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Review

The circulatory systemic environment as a modulator of neurogenesis and brain aging

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ABSTRACT

The ability of the adult brain to generate newly born neurons dramatically declines during aging, and has even been proposed to contribute, in part, to age-related cognitive impairments. While intrinsic molecular mechanisms underlying decreased neurogenesis during aging have begun to be elucidated, relatively little is still known as to the contribution of the systemic environment. Interestingly, immune signaling has quickly emerged as a key negative regulator of adult neurogenesis, and has more recently been functionally linked to the aging circulatory systemic environment. In this review we examine the role of the aging systemic environment in regulating adult neurogenesis and cognitive function. We discuss recent work from our group using the aging model of heterochronic parabiosis – in which the circulatory system of two animals is connected – to highlight the contribution of circulatory immune factors to age-related impairments in adult neurogenesis and associated cognitive processes. Finally, we propose the possibility of combating brain aging by tapping into the 'rejuvenating' potential inherent in a young circulatory systemic environment.

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Contents

The possibility of harnessing stem cells to reverse normal aging is an interesting prospect, but one that first requires a better understanding of how the aging process itself modulates tissue specific stem cell activity to maintain the structure and function of organs. This understanding is of particular interest in tissues with a high incidence of age-dependent degeneration and degenerative diseases and limited regenerative capacity due to low stem cell activity during aging. In this context investigating the effect of aging on neural stem cell (NSC) function in the central nervous system (CNS) is of particular interest due to the associated onset of cognitive impairments and lack of neural repair in response to neurodegenerative diseases such as Alzheimer's disease [1].

Stem cells in the adult CNS have been observed in mammals including rodents, primates and humans primarily in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampus [2–5]. Adult NSCs are a relatively quiescent population that can both self-renew and give rise to more rapidly dividing progenitors that in turn produce neurons (neurogenesis), as well as astrocytes and oligodendrocytes (gliogenesis) [6,7]. Ultimately, newly born neurons in the SVZ migrate and incorporate in the olfactory bulb where they are thought to mediate olfaction [8]. In a similar fashion neurons born in the SGZ become granule neurons that integrate into the existing circuitry of the hippocampus and have been recently implicated to directly influence learning and memory [9,10]. Previous studies have established that adult NSCs are not distributed throughout the CNS at random, but rather that they are centralized to local microenvironments, or neurogenic niches [7,11]. These niches are composed of surrounding cells such as astrocytes and oligodendrocytes, soluble factors, membrane bound molecules and extracellular matrix molecules that together are hypothesized to provide the permissive cues necessary for NSC maintenance, differentiation, and neural integration into the circuitry of the brain [7,11]. Importantly, the neurogenic niche is

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exclusively concentrated around blood vessels, which allows for the communication with the systemic environment [11–13]. Moreover, brain blood vessels in the SVZ are closely associated with the basal lamina and are thought to modulate cytokines and growth factor availability in the neurogenic niche [11]. To date, while adult NSC populations and their respective microenvironments have been characterized little is still known about both the intrinsic and the extrinsic regulation of NSCs during the aging process.

Aging in mammals is associated with a global decline in the function and regenerative capacity of tissue specific stem cells [14]. In the brain the cellular and molecular composition of the neurogenic niche is dynamically altered during aging. The number of adult NPCs, and subsequently neurogenesis, has been observed to dramatically decline with age [15,16], while neuroinflammation increases [17]. Additionally, this decline in NPC function has now been linked to functional impairments in olfaction and in hippocampal-dependent learning and memory [18–21]. Intracellular studies in the aging brain have demonstrated that the decline in SVZ progenitor function and olfactory bulb neurogenesis is partially mediated by an age-dependent increase in expression of $p16^{INK4a}$, a cycline-dependent kinase inhibitor linked to cellular senescence mechanisms [22]. Subsequently, the disregulation of the polycomb gene Bmi-1 signaling pathway has been shown to promote premature senescence of NPCs [23]. More recently, studies in the SGZ have linked the age-related decrease in adult hippocampal neurogenesis to the transition of actively proliferating NPCs to a more quiescent state regulated by canonical Notch signaling [24]. Interestingly, genes associated with the aging process and longevity also have been shown to regulate NPC function in the adult brain [25–27]. For example, telomerase, the enzyme responsible for repairing genomic DNA damage associated with the aging process, has been shown to induce NPC proliferation upon reactivation in accelerated models of aging [27]. Additionally, FoxO3a, a forkhead transcription factor known to promote lifespan, has been shown to regulate the homeostasis of NPC populations in both the SVZ and SGZ inducing a program of genes that prevents premature differentiation [25]. While such work begins to address how age-related intracellular changes influence the regulation of NPC function, less effort has been focused in understanding how changes to the molecular composition of the neurogenic niche can alter and impair NPC function during normal aging. Indeed, the age-associated reduction in adult neurogenesis may be the result of a decline in the intrinsic responsiveness of NPCs to environmental cues, a disappearance of such environmental cues, or conversely the appearance or accumulation of inhibitory cues.

Interestingly, aging studies done in muscle have demonstrated the importance of peripheral systemic factors in the regulation of stem cell function with age [28,29]. Specifically, in this work *in vivo* exposure of old muscle progenitors to factors from a young systemic environment by heterochronic parabiosis – in which young and old circulatory systems are joined – resulted in the rejuvenation of aged progenitors [28,29]. In light of this work, the proximity of the adult neurogenic niche to blood vessels, together with the composition of the niche itself, raises the possibility that NSC function during the aging process may be regulated by the balance of two independent forces — intrinsic CNS derived cues as previously reported, and external peripheral cues delivered in part by blood. Consistent with this notion changes made to the aging peripheral milieu of adult animals *via* exercise or dietary restriction have resulted in increased levels of neural progenitor proliferation and neurogenesis [30–32]. In particular, the enhancement observed with increased exercise is thought to be mediated in part by elevated levels of circulating growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1), which have both been shown to directly mediate NSC proliferation [33,34]. Coincidently, the levels of IGF-1 decrease with age and the restoration to levels resembling a younger environment up-regulate neurogenesis and improve learning [35]. More recently, investigations looking at MRI measurements of cerebral blood volume (CBV) in the hippocampus demonstrated that exercise selectively increases the CBV of the dentate gyrus [36]. Additionally, exercise-induced increases in the dentate gyrus CBV were found to correlate with postmortem increase in neurogenesis [36]. Together, this body of work argues that the regulation of adult NSC is influenced through changes in the extrinsic cues derived from the systemic environment.

Our group therefore hypothesized that age-related systemic molecular changes could cause a decline in neurogenesis and impair associated cognitive functions during aging [37]. Using an experimental aging model (heterochronic parabiosis) we discovered that the systemic environment regulates neurogenesis in an age-dependent fashion (Fig. 1). Furthermore, these changes in the aging systemic environment can functionally alter the circuitry of the hippocampus by decreasing synaptic plasticity in the young adult brain. Additionally, our work demonstrated that systemically exposing young animals to old plasma is capable of recapitulating the effects of heterochronic parabiosis and physiologically results in cognitive impairments. While the effect of peripherally derived cells has been described to influence adult neurogenesis [38], our data indicate that the influence of molecular changes in the aging systemic environment is truly significant, and one that changes in an age-dependent fashion. Cumulatively, our data links age-related molecular changes in the systemic environment to the decline in adult neurogenesis and associated impairments in synaptic plasticity and cognitive function observed during aging [37]. Our findings point to the potential role of the aging circulatory systemic environment in contributing to the susceptibility of the adult brain to aging associated cognitive impairments (Fig. 1A).

To further understand the involvement of the systemic environment we made use of a targeted proteomic screen. We identified a conserved subset of blood borne chemokines – including CCL2/MCP-1 and CCL11/Eotaxin – whose plasma levels correlate with reduced neurogenesis observed in normal and experimental (*i.e.* heterochronic parabiosis) aging in mice. Importantly, these systemic changes could also be detected in the plasma and cerebral spinal fluid of healthy aging humans. Moreover, mimicking an aged systemic environment by increasing the level of CCL11 in the periphery of young adult mice resulted in a decrease in neurogenesis *in vivo*. At a cellular level we showed that the age-related factor CCL11, could decrease progenitor frequency and neural differentiation *in vitro*, and that the inhibitory effects of systemically administered CCL11 can be mitigated by neutralization either systemically or directly within the central nervous system. Functionally, we could demonstrate that increasing peripheral chemokine levels impairs hippocampal dependent learning and memory. Together this body of work indicates that the decline in adult neurogenesis observed during aging can be attributed, at least in part, to naturally occurring changes in the levels of immune-related factors within the aging systemic milieu [37]. Interestingly, in the adult brain immune signaling is quickly emerging as one of the influential variables modulating stem cell function [39,40] and neurodegeneration [17]. However, to date most research focused on the effect of brain-derived chemokines on adult neurogenesis [39,40], while the influence of the systemic milieu has been poorly investigated. By identifying age-related chemokines classically involved in peripheral inflammatory responses, our work highlights the biological relevance of systemically derived immune factors as pertinent for brain aging.

Notably, our work also demonstrates the potential of the old brain for enhanced neurogenesis and points to the existence of "rejuvenating" factors present in the blood of young animals that remain to be identified (Fig. 1B). While the proteomic platform we used in our current work was sufficient to identify systemic inhibitory 'aging' factors it will be critical for future studies to develop and utilize broader proteomic screens to facilitate the discovery of systemic pro-neurogenic 'rejuvenating' factors with the ability to ameliorate age-related cognitive dysfunction. As an exciting possibility, the identification of such factors would provide a rich source of potential therapeutic targets

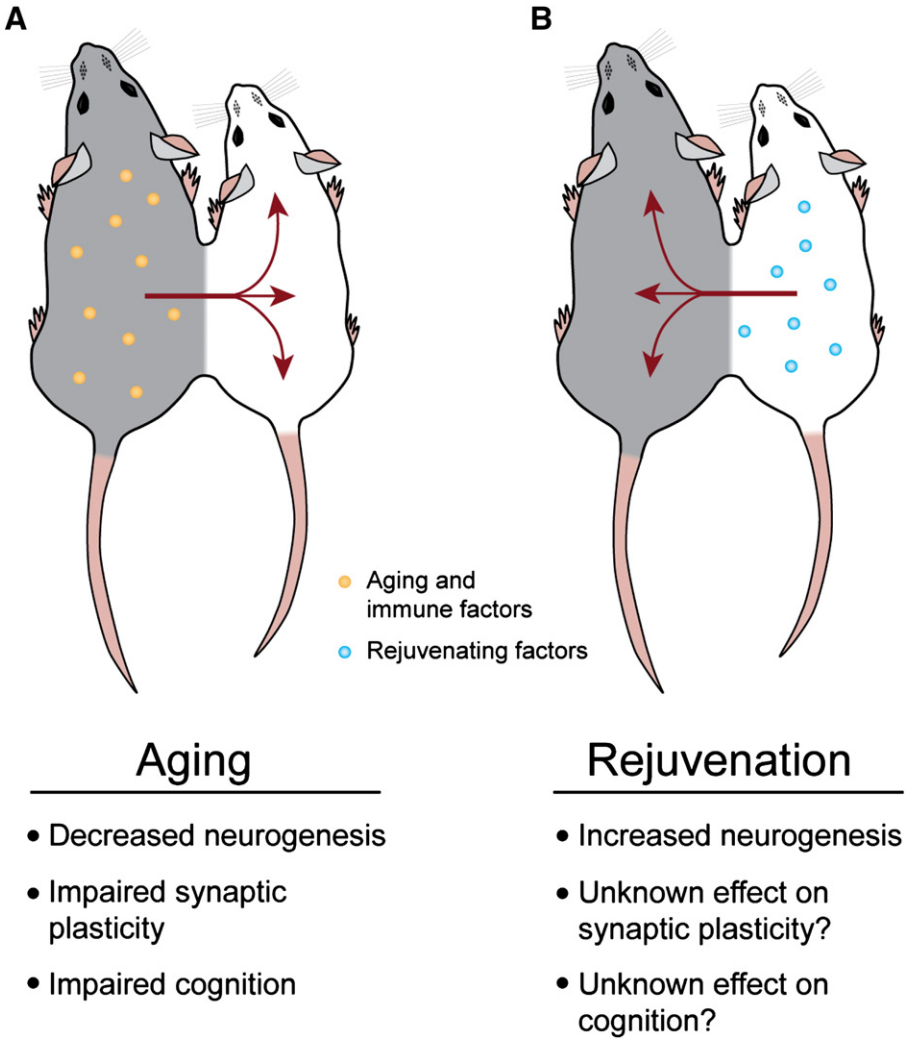

Fig. 1. The systemic circulatory environment regulates neurogenesis in an age-dependent fashion. Schematic illustrates heterochronic parabiosis in which the circulatory systems of a young and old animal are joined. A. During aging the levels of immune-related molecules, as well as unknown "aging" factors, increase in the systemic environment. Heterochronic parabiosis indicates that these "aging" factors functionally contribute to age-related impairments in neurogenesis, synaptic plasticity and cognitive functions. B. Heterochronic parabiosis suggests that the young systemic environment contains unknown "rejuvenating" factors with the capacity to increase neurogenesis in the old animal. It remains to be investigated whether such "rejuvenating" factors can also alter functions beyond regeneration that may improve cognition.

to combat the degenerative effects of aging inherent to both brain regeneration and cognitive impairment.

Take-home messages

- The aging circulatory systemic environment impairs neurogenesis and cognitive functions.
- Increased levels of immune signaling molecules comprise the aging systemic environment.
- Increasing systemic chemokine levels mimic the effects of aging on neurogenesis and cognitive functions.
- Rejuvenating factors exist in the young systemic environment.

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Disease activity can be accurately assessed in patients with systemic lupus erythematosus by measuring circulating anti-dsDNA antibody-secreting cells

Serum antibodies to double-stranded DNA (dsDNA) are established biomarkers for systemic lupus erythematosus (SLE), being a valuable diagnostic and prognostic tool. Anti-dsDNA antibodies are directly involved in organ damage, primarily lupus nephritis; however, the clinical significance of the induction of dsDNA autoimmune response is still under debate. Recently, Hanoka *et al*. (**Lupus 2012;21:1284-93**) characterized and quantified circulating anti-dsDNA antibody-secreting cells in lupus-prone mice and SLE patients by a modified enzyme-linked immunospot (ELISPOT) assay, in order to assess the clinical utility of this laboratory parameter as a novel SLE biomarker. Anti-dsDNA antibody-secreting cells were detected in the spleen, bone marrow and peripheral blood from MRL/*lpr* lupus-prone but not BALB/c control mice, and in peripheral blood mononuclear cells from 29/130 (22%) SLE patients, but not from healthy subjects or non-SLE connective tissue disease controls. ELIOSPOT assay applied to monoclonal antibody-immunodepleted mononuclear cells, demonstrated that circulating anti-dsDNA antibody-secreting cells were both CD19+ B cells and CD138+ plasmablasts or plasma cells. Cells secreting anti-dsDNA antibodies were significantly associated with serum anti-dsDNA antibodies, persistent proteinuria, and SLE disease activity measures. Moreover, in a cohort of inactive patients with high-titre serum anti-dsDNA antibodies, prospectively followed for up to 25 months, only patients positive for anti-dsDNA antibody-secreting cells relapsed, nearly all within 12 months. The authors concluded that circulating anti-dsDNA antibody-secreting cells should be measured in addition to serum anti-dsDNA antibodies, as a specific biomarker for disease activity in SLE patients.

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