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The Role of the Microenvironmental Niche in Declining Stem-Cell Functions Associated with Biological Aging

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Aging is strongly correlated with decreases in neurogenesis, the process by which neural stem and progenitor cells proliferate and differentiate into new neurons. In addition to stem-cell-intrinsic factors that change within the aging stem-cell pool, recent evidence emphasizes new roles for systemic and microenvironmental factors in modulating the neurogenic niche. This article focuses on new insights gained through the use of heterochronic parabiosis models, in which an old mouse and a young circulatory system are joined. By studying the brains of both young and old mice, researchers are beginning to uncover circulating pro-neurogenic "youthful" factors and "aging" factors that decrease stem-cell activity and neurogenesis. Ultimately, the identification of factors that influence stem-cell aging may lead to strategies that slow or even reverse age-related decreases in neural-stem-cell (NSC) function and neurogenesis.

Aging is a process by which cells alter their biochemical and genetic functions through cell-intrinsic and cell-extrinsic (microenvironment and systemic) factors. Aging manifests in many ways including dysregulation of tissue homeostasis and the gradual loss of regenerative capacity (Lopez-Otin et al. 2013). One of the main goals of regenerative medicine and stem-cell biology is to overcome the deleterious cellular effects of aging and, ultimately, to reverse them. Stem cells play a two-pronged role in tissue maintenance through divisions: on one hand, stem cells divide asymmetrically to produce a daughter cell that can differentiate and maintain tissue homeostasis and repair tissue damage; on the other hand, stem cells must divide asymmetrically to maintain themselves ("self-renewal") and to provide a long-lasting source of cells with stem-like potential. To this end, one of the long-term effects associated

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with aging is the loss of cell "stemness" in aging tissue, either through stem cells dividing symmetrically into two new daughter cells and thus depleting the stem-cell pool, or by replicative senescence, whereby cells with stem-like potential exit the cell cycle and no longer contribute to tissue maintenance. In the either case, loss of stem cells can occur through cell-intrinsic effects or from loss of the microenvironmental niche that normally facilitates continued asymmetric divisions of stem cells and maintenance of homeostasis.

In the adult brain, stem cells persist in several discrete areas, contributing to adult neurogenesis. Neurogenesis is the process by which a proliferating cell exits the cell cycle and differentiates into a neuron, ultimately incorporating into the neuronal circuitry. Although it is widespread during embryogenesis, neurogenesis becomes increasingly restricted as the animal ages. Specifically in mice and humans, neurogenesis within the cortex of the brain is complete during the early postnatal period. However, there are at least two areas of the brain with well-established and substantial neurogenesis throughout the life of most mammals: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus. Despite ongoing research into the cellular origins of neurogenesis, debate continues as to the stem-like cell within each of these two regions (Carlen et al. 2009; Ma et al. 2009; Bonaguidi et al. 2011, 2012; Encinas et al. 2011; Goritz and Frisen 2012; DeCarolis et al. 2013). Although the identity of the stem cell remains controversial, one thing is clear: Cells with stem-like and neurogenic potential persist in the SVZ and SGZ and new neurons are born throughout the mammalian life, including in humans (Eriksson et al. 1998; Sanai et al. 2004, 2011; Curtis et al. 2007). In rodent models, SGZ stem-like populations give rise to new neurons that migrate a short distance in to the dentate gyrus granular layer and become new granule cells. In contrast, new neuroblasts derived from SVZ stem cells migrate a long way in what is known as the rostral migratory stream, from the SVZ to the olfactory bulb (OB), where they become new inhibitory neurons. In the adult hippocampus, new immature neurons are highly plastic and hypothesized to have crucial roles in memory function (Clelland et al. 2009; Sahay et al. 2011; Aimone et al. 2014; Rangel et al. 2014). New olfactory neurons may play a role in olfactory memory or discrimination (Lazarini and Lledo 2011).

Some aspects of these adult neurogenic systems appear to be conserved in humans. In the human, the dentate gyrus has decreased levels of neurogenesis with age, but recent work by Frisen and colleagues suggests that the age-related decline is much more gradual than previously thought (Spalding et al. 2013). Neurogenic precursor cells have been observed in the dentate gyrus of humans up to 100 years of age (Knoth et al. 2010). On the other hand, in the human OB, recent evidence suggests negligible amounts of adult neurogenesis (Sanai et al. 2011; Wang et al. 2011; Bergmann et al. 2012; Ernst et al. 2014), despite robust neurogenesis in mouse, rat, and nonhuman primates (Kornack and Rakic 1999; Pencea et al. 2001). Additional work is needed in humans to observe and characterize stem-cell function and neurogenesis.

To this end, we define neural-stem-like cells as cells, which can divide asymmetrically to produce a daughter cell with neurogenic potential while maintaining itself in an undifferentiated state. Our current understanding is that stem-like cells divide infrequently in vivo (Morshead et al. 1994). We define progenitor cells as rapidly dividing cells with neurogenic potential that cannot divide continuously and thus deplete after multiple rounds of successive division (Encinas et al. 2011).

Regarding the important intersections of aging and neurogenesis, two key features are well established. First, as an animal ages, there are fewer dividing cells and fewer neurogenic precursor cells in neurogenic regions in rodents and in humans (Kuhn et al. 1996; Rao et al. 2005, 2006; Ben Abdallah et al. 2010; Spalding et al. 2013). Second, as an animal ages, fewer cells maintain neurogenic potential as they differentiate (Ahlenius et al. 2009; Encinas et al. 2011; Villeda et al. 2011); in other words, as an animal gets older, fewer cells become neurons and more cells become astrocytes, the ma-

jor cell fate alternative for neural precursors that are differentiating after cell cycle exit (although see Rao et al. 2005; Hattiangady and Shetty 2008). There are a number of possible explanations for the age-related decrease in neurogenesis, including the progressive loss of stem cells (as suggested by Encinas et al. 2011 and others), the potentially reversible loss of replicative activity in stem cells (Lugert et al. 2010), or the decrease in permissive microenvironment surrounding the stem cells (as suggested by Bernal and Peterson 2011; Villeda et al. 2011). It has also recently been found that stem and progenitor cells may also regulate their own microenvironment via secreted factors (Mosher et al. 2012; Butti et al. 2014; Kirby et al. 2015). For example, Wyss-Coray and colleagues recently showed that undifferentiated adult neural stem and progenitor cells secrete up to a third of the vascular endothelial growth factor (VEGF) in the young adult dentate gyrus, and that loss of VEGF from just the stem and progenitor population causes long-term depletion of the neurogenic pool (Kirby et al. 2015). VEGF is a neurogenic niche factor known to decrease with aging, and this recent work suggests the possibility that the loss of local growth factors that regulate neurogenesis may not be solely caused by local astrocytes. However, the secretome of stem and progenitor cells and its contribution to aging of the brain remain relatively unexplored.

In this review, we focus on changes associated with the neural-stem-cell (NSC) niches in the brain. Our current understanding is limited regarding the cellular and molecular mechanisms behind the diminished capacity for neurogenesis in the adult brain, but likely there is strong interplay between the stem-like cells in the brain and their permissive neurogenic niche. Recent studies have attributed the decline in neuron production with loss of NSCs in the hippocampus (Encinas et al. 2011) and in the SVZ (Maslov et al. 2004). However, other studies have argued that the number of stem-like cells (Hattiangady and Shetty 2008; Lugert et al. 2010) and the number of neurosphere-forming cells remains constant with aging (Ahlenius et al. 2009). These results suggest that the neurogenic niche becomes less supportive (Luo et al. 2006; Ahlenius et al. 2009; Bouab et al. 2011) and/or that the NSCs shift into a quiescent state (Hattiangady and Shetty 2008; Lugert et al. 2010; Bouab et al. 2011). It is likely that a combination of factors contribute to the diminished neurogenic potential of the brain neurogenic niches, and we highlight what is known and emphasize that there is still much that we do not understand about aging and stem cells in the brain.

Although there has been a surge in research and reviews on aging and stem cells (Pollina and Brunet 2011; Artegiani and Calegari 2012; Conboy and Rando 2012; Lee et al. 2012; Lopez-Otin et al. 2013; Rolando and Taylor 2014), unfortunately, relatively little is known about aging NSCs, in part, because of technical challenges. Within the context of the adult mammalian brain, it has been difficult to identify stem cells from progenitor cells (DeCarolis et al. 2013; Knobloch et al. 2014). Further, protocols have been established to grow cells with stem-like potential in vitro as neurospheres or in monolayers (Reynolds and Weiss 1992; Morshead et al. 1994; Babu et al. 2007), but these protocols require removing cells from their in vivo microenvironmental niche. Given the complex interplay between neurogenic cells and their niches (Palmer et al. 2000; Shen et al. 2008; Tavazoie et al. 2008), new paradigms have emerged to explore age-related changes in neurogenesis within the complex stem-cell niche. The parabiosis model is one such method recently applied to the adult stem-cell niche and revealed numerous novel insights to how stem cells respond to an aging environment. In parabiosis, two mice are surgically connected and their circulatory systems become partially shared (Conboy et al. 2005). By pairing a young mouse with an older mouse in "heterochronic" pairings (Conboy and Rando 2012; Paul and Reddy 2014), researchers have explored age-associated changes in stem-cell function in muscle (Conboy et al. 2005; Brack et al. 2007), the heart (Loffredo et al. 2013), and, recently, the brain (Ruckh et al. 2012; Katsimpardi et al. 2014; Villeda et al. 2011, 2014). This work will explore briefly the cell-intrinsic changes associated with

stem-cell decline in aging, then focus more broadly on the niche-specific effects that suggest that systemic circulation and the vasculature interposed within the neurogenic niche.

CELL-INTRINSIC CHANGES

Accumulating evidence suggests a battery of changes within stem cells that correlate with aging. For example, in nonneuronal systems like the hematopoietic system, stem cells reduce proliferation and differentiation capacity, accumulate marks of DNA damage, reduce activity of telomerase, change epigenetic marks, and alter transcription factor profiles (DeCarolis et al. 2008; Jaskelioff et al. 2011; Lopez-Otin et al. 2013). Importantly, although these age-related changes have been described in peripheral stem-cell pools, aging factors in the brain and NSC pools remain largely unexplored and poorly understood.

The best-characterized change related to neurogenesis is the significant decrease in proliferative capacity of the neurogenic regions with increasing age. The precipitous drop in proliferation of neurogenic cells was first characterized in the dentate gyrus of the rodent (Kuhn et al. 1996) and later in the OB (Molofsky et al. 2006), as noted above.

There is some limited evidence for cell-intrinsic aging of NSCs in adults. For example, recent studies suggest the accumulation of DNA damage (as indicated by genomic marks like γ-H2AX and 53BP1) in stem-cell populations like the hematopoietic system (Rossi et al. 2007) and in the dentate gyrus neurogenic niche (DeCarolis et al. 2014). Other reports have suggested the accumulation of mutations in DNA and genomic instability within the NSC pool with age (Mikheev et al. 2012; Dong et al. 2014) but additional research is needed. Other cell-intrinsic facets of aging have been characterized in peripheral stem-cell pools (Lopez-Otin et al. 2013), including decreased telomerase activity associated with shortened telomeres (Sahin and Depinho 2010), epigenetics changes (Webb et al. 2013; Brunet and Berger 2014), and asymmetric nonrandom chromosome segregation (Charville and Rando 2011). However, similar changes in NSC pools are under investigation. Specifically, telomerase activity has been an active area of research, and promoting telomerase activity increases neurogenesis in vitro and in vivo (Caporaso et al. 2003; Ferron et al. 2009; Jaskelioff et al. 2011; Liu et al. 2012). These studies suggest that reversing the declines in telomerase activity can prevent aging-associated declines in stem-cell function and cognition.

SYSTEMIC FACTORS AND THE "NICHE"

The neurogenic niche that surrounds adult neural stem and progenitor cells is populated by a variety of cell types, including astrocytes, microglia, mature neurons, and endothelial cells. All of these cell types show age-related changes that could impact adult NSCs. Both astrocytes and microglia show increased activation with age (Conde and Streit 2006; Norden and Godbout 2013; Sierra et al. 2014; Rodriguez-Arellano et al. 2015) potentially as a part of increased immune activation with aging (termed "inflammaging"). This activation likely changes their secretory profile. For example, secretion of neurogenic growth factors commonly derived from glia, such as fibroblast growth factor 2 (FGF-2) and VEGF, decreases prominently with age (Shetty et al. 2005; Bernal and Peterson 2011). The vasculature also may deteriorate with age, occupying less volume and providing less blood flow to brain regions, such as the SVZ (Katsimpardi et al. 2014). If any of these changes are necessary or sufficient for inducing age-related neurogenic decline remains unclear. However, the potential involvement of the vasculature and immune responses strongly suggests a third player in inducing the aging phenotype in NSCs: the systemic environment.

SYSTEMIC CIRCULATION

The role of systemic circulation in aging of NSCs appears to be particularly potent. Like aging muscle, the aging brain has a persistent population of resident stem cells that lose proliferative activity with age. Using the heterochronic parabiosis model, Villeda, Wyss-Coray,

and colleagues (Villeda et al. 2011) have recently shown that this proliferative capacity can be bidirectionally modulated by the "age" of the systemic circulation. Heterochronic young mice have significantly reduced numbers of new, doublecortin (DCX^+)-labeled neurons in the hippocampus, whereas their older counterpart shows partial restoration of new DCX^+ neuron number (Villeda et al. 2011). A similar increase in progenitor proliferation with parabiosis to a younger mouse has been recently found in the SVZ (Katsimpardi et al. 2014), suggesting that the rejuvenating effects of young blood extend to both neurogenic niches. However, it remains unknown which neurogenic populations are most affected by systemic factors. Are these stem cells or progenitors (or both) that are induced to proliferate? The answer to this question has relevance to the sustainability of young blood as a therapeutic intervention because stimulation of only progenitors could wane over repeated treatments if the stem-cell population does not replenish the progenitor pool.

Although parabiosis allows for sharing of both soluble blood-derived proteins and circulating cell populations, it appears that the operative components of the blood for aging of stem cells are soluble plasma proteins. Parabiotic pairing with a GFP^+ mouse reveals very little infiltration of GFP^+ cells in the brain of a wild-type parabionts (Villeda et al. 2011), suggesting that direct cellular contribution is unlikely. Moreover, the antineurogenic effects of heterochronic pairing with an old mouse can be recapitulated by injection with plasma isolated from aged mice (Villeda et al. 2011). Several recent studies have implicated growth differentiation factor 11 (GDF11), a transforming growth factor β (TGF-β) family member, as a key blood-derived "youthful" factor that reverses aging of SVZ proliferation, vascular deterioration, skeletal muscle, and heart (Loffredo et al. 2013; Katsimpardi et al. 2014; Sinha et al. 2014). Recent work suggests that the role of systemic GDF11 in aging of other tissues may differ from the brain (Egerman et al. 2015). CCL11, a circulating immune cytokine, has also been shown to be associated with age-related decline in hippocampal neurogenesis (Villeda et al. 2011).

The question of which factors drive the rejuvenating properties of young blood remains open. Most likely, the rejuvenating cocktail is complex and possibly tissue-specific such that factors or mechanisms that rejuvenate myogenic progenitors may not be the same ones that rejuvenate neural progenitors. More broadly, the reliance on soluble factors may even differ for different tissues and cell types. Although muscle cell aging is rejuvenated by young serum-derived proteins much like CNS stem cells (Conboy et al. 2005; Brack et al. 2007), oligodendrocyte progenitor cells (OPCs) appear to be rejuvenated by the cellular component of young blood (Ruckh et al. 2012). Heterochronic parabiosis with a young mouse rescues age-related deficits in OPC-mediated remyelination after injury, but the rescue relies on recruitment of circulating young monocytes to clear myelin debris that then allows resident old OPCs to function better (Ruckh et al. 2012).

Part of determining what factors mediate systemic regulation of CNS stem cells is determining which cells respond directly to soluble factors. For example, although effects of CCL11 on isolated hippocampal NSCs suggest that these cells respond negatively to this "aging" factor (Villeda et al. 2011), numerous other aspects of hippocampal function are impacted by plasma-borne factors and aging, including hippocampal long-term potentiation (LTP) (Villeda et al. 2011, 2014), dendritic spine density (Villeda et al. 2014), immediate early gene expression (Villeda et al. 2014), and vascularization (Katsimpardi et al. 2014). Where do plasma proteins act first? The NSCs? The vasculature? The mature neurons and astrocytes? All these pieces of the neurogenic niche rely on each other extensively, and alterations in one cell population will likely echo through the others. The order of cause and effect is not yet clear. Teasing apart the varied players in maintaining a neurogenic niche on an aging systemic background remains a challenge.

THE VASCULAR NICHE

The reliance of the aging of adult NSCs on circulating plasma-borne proteins is perhaps not

surprising given the highly vascularized nature of both the SVZ and SGZ neurogenic niches. Adult NSCs in both the SVZ and SGZ reside in complex, multicell niches in close association with local capillaries.

The SVZ is covered by a planar vascular plexus spanning its entire length, which is quite distinct from the more segmented capillary supply found in other, nonneurogenic brain regions, such as the cortex (Tavazoie et al. 2008). Proliferating SVZ progenitors and stem cells are found in close association with this vascular supply, especially when repopulating after depletion by antimitotic treatment. The SVZ may also show unique permeability of the blood–brain barrier, allowing small molecules to diffuse through gaps between the astrocytic endfeet that typically insulate the brain from the circulating factors (Tavazoie et al. 2008).

In the SGZ, proliferating cells are similarly found in close apposition to blood vessels (Palmer et al. 2000). There is an intimate asso-

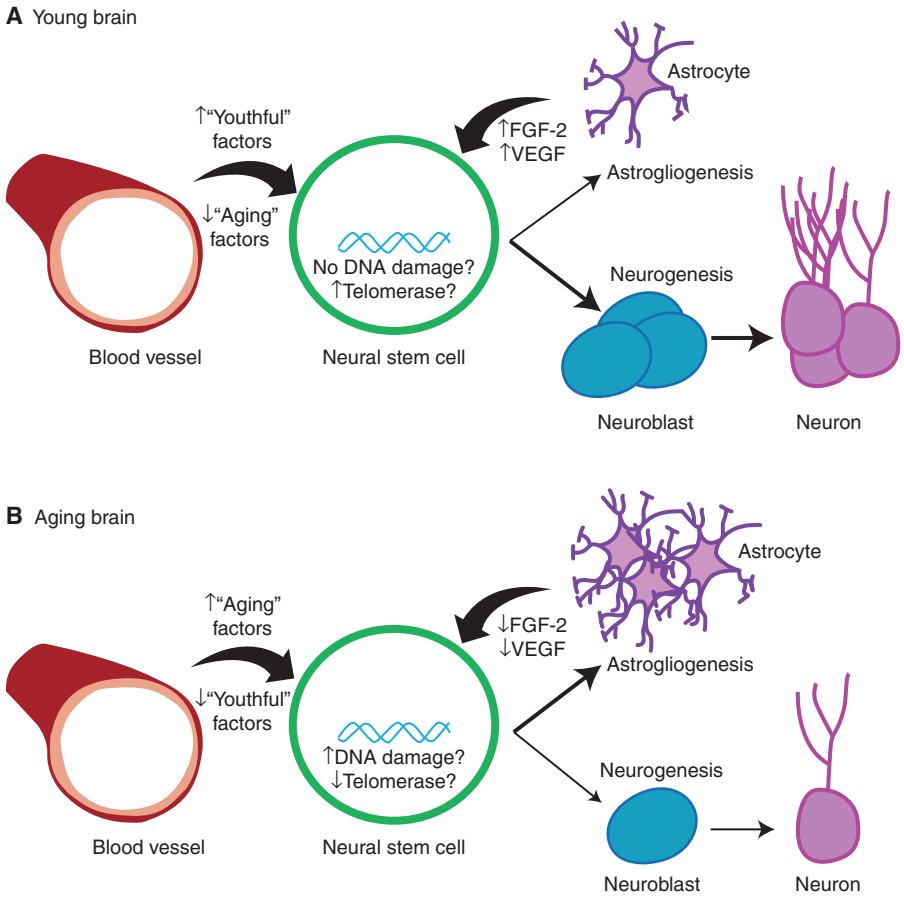

Figure 1. Hypothesized aging effects on neural stem cells. (*A*) In the young brain, neural stem cells (green) have low amounts of DNA damage but high amounts of telomerase activity. Astrocytes (purple) provide trophic support and circulating "youthful" factors from the blood (red) support a neurogenic environment, in which neural stem cells divide into neuroblasts (blue), which mature into neurons (magenta). (*B*) In contrast, in the aging brain, neural stem cells accumulate DNA damage and show decreased telomerase activity. Further, astrocytes provide less trophic support and "aging" factors increase in concentration in blood. In the aging brain, therefore, fewer neuroblasts are produced and neurogenesis is decreased; on the other hand, more astrocytes are produced. FGF, Fibroblast growth factor; VEGF, vascular endothelial growth factor.

ciation between the blood vasculature and neurogenic progenitors in the SGZ (Palmer et al. 2000; Pereira et al. 2007), which has been tied to the neurogenic response after exercise. Specifically, circulating increases in both VEGF and insulin-like growth factor 1 (IGF-1) have been suggested to drive exercise-induced increases in progenitor proliferation (Trejo et al. 2001; Fabel et al. 2003).

The vasculature may not simply be a means of conveying blood-borne factors, though, as it shows prominent age-related degradation that may be a driving factor in cognitive decline and neurodegenerative disease (Tarumi and Zhang 2014). Recent work by Katsimpardi, Rubin, and colleagues (2014) suggests that this decline in vascularization in the SVZ is closely linked with the decline in neurogenesis in this area and that both declines can be rescued by exposure to a young systemic environment. However, it remains unclear whether vascular endothelial cells and neural progenitors are both responding to systemic factors directly or to some indirect signal from each other or another niche cell type. The enhanced contact of adult neural stem and progenitor cells with the vasculature increases progenitor cell exposure both to the systemic circulation and to the vascular endothelium itself, which secretes a variety of proteins that impact NSC maintenance (Shen et al. 2004). The secretory profile of endothelium could change depending on the composition of the blood supply and thereby drive changes in closely associated stem and progenitor cells.

CONCLUSIONS

Taken together, current literature supports that a combination of factors contribute to changes in NSC function in aging, summarized in Figure 1. In the young brain, the local microenvironment combined with young stem cells produce an abundance of new neurons. Circulating "youthful" factors lead to the activation of cAMP-response element-binding protein (Creb), which promotes neurogenesis (Villeda et al. 2011). In a similar vein, Rubin and colleagues identified GDF11 as a circulating factor promoting vascularization and neurogenesis (Katsimpardi et al. 2014). The niche astrocytes in the young brain also provide abundant trophic support to promote neurogenesis, including FGF-2, VEGF, and IGF (Shetty et al. 2005); as the brain ages, growth factor secretion decreases and, consequently, so does neurogenesis. Taken together, these results suggest that some (though likely not all) age-mediated decreases in neurogenesis can be rescued and perhaps even reverse the cognitive decline associated with aging.

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