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Influence of Hippocampal Niche Signals on Neural Stem Cell Functions During Aging

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Abstract

The genesis of new neurons from neural stem cells in the adult brain offers the hope that this mechanism of plasticity can be harnessed for the treatment of brain injuries and diseases. However, neurogenesis becomes impaired during the normal course of aging, which is also the primary risk factor for most neurodegenerative diseases. The local microenvironment that regulates the function of resident neural stem cells (the “neurogenic niche”) is a particularly complex network of different signaling mechanisms, rendering it especially challenging to dissect how these cells are controlled but offering the potential to advance our understanding of how neurogenesis is regulated/misregulated. In this review, we examine the factors that control neurogenesis in an age-dependent manner, and define these signals by the extrinsic mechanism through which they are presented to the neural stem cells. Secreted signals, cell-contact dependent signals, and extracellular matrix cues all contribute to the regulation of the aging neurogenic niche, as well as offer points of therapeutic intervention.

Keywords

neural stem cells; neurogenic niche; aging; neurogenesis; stem cell microenvironment interactions

Introduction

It is now well established that new neurons are continuously produced in specific regions of the adult brain via the proliferation and differentiation of adult neural stem cells (NSCs). However, the existence of adult neurogenesis only became widely accepted in the mid 1990s (Gross 2000), and even then, its biological significance was questioned. Perhaps, it was supposed, postnatal neurogenesis was merely a remnant of development. However, a series of elegant studies demonstrated that the birth of new adult neurons could be regulated by environmental and behavioral experiences – such as stress (Gould & Tanapat 1999), exercise (van Praag et al. 1999), and enrichment (Kempermann et al. 1997) – and that the new

neurons arising from NSCs mature and integrate into existing brain circuits (van Praag et al. 2002). Later, a number of studies demonstrated that ablation of neurogenesis impairs performance in various learning tasks (for example: (Winocur et al. 2006, Saxe et al. 2006, Dupret et al. 2008, Imayoshi et al. 2008, Deng et al. 2009) and reviewed in (Marín-Burgin & Schinder 2012)). Exploration of this field has thus become crucial for understanding learning and memory formation, and furthermore offers hope that the maintenance of this plasticity in the adult brain can be tapped to treat neurodegenerative conditions.

Mammalian adult neurogenesis is known to occur in two distinct brain regions: the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus and, in rodents if not humans, the subventricular zone (SVZ) of the lateral ventricles (Sanai et al. 2004). Within these “neurogenic niches” or microenvironments, neurogenesis is tightly regulated by a range of regulatory signals. Though these niches likely share underlying similarities, in this review we will focus primarily on the hippocampal niche. Adult hippocampal neurogenesis is a multistage process in which, quiescent radial glia-like cells (Type-1 cells) are activated and give rise to transiently amplifying neural progenitor cells (NPCs, Type-2), which in turn generate neuroblasts (Type-3) that will differentiate into new neurons, migrate to the granule cell layer, and mature to develop dendritic arborizations and axonal projections (Aimone et al. 2014). Our emphasis here will lie on the initial stages of this process, *i.e.* NSC proliferation and neuronal differentiation, and other reviews in this Special Issue highlight other steps leading to network integration.

To gain a deeper understanding of the contributions neurogenesis offers to CNS function, as well as to potentially harness this process for therapeutic application, we must gain a greater understanding of the specific mechanisms that regulate this process. Adult neurogenesis involves a particularly complex network of intercellular communications. NSCs directly contact multiple resident cells of the DG including neuroblasts, neurons, astrocytes, and oligodendrocytes (which may all differentiate from the NSCs themselves), as well as microglia and endothelial cells. Blood vessels and factors associated with the circulatory system can also contribute to the niche (Palmer et al. 2000, Alvarez-Buylla & Lim 2004, Decimo et al. 2012). Furthermore, the neurogenic niche network is comprised not only of many different cell types but also multiple modes of signaling. In particular, resident niche cells secrete numerous paracrine factors that regulate NSCs, and contact-dependent juxtacrine signaling can also occur via membrane-bound ligands and receptors on adjacent cells. Furthermore, the extracellular matrix (ECM), in addition to providing a physically supportive structure to the niche, is comprised of molecules that stimulate signaling and regulate NSC functions. Here, we will use these signal classifications to guide our discussion (Fig. 1).

Interestingly, among the early studies demonstrating the effects of environment and experience on adult neurogenesis was the discovery that neurogenesis decreases with age (Kuhn et al. 1996). This finding raised the question of whether this decline could contribute to age-associated memory and cognitive impairments. In fact, aging is among the most well-studied and, at least in rodents, substantial negative regulators of neurogenesis, resulting in reduced cell proliferation, survival, and differentiation (Aimone et al. 2014).

Are the effects of organismal aging on hippocampal neurogenesis cell-intrinsic, or are they mediated by changes in signaling factors, and if so, which ones? This has become a topic of considerable focus and research, and in recent years there has been particular interest on the effects of systemic circulation on stem cell decline with aging (Villeda & Wyss-Coray 2013, DeCarolis et al. 2015). A number of impactful studies utilized the heterochronic parabiosis model to demonstrate that neural progenitor cells are affected by the relative age of the systemic environment, such that exposure to a young circulatory system increases proliferation, whereas exposure to an old system decreases proliferation (Villeda et al. 2011, Katsimpardi et al. 2014, Smith et al. 2015). This research is summarized in detail in another review within this Special Issue. However, briefly, the parabiosis studies have led to the identification of a number of soluble, plasma-borne proteins that are implicated in this role, including CCL11, growth differentiation factor 11 (GDF11), and β 2-microglobulin. Given the intervening blood brain barrier, a major question that remains is how plasma proteins exert their effects on the NSCs or by indirect effects mediated by other components of the niche such as the vasculature or other cell types.

In this review, we summarize what is currently known about neurogenic niche signals that affect NSCs proliferation and differentiation and that are altered during the course of normal aging (Table 1). Work with heterochronic parabiosis and plasma proteins demonstrates the importance of identifying systemic proteins that control neurogenesis. Additionally, other paracrine factors that are known to act over shorter distances within the niche and directly upon NSCs will be discussed. In parallel, we will highlight cell-contact dependent and extracellular matrix signals, where there has been comparatively less work studying factors that may regulate neurogenesis in an age-dependent fashion. We thus aim not only to review what is already known about the communication network of the aging neurogenic niche, but also to highlight areas for which much remains to be explored.

Secreted Signals

By far, the majority of signaling factors that are known to regulate neurogenesis and are also altered with aging are secreted. As mentioned above, CCL11 and β 2-microglobulin – generally known as immune system associated proteins – are systemic factors that regulate neurogenesis and whose levels in plasma increase during aging ((Villeda et al. 2011) and (Smith et al. 2015), respectively). Whether these proteins exert their effects via direct or indirect mechanisms on NSCs remains to be examined, however, and it has been suggested that they could function via other cell types, such as microglia (Ransohoff 2011).

Microglia function in part through secreting secreted cytokines and chemokines, molecules that are generally thought of as mediating intercellular communication between immune cells but that can also regulate NSCs (Mosher & Wyss-Coray 2014). In addition, microglial behavior itself is altered during aging, including increased cell proliferation and density (Long et al. 1998, Hua et al. 2012). Furthermore, the aged microglia secretory profile is different from that of their young counterparts, including production of greater levels of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and IL-1 β (Gemma et al. 2007, Bachstetter et al. 2011, Njie et al. 2012). These three are the primary proinflammatory

cytokines that are known to prominently inhibit adult neurogenesis (reviewed in (Carpentier & Palmer 2009)). Numerous studies of these proteins have varied somewhat in their reported effects on NSCs, perhaps owing to the context in which the signal is presented. However, there is general consensus overall that they can act at least in part through direct interactions with receptors on NSCs. IL-6 signals through its primary receptor and co-receptor gp130 to decrease NSC differentiation into neurons but increase astrocyte production (Monje et al. 2003, Nakanishi et al. 2007). TNF- α can signal through two receptors, TNFR1 or TNFR2, which have the opposing functions of mediating apoptosis or survival pathways, respectively. Though NSCs express both receptors, several *in vitro* studies have found that signaling through TNFR1 induces NSC apoptosis (Cacci et al. 2005, Sheng et al. 2005, Widera et al. 2006). Finally, IL-1 β acts directly via the receptor IL-1R1 to inhibit proliferation (Koo & Duman 2008).

However, microglia are far from the only cell type in the neurogenic niche to influence NSC functions, and the source of a signal can strongly influence how that factor regulates neurogenesis. For example, IL-6 is also produced by astrocytes, and astrocyte-derived IL-6 has been found in different studies to either inhibit neurogenesis (Vallières et al. 2002) or promote neuronal differentiation (Barkho et al. 2006, Oh et al. 2010). It is unclear whether IL-6 expression is altered in aged astrocytes (Ye & Johnson 1999), however, such that IL-6 from microglia may be more relevant in considering the age-associated reduction in neurogenesis. Like IL-6, transforming growth factor- β (TGF- β) is expressed by multiple sources – including microglia, endothelial cells, and astrocytes – and increases locally in the hippocampi of aged mice. This cytokine has garnered particular interest over the past decade as it can activate both pro- or anti-inflammatory pathways, depending on the context of activation, and has been found to both positively (Battista et al. 2006) and negatively (Buckwalter et al. 2006, Yousef, Conboy, et al. 2015) impact neurogenesis. The TGF- β superfamily of proteins, which signal intracellularly through the SMAD pathway, also includes bone morphogenetic proteins (BMPs). Recently, BMP4 and BMP6 were also found to increase with age in the hippocampus, with BMP4 expression mainly localized to endothelial cells and BMP6 to microglia (Yousef, Morgenthaler, et al. 2015). In this same study, BMP4 treatment directly inhibited NSC proliferation *in vitro*; moreover, inhibiting BMP signaling *in vivo* in the hippocampus of aged mice partially rescued the aged-associated decrease in NSC proliferation and neural differentiation. Future work may explore the specific contributions of BMPs from each secreting cell type.

In addition to an elevation of inhibitory factors, a number of pro-neurogenic secreted proteins have been found to decrease with aging. These include vascular endothelial growth factor (VEGF), insulin growth factor-I (IGF-1), IGF-2, FGF-2, and Wnt3, and direct administration of several of these factors can rescue the age-related decline in neurogenesis. All of these proteins can be secreted by astrocytes, which produce lower levels of all of these factors with aging (Shetty et al. 2005, Bernal & Peterson 2011, Okamoto et al. 2011, Miranda et al. 2012). However, it is interesting to note in this context that unlike microglia, the total number of astrocytes in the hippocampus is generally believed to remain consistent throughout aging (Shetty et al. 2005), suggesting astrocytes may instead undergo age-associated, intrinsic changes that alter activities and functions that in turn influence neighboring NSCs.

The production of these pro-neurogenic proteins is also not limited to astrocytes. For instance, IGF-1 and IGF-2 are also produced by microglia, and their production levels are differentially regulated by the activation state of these immune cells (Suh et al. 2013). Both IGF-1 and IGF-2 signal through the IGF-1R expressed on NSCs to regulate proliferation (Åberg et al. 2003, Bracko et al. 2012), and thus local changes in the levels of these proteins in the hippocampus can directly impact neurogenesis. Additionally, IGF-1 is also found as a blood-borne circulating protein that can mediate the positive effects of external experiences, such as exercise, on neurogenesis (Trejo et al. 2001). The IGFs have been of particular interest in the aging field due to their fluctuations in expression across lifespan and correlation with periods of neurogenesis, and direct administration of IGF-1 (Lichtenwalner et al. 2001) or IGF-2 (Steinmetz et al. 2016) to the hippocampus can rescue the aging-related decline in NSC proliferation and even some aspects of memory loss.

VEGF is expressed by not only astrocytes but also neurons and endothelial cells (Cao et al. 2004), as well as by the NSCs themselves, which can have autocrine effects on neurogenesis (Kirby et al. 2015). Furthermore, as a classic angiogenic factor, VEGF likely also regulates the NSCs indirectly through vascular remodeling (Licht et al. 2016). Restoring VEGF levels in the brains of aged animals (in this case through conditional transgenic induction) attenuated the age-related decline in hippocampal neurogenesis and improved memory performance (Licht et al. 2016). The VEGF restoration could have acted directly on NSCs, though because the VEGF exposure was short-term and episodic in this study, the improvements in neurogenesis were also attributed to a rejuvenation of the niche vasculature, which hypothetically could have longer-lasting effects on the neurogenic microenvironment beyond the initial upregulation. This exemplifies the complex interplay of cellular communication networks within the adult neurogenic niche, in which even a single factor can have multi-faceted effects.

Cell-Contact Dependent Signals

In addition to secreted signals, cell-contact dependent signaling mechanisms, in which adjacent cells communicate directly with one another through membrane bound proteins, can regulate NSCs. Though the number of such pathways is perhaps less numerous than secreted signals, cell-contact dependent mechanisms have the potential to exert important roles within the adult neurogenic niche, especially considering the essential roles that they play in neural development. For example, within the developing nervous system Eph/ephrin signaling is critical for axon guidance and proper cell migration, and Notch signaling maintains neural progenitor cells in a proliferating state and prevents premature differentiation (Louvi & Artavanis-Tsakonas 2006). Following early development however, Eph receptors and ephrin ligands, as well as components of the Notch pathway—i.e., the receptor Notch1, the ligands Jagged1 and Jagged2, and the downstream target Hes5—are still expressed in the dentate gyrus (Stump et al. 2002, Chumley et al. 2007, Hara et al. 2010). These two pathways also regulate key aspects of adult neurogenesis (Jiao et al. 2008, Ashton et al. 2012, Wilhelmsson et al. 2012). However, only Notch has been described in the context of aging and hippocampal neurogenesis, and even then only somewhat peripherally.

Lugert et al. (2010), using a reporter of canonical Notch signaling (Hes5::GFP), found that Notch activity defines a distinct subpopulation of early progenitor cells in the adult SGZ. The overall density of this Hes5::GFP+ population was not significantly reduced in the SGZ of aged mice, but the fraction actively undergoing division dramatically decreased. This suggests that reduced neurogenesis with age is not due to a loss of Notch-dependent NSCs but rather to their transition to quiescence (Lugert et al. 2010). Although in this study expression of the downstream Notch target *hes5* did not change with aging, other studies of the SVZ niche have found age-associated decreases in both Notch and Jagged1 expression (Givogri et al. 2006, Sun et al. 2013). Expression of Jagged1 on juxtaposed astrocytes inhibits differentiation of adult NSCs (Wilhelmsson et al. 2012), and another Notch ligand, Delta-like 1 (Dll1) is similarly necessary for maintaining NSC quiescence (Kawaguchi et al. 2013). Interestingly, Lugert et al. also found that Hes5::GFP+, Notch-dependent NSCs could be “re-activated” in aging mice, such that under the right conditions, the remaining quiescent cells could still enter a proliferative state. Thus understanding how different Notch ligands regulate the balance between quiescence, proliferation, and differentiation in the aged hippocampus may well be of interest for identifying interventions to improve the age-associated reductions in neurogenesis. Furthermore, as most studies examining Notch and Notch ligand expression in aging have focused on the SVZ, much remains to be explored for this pathway in the aging hippocampus.

The epidermal growth factor receptor (EGFR) has also been considered for its role in aging neurogenesis, though questions remain. EGFR can function via both secreted and cell-contact dependent mechanisms since the ligands for this receptor (EGF, TGF- α , heparin-binding EGF (HB-EGF), amphiregulin, betacellulin, and epiregulin) have both membrane-bound and soluble forms, and these forms can have differential effects on the receiving, EGFR-expressing cell (Dong & Wiley 2000). SGZ NSCs express EGFR (Okano et al. 1996), and the pro-proliferative effects of EGF are well-described, to the extent that it is often included in the proliferation growth medium for culturing NSCs. The TGF- α ligand is also pro-proliferative and is expressed by hippocampal neurons (Ferrer et al. 1995, Alipanahzadeh et al. 2014). Aging leads to a decrease in EGFR and TGF- α , however, as with Notch, these changes have thus far only been described for the SVZ (Enwere et al. 2004, Moraga et al. 2015).

Extracellular Matrix Signals

Whereas the secreted and cell-contact dependent cues discussed above can be considered primarily biochemical signals, the ECM can exert both biochemical and biophysical effects on stem cell functions. On the biochemical side, motifs within ECM molecules bind directly to receptors on stem cells to regulate fate and function. In addition, ECM proteins and proteoglycans can have binding sites for soluble factors (*e.g.* heparan sulfate), and they can thereby modulate the activity and/or availability of those factors. However, the mechanical properties of the ECM such as stiffness can also modulate NSC behavior (Saha et al. 2008, Keung et al. 2011). How then, might ECM alterations with aging impact neurogenesis functions?

Reelin is a large extracellular glycoprotein that during development is essential for normal migration of cells in the neocortex, cerebellum, and hippocampus. In addition to this migration function, however, Reelin also regulates adult hippocampal neurogenesis, as Reelin deficiency results in reduced NSC proliferation and neuronal differentiation, but increased gliogenesis, in the adult SGZ (Zhao et al. 2007, Sibbe et al. 2015). Furthermore, in the aged hippocampus normal Reelin expression is reduced, and aberrant Reelin-enriched “plaques” accumulate, suggesting that production, processing, and signaling associated with this protein become impaired (Knuesel et al. 2009). The mechanism by which Reelin acts on NSCs is not yet well understood, as this likely occurs through indirect signals. One possibility, however, is that this protein helps to maintain the structure of the dentate gyrus, and its loss of function, perhaps through aging, leads to decreased neurogenesis.

Similarly to Reelin, heparan sulfate proteoglycans (HPSGs) and laminin have been identified as components of fibrillar aggregates found in the aged brain, as well as in A β plaques of Alzheimer’s disease models (Jucker & Ingram 1994, Morawski et al. 2014). Though HPSGs can regulate NSCs by binding, presenting, and sequestering growth factors, and thus control the availability of these chemical cues to receiving cells (Mercier 2016), the effects of age-associated HPSG aggregates are not clear. As with Reelin, these accumulations could be pathological in nature, and it would be interesting to examine whether age-related aggregations of HPSGs alter the availability of growth factors to NSCs and thereby contribute to neurogenesis deficits with aging. Laminins, meanwhile, could act directly via signaling through β 1-integrin, a receptor that is expressed by NSCs in the adult SGZ and is critical for regulating neural versus astrocytic differentiation and maintaining the NSC pool (Porcheri et al. 2014, Faissner & Reinhard 2015, Brooker et al. 2016). β 1-integrin also binds and mediates signaling of another ECM protein, tenascin-R, which apparently negatively regulates NSC proliferation in the adult SGZ (Xu et al. 2014). While the possible role of β 1-integrin in the decline of neurogenesis with aging has not been directly explored, it is interesting that integrin signaling has been implicated in the aging of various other systems in multiple organisms, including cardiac aging in *Drosophila* (Nishimura et al. 2014) and longevity in *C. elegans* (Kumsta et al. 2014).

Like the laminins and tenascin-R, the ECM molecule glycosaminoglycan hyaluronan (HA) can act directly on NSCs to regulate neurogenesis. The HA receptor, CD44, is expressed by NSCs in the adult SGZ, and CD44-null NSCs demonstrate increased proliferation rates and delayed neuronal maturation, while treatment with HA correspondingly inhibits proliferation in wildtype, but not CD44-null, NSCs (Su et al. 2017). Furthermore, HA is elevated in the aged SGZ (Su et al. 2017). β 1-integrin signaling and HA/CD44 signaling could thus both be interesting avenues for future research on the impact of the aging ECM on adult neurogenesis.

Finally, there is emerging evidence that biophysical properties of the NSC microenvironment regulate proliferation and differentiation. The geometry, density, and volume of the extracellular space, for example, can impact signaling between cells of the neurogenic niche. Specifically, these parameters have been examined for their role in the diffusion behavior of signaling factors within the brain. Syková et al. (2002) examined extracellular space diffusion parameters in young and aged rats and found a reduction in hippocampal volume,

ECM molecules, and diffusion in aged animals. In addition, the authors examined hippocampal-dependent learning tasks in the same animals, and upon separating the groups by performance, found that the most impaired aged learners had significantly lower volume and diffusion parameters even compared to mildly impaired learners in the same age group (Syková et al. 2002).

The ECM also contributes to brain tissue stiffness, the extent to which a material deforms upon application of a force. To examine the impact of stiffness on NSC behavior, the Schaffer and Healy laboratories developed synthetic hydrogel culture systems with variable elastic moduli and found that modulus strongly influences neuronal vs. astrocytic differentiation of adult hippocampal NSCs, with softer gels favoring neurons and harder gels promoting astrocytes (Saha et al. 2008). In addition, the hippocampal NSC niche has local stiffness gradients (Luque et al. 2016). Though changes in brain stiffness have been attributed to pathology associated with neurodegeneration, cancer, and acute injuries that cause glial scarring, the reported research on brain stiffness parameters in elderly individuals is more limited, with most age-related studies focusing on early development versus young adult brains. Two studies used magnetic resonance elastography (MRE) to measure tissue stiffness non-invasively in patients, and the conclusions from this work were that the human brain softens slightly in advanced age (Sack et al. 2009, Arani et al. 2015). However, a very recent study using Atomic Force Microscopy (AFM) found no significant effect of age on the stiffness of the hippocampi of mice (Jorba et al. 2017). Additional examination of this area is warranted, as effects on brain structure could be differentially affected by variable age-associated factors (such as the presence of plaques or vascular changes), and furthermore the overall influence of tissue mechanics on brain functions is still relatively unknown.

Concluding Remarks

The cells, factors, and modes of signaling described above collectively begin to form a picture of the signaling network functioning within the hippocampal neurogenic niche. This image is not complete, as many factors, both biochemical and biophysical, likely remain to be discovered. Nevertheless, the studies conducted to date have already implicated numerous members of this signaling network as playing a role in the age-associated decline in neurogenesis.

Secreted signals make up the majority of known age-associated neurogenesis factors, in part due to the great number of soluble proteins in general that mediate signaling. In addition, intriguing recent work indicates that systemic factors can regulate aging at the organismal level and in particular within the brain. By examining the neurogenic niche through the lens of cell signal transduction mechanisms, it also become evident that our knowledge of contact-dependent and ECM signaling interactions within this microenvironment is much more limited. Juxtacrine and matrix signals are recently becoming more well-recognized for their part in regulating the adult neurogenic niche of the hippocampus, but little is known about their modulation with aging. As aging is the primary risk factor for the majority of neurodegenerative diseases, understanding why aged microenvironments are in general less

conducive to maintaining healthy NSC populations will be a significant step towards harnessing stem cell treatments for these afflictions.

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Fig. 1.

Cell signaling mechanisms that regulate neural stem cell fate and functions

Within the hippocampal neurogenic niche, adult neural stem cells are subject to regulation by a host of signaling factors. These signals may be defined by the extrinsic mechanism in which they are presented to the receiving stem cell. The specific signals that are discussed in this review are depicted here as secreted, cell-contact dependent, or extracellular matrix cues. Icons representing the signals are color-coded based on the cellular source from which they are derived.

Table 1
Summary of SGZ neurogenic niche signaling factors

Specific proteins that are discussed throughout the review are summarized below. For cell-contact dependent factors, the NSC-bound receptor is listed first with the hypothesized associated ligand indicated in parentheses.

Factor	Effects on Neurogenesis	Changes with Aging	Source	References
Secreted				
CCL11	Inhibits neuroblast number in vivo	Increases	Plasma; other?	(Villeda et al. 2011)
B2M	Inhibits neuroblast number in vivo	Increases	Plasma; other?	(Smith et al. 2015)
IL-1 β	Inhibits NPC proliferation in vivo	Increases	microglia	(Gemma et al. 2007, Koo & Duman 2008, Bachstetter et al. 2011)
IL-6	Inhibits differentiation in vitro	Increases	Microglia; astrocytes?	(Vallières et al. 2002, Monje et al. 2003, Barkho et al. 2006, Nakanishi et al. 2007, Oh et al. 2010, Njie et al. 2012)
TNF- α	Increases NSC apoptosis	Increases	microglia	(Cacci et al. 2005, Sheng et al. 2005, Widera et al. 2006, Njie et al. 2012)
TGF- β	Increased neuronal differentiation in vivo Decreased differentiation and proliferation in vivo via overproducing astrocytes and in vitro Inhibition of pathway led to increased NPC proliferation and neuronal differentiation in vivo	Increases	Microglia; Astrocytes; endothelial cells	(Battista et al. 2006) (Buckwalter et al. 2006) (Yousef, Conboy, et al. 2015)
BMP4 and BMP6	Inhibits NSC proliferation	Increases	endothelial cells; microglia	(Yousef, Morgenthaler, et al. 2015)
FGF-2	Promotes NPC proliferation	Decreases	astrocytes	(Shetty et al. 2005, Bernal & Peterson 2011)
Wnt-3	Promotes NSC survival, proliferation, and neuronal differentiation	Decreases	astrocytes	(Okamoto et al. 2011, Miranda et al. 2012)
IGF-1	Promotes NSC proliferation and neuronal differentiation	Decreases	Astrocytes; microglia; plasma	(Trejo et al. 2001, Lichtenwalner et al. 2001, Åberg et al. 2003, Shetty et al. 2005, Suh et al. 2013)
IGF-2	Promotes NSC proliferation	Decreases	Astrocytes; microglia; NSCs	(Bracko et al. 2012, Suh et al. 2013, Ferrón et al. 2015)
VEGF	Promotes proliferation and neuronal differentiation; might also act indirectly by remodeling vasculature	Decreases	Astrocytes; neurons; endothelial cells; NSCs	(Cao et al. 2004, Shetty et al. 2005, Bernal & Peterson 2011, Kirby et al. 2015, Licht et al. 2016)
Cell-Contact Dependent				

Factor	Effects on Neurogenesis	Changes with Aging	Source	References
Notch (Jagged)	Maintains a pool of undifferentiated, proliferating NPCs while repressing neuronal differentiation	Decreases?	Jagged ligand is expressed by astrocytes	(Stump et al. 2002, Givogri et al. 2006, Lugert et al. 2010, Wilhelmsson et al. 2012, Kawaguchi et al. 2013, Sun et al. 2013)
EGFR (TGF- α)	Promotes NPC proliferation	Decreases?	Neurons	(Ferrer et al. 1995, Okano et al. 1996, Dong & Wiley 2000, Enwere et al. 2004, Alipanahzadeh et al. 2014, Moraga et al. 2015)
Extracellular Matrix				
Reelin	Promote NSC proliferation and neuronal differentiation; inhibits glial differentiation	Decreases; accumulates in pathological plaques	Extracellular	(Zhao et al. 2007, Knuesel et al. 2009, Sibbe et al. 2015)
HSPGs	Regulates NSCs through binding and release of growth factors	Accumulates in plaques	Extracellular	(Jucker & Ingram 1994, Morawski et al. 2014, Mercier 2016)
Laminins, tenascin-R	Regulate neuronal differentiation and NSC proliferation through β 1-integrin	Laminins are components of age-associated aggregates	Extracellular	(Xu et al. 2014, Porcheri et al. 2014, Faissner & Reinhard 2015, Brooker et al. 2016)
HA	Ligand for CD44, which is expressed on NSCs and inhibits proliferation	Increases	Extracellular	(Su et al. 2017)
Diffusion	Affects transmission of signals within the neurogenic niche	Decreases		(Syková et al. 2002)
Stiffness	Softer substrates promote neural differentiation over glial differentiation	Varying reports; decreasing stiffness using MRE but no changes observed with AFM		(Saha et al. 2008, Sack et al. 2009, Keung et al. 2011, Arani et al. 2015, Luque et al. 2016, Jorba et al. 2017)