lichtenwalner et al. 2006). Store-operated calcium channels (SOCS)-2 have been found to interact with the cytoplasmic domain of IGF-1 receptor and are thought to be involved in the regulation of IGF-1-recep-

tor-mediated cell signaling. Transgenic mice overexpressing SOCS-2 show increased survival of adult-born hippocampal neurons, which correlates with improved performance in a hippocampal-dependent cognitive task (Ransome and Turnley 2008).

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Hormones

Hormonal signals control many aspects of neuronal development, including cell survival. It is, therefore, no surprise that adult neurogenesis is under strong hormonal influence. In short, stress hormones negatively regulate the number of new neurons by reducing proliferation as well as survival of progenitor cells (for more details, see Lucassen et al. 2010). Gonadal hormones and neurosteroids, on the other hand, stimulate the generation of new neurons (Karishma and Herbert 2002; Mayo et al. 2005; Galea et al. 2006). Steroid hormones act via nuclear hormone receptors, which bind to promoter regions in key genes for neuronal survival. BDNF and the Bcl-2 gene family are downstream targets from steroid hormone receptor activation (Almeida et al. 2000; Charalampopoulos et al. 2006; Scharfman and MacLusky 2006; Yao et al. 2007). Signaling through thyroid hormone and retinoic acid receptors appears to have a strong stimulatory effect on proliferation and survival of neuronal progenitor cells and appears to be important for maintaining postnatal and adult neurogenesis (Ambrogini et al. 2005; Desouza et al. 2005; Lemkine et al. 2005; Wang et al. 2005; Jacobs et al. 2006; Kornyei et al. 2007). Thyroid hormone receptor (TR)- α 1-null mice show a significant increase in DCX-positive cells and increased survival of bromodeoxyuridine-positive cells compared with wild-type controls (Kapoor et al. 2010). TR- α 2-null mice, on the other hand, show significantly less survival of newly generated cells and decreased numbers of polysialylated neuronal cell-adhesion molecule (PSA-NCAM)- and NeuroD-positive progenitor cells, suggesting negative effects on early postmitotic progenitors (Kapoor et al. 2010).

NEUROTRANSMITTERS AND SYNAPTIC ACTIVITY

As immature neurons strive to integrate into functional networks, neuronal communication becomes an important survival-promoting factor. Neural progenitor cells receive neurotransmitter input at an early stage while still undergoing cell division. It appears that neurotransmitters, such as γ -aminobutyric acid

(GABA), glutamate, acetylcholine, and serotonin, which are released in or near the neurogenic regions, are involved in adult neurogenesis mainly via regulation of cell-cycle entry and exit (for review, see Berg et al. 2013). This section focuses specifically on the effects of neurotransmitters on progenitor cell survival.

GABA

Although GABA is the main inhibitory neurotransmitter for mature neurons, it can act as a trophic factor for immature neurons and progenitor cells through Cl^- -mediated depolarization. GABA_A receptor activation inhibits proliferation and up-regulates neuronal determination factors, such as NeuroD, which stimulates cell-cycle exit and neuronal differentiation (for review, see Dieni et al. 2012). Fewer details are known about the effects of GABA on apoptosis of newly generated cells, although GABA depolarization has been shown to lead to cell death in 1- to 2-week-old cells, an effect that is rescued by CREB signaling (Jagasia et al. 2009). It is quite likely that mechanisms of synaptic integration induce cell survival in the hippocampus.

Glutamate

Reduced glutamatergic input via entorhinal cortex lesion or treatment with both competitive and noncompetitive NMDA receptor antagonists stimulated the proliferation of granule cell precursors and subsequent production of new granule cells (Cameron et al. 1995), although possibly in response to significant cell death. In contrast, a cell-specific knockout of the NMDA NR1 subunit in adult-born neurons of the dentate gyrus dramatically decreased their survival (Tashiro et al. 2006). Ionotropic and metabotropic glutamate receptors are also capable of modulating adult hippocampal neurogenesis (Bernabeu and Sharp 2000; Yoshimizu and Chaki 2004).

Acetylcholine

Lesions of the basal forebrain cholinergic system lead to significantly reduced survival rates of

newly generated cells in the hippocampus and OB despite no changes in proliferation of progenitor cells (Cooper-Kuhn et al. 2004; Mohapel et al. 2005). Neuronally committed progenitors express multiple acetylcholine receptor subunits and make contact with cholinergic fibers (Kaneko et al. 2006). Pharmacological alterations in cholinergic signaling confirmed the positive influence of acetylcholine on hippocampal neurogenesis (Kaneko et al. 2006; Kotani et al. 2006), and in knockout mice for the nicotinic acetylcholine receptor α containing the $\alpha 7$ subunit, adult-born neurons developed less complex dendritic trees. These neurons appeared to be more immature, as indicated by a prolonged period of GABAergic depolarization. They also received less synaptic input and were more prone to undergo developmental cell death (Campbell et al. 2010).

Serotonin

Almost all antidepressants, which act through enhancement of serotonergic neurotransmission, stimulate hippocampal granule cell production. Chronic depletion of serotonin reduces neurogenesis (Brezun and Daszuta 1999), whereas antidepressants up-regulate neurotrophic factors CREB and Bcl-2, which suggests a survival-promoting effect of serotonin (Nibuya et al. 1995, 1996; Chen et al. 2007).

Nonclassical neurotransmitters are also potent regulators of adult neurogenesis. Neuropeptide Y positively regulates hippocampal and SVZ cell proliferation (Howell et al. 2005, 2007; Stanic et al. 2008; Thiriet et al. 2011), whereas substance P and nitric oxide signaling appear to be detrimental to adult neurogenesis by repressing survival signals, such as BDNF and phosphorylated (p)CREB signaling (Morcuende et al. 2003; Packer et al. 2003; Reif et al. 2004; Zhu et al. 2006).

SYNAPTIC ACTIVITY AND SURVIVAL

Synapse formation is a critical step in the survival of newly formed neurons, because target-derived factors are transported from the synapse to the soma to influence apoptotic signaling. In

the OB neurogenesis system, the majority of dying cells have already matured to the point of forming dendritic spines and have the potential to receive synaptic input (Petreanu and Alvarez-Buylla 2002). Their survival seems to be very much dependent on sensory input (Corotto et al. 1994; Petreanu and Alvarez-Buylla 2002; Rochefort et al. 2002). Increased cell survival is observed under olfactory learning conditions, with higher numbers of surviving new neurons in more activated glomeruli (Alonso et al. 2006). Using in vivo multiphoton microscopy, it was shown that the loss and replacement of periglomerular neurons in the OB was highly specific, leading to recruitment of new cells into vacant spots within the glomeruli (Sawada et al. 2011). Similarly, in the dentate gyrus, neuronal activity within a short, critical time window of about 3 weeks after neuronal birth seems to determine the survival and resulting formation of new circuits. This critical period is associated with a high degree of morphological changes in new neurons, including synapse formation and NMDA receptor NR1 expression (Tashiro et al. 2006).

CELL DEATH AND PROLIFERATION

A large number of progenitor cells is eliminated during proliferation and maturation and thus it is no surprise that preventing activation of the cell-death cascade by overexpression of Bcl-2 or deletion of BAX leads to an increase in neurogenesis (Sun et al. 2004; Kuhn et al. 2005). But, an interesting aspect in neurogenesis regulation is the question whether cell death triggers changes in proliferation or vice versa. Manipulations that induce neuronal cell death, such as high levels of cortisol or ischemia, also stimulate cell-cycle entry. Moreover, differentiated neurons, when forced to enter cell cycle, undergo apoptotic cell death (for review, see Liu and Greene 2001). Nevertheless, is progenitor proliferation a direct result of the “vacant spot”? The most direct evidence contradicting this hypothesis comes from Bax-deficient and Bcl-2-overexpressing mice, in which a decrease in cell death did not lead to changes in proliferation (Sun et al. 2004; Kuhn et al. 2005). In contrast,

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decreased S phase entry in mice deficient for the cell-cycle-activator protein E2F1 leads to decreased cell death (Cooper-Kuhn et al. 2002), indicating that cell-death regulation during adult neurogenesis occurs downstream from proliferative signals.

MICROGLIA SIGNALING

Apoptosis can be externally induced through death receptors, such as Fas or Toll-like receptors (TLRs), during inflammatory responses that involve microglia and/or T-cell activation. It was assumed that activated immune cells do not play a major role in the intact brain, because inflammatory signals are largely absent and microglia remain unchallenged (Ekdahl et al. 2003). However, this view was contested by a study in which CNS-specific autoimmune T cells cross talked with resident microglia to stimulate progenitor proliferation in a model of environmental stimulation (Ziv et al. 2006). In this study, T-cell deficiency also induced decreased BDNF and IGF-1 levels, thereby possibly influencing cell survival.

TLRs are innate immune receptors that have recently emerged as regulators of neuronal survival and developmental neuroplasticity. TLR-3-deficient mice show increased hippocampal neurogenesis and elevated levels of the transcription factor CREB, suggesting that constitutive TLR-3 signaling negatively regulates cell maturation and survival (Okun et al. 2010). TLR-2 deficiency was shown to impair dentate gyrus neurogenesis in adult mice, whereas the absence of TLR-4 resulted in enhanced proliferation, differentiation, and survival of new neurons (Rolls et al. 2007).

Although activated microglia influence survival mechanisms in adult neurogenesis in situations of inflammation and increased immune responses, nonactivated microglia might also play an important role. The large amount of developmental cell death in the adult dentate gyrus and SVZ/OB system requires rapid and efficient phagocytosis of apoptotic cell bodies, which is performed by nonactivated, ramified microglia (Sierra et al. 2010; Lazarini et al. 2012).

SUMMARY

Naturally occurring cell death claims more than half of the differentiating neurons in the adult brain. Their survival depends on paracrine and target-derived substances with neurotrophic activity, afferent synaptic activity, cell–cell and cell–matrix interactions, as well as hormonal and other blood-borne signals. An infinite combination of factors can serve to rescue or influence the survival of immature neurons. As cells transition through a several-month-long differentiation and integration period, the fine balance of signals is easily disrupted at many points along the way.

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H. Georg Kuhn

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