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Blood-to-brain communication in aging and rejuvenation

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Aging induces molecular, cellular and functional changes in the adult brain that drive cognitive decline and increase vulnerability to dementia-related neurodegenerative diseases. Leveraging systemic and lifestyle interventions, such as heterochronic parabiosis, administration of 'young blood', exercise and caloric restriction, has challenged prevalent views of brain aging as a rigid process and has demonstrated that aging-associated cognitive and cellular impairments can be restored to more youthful levels. Technological advances in proteomic and transcriptomic analyses have further facilitated investigations into the functional impact of intertissue communication on brain aging and have led to the identification of a growing number of pro-aging and pro-youthful factors in blood. In this review, we discuss blood-to-brain communication from a systems physiology perspective with an emphasis on blood-derived signals as potent drivers of both age-related brain dysfunction and brain rejuvenation.

The intimate relationship between the brain and cognition grounds the very perception of ourselves, and therefore it is not surprising that we often think of the brain as a separate entity all on its own, isolated from the interactions of the periphery. However, no other process may oppose this impression more strongly than aging itself, with its ever-present reminder as our hair grays, muscles weaken and memories become more distant. Indeed, aging is a process that affects all organs in the body, leading to substantial alterations in intertissue communication and regulation. Researchers have recently leveraged evolving proteomic approaches and single-cell RNA-sequencing technologies to begin to decode the functional impact of intertissue communication on brain aging[1,2]. The application of molecular approaches to investigate systemic and lifestyle interventions, such as heterochronic parabiosis (in which the circulatory systems of young and aged animals are surgically connected), young blood plasma administration, exercise and caloric restriction, has uncovered broad rejuvenating effects on the aged brain that are mediated through blood, which question the very notion that brain aging is immutable[3–10]. This review will first survey well-documented and emerging cellular hallmarks of brain aging, next categorize how bloodborne cellular and soluble signals drive brain aging and finally give an overview of the tissues, cells and downstream blood factors involved in transferring the benefits of systemic and lifestyle interventions to the brain. In this review, we refer to the process of restoring cognitive function and reversing cellular hallmarks of aging to a more youthful state as 'rejuvenation'.

Impact of aging on the brain

The functional consequence of aging in the brain is the decline of cognitive faculties, such as memory loss, which at its core is driven by cellular and molecular changes. Here, we touch upon well-documented and emerging cellular hallmarks of brain aging with a focus on those amenable to pro-aging and rejuvenating interventions (Fig. 1)[11–13]. We differentiate between physiological aging and progression to neurodegenerative diseases, with the latter being characterized by selective neuronal cell loss, protein-aggregation pathology and additional molecular and cellular changes that each warrant their own review. Nevertheless, given that aging remains a prominent risk factor for age-related diseases such as Alzheimer's disease (AD), systemic interventions that ameliorate cognitive and cellular function in aging may extend to neurodegenerative conditions.

Neuronal dysfunction

A central hallmark of brain aging is maladaptive changes in the functional properties of neurons, reflected in decreased synaptic plasticity-related gene expression, reduced synaptic density and aberrant electrophysiological processes[12,14,15]. While overt signs of neuronal

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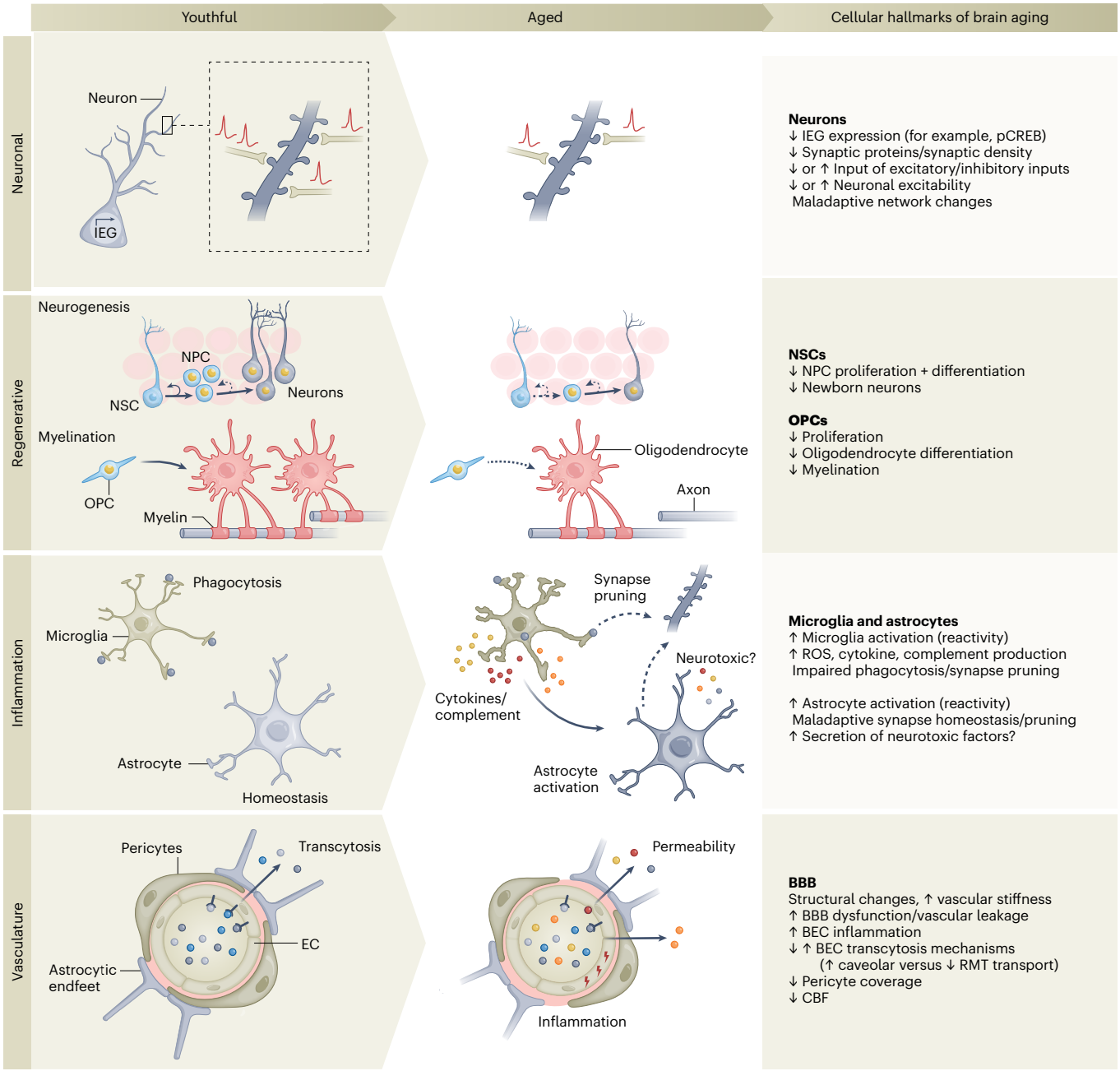

Fig. 1 | Cellular hallmarks of brain aging. The figure shows cellular hallmarks of brain aging that have been investigated in the context of blood-based pro-aging and rejuvenating interventions. Hallmarks have been divided into four categories: functional changes of neurons and circuits ('neuronal'), regenerative changes relating to adult NSCs and neurogenesis as well as OPCs and myelin renewal ('regenerative'), inflammatory changes associated with microglia and astrocytes ('inflammation') and vasculature changes relating to the BBB ('vasculature'). Abbreviations: ↓, decreased; ↑, increased; EC, endothelial cell; IEG, immediate early gene; NPC, neural progenitor cell; pCREB, phosphorylated CREB; RMT, receptor-mediated transport; ROS, reactive oxygen species. Red lightning bolts indicate inflammatory changes in BECs.

aging are not exhibited equally by all brain regions, some areas, including the hippocampus, are particularly susceptible to the effects of aging[12]. Functionally, age-related molecular and cellular changes can lead to both decreased and increased neuronal excitability, depending on the neuronal cell type and brain region[16]. The specificity of these changes suggests a complex dysregulation of excitatory and inhibitory inputs and broader maladaptive circuit changes that drive cognitive decline in processes such as spatial learning and memory, associative memory and episodic and working memory[12,15,16].

Regenerative decline

Brain aging in mammals is characterized by a precipitous decline in regenerative capacity, mediated through changes in adult neuronal stem cells (NSCs) and oligodendrocyte progenitor cells (OPCs). Adult neurogenesis, the process through which NSCs give rise to new neurons, decreases dramatically across all three neurogenic regions[17–19]: the hippocampal dentate gyrus (DG), the subventricular zone (SVZ) lining the lateral ventricle and the hypothalamus[20]. Of note, the persistence of adult NSCs in the human DG remains controversial[21–23]. Neurogenesis

regulates learning and memory in young adult rodents[24,25]; however, the functional impact of decreased neurogenesis on cognitive decline during old age remains unclear. By contrast, the number of OPCs distributed in gray and white matter remains relatively stable, although the rate of oligodendrocyte differentiation and myelin renewal is greatly decreased with age[26]. Age-related regenerative decline is mediated by both cell-intrinsic mechanisms and extrinsic changes to the neurogenic niche and systemic environment[12,20].

Neuroinflammatory changes

An increasingly appreciated hallmark of brain aging is neuroinflammation. This process is predominantly mediated by microglia, the brain-resident macrophages. Microglial aging is characterized by increased production of reactive oxygen species, pro-inflammatory cytokines and components of the complement system[27,28], extensive morphological changes and impairments in phagocytosis[27,29,30]. Functionally, age-related microglial phagocytic dysfunction has been linked to cognitive decline[31]. Microglia have also been suggested to play a critical role in astrocyte reactivity through secretion of pro-inflammatory cytokines and complement components in the aging brain[32]. In contrast to microglia, relatively few studies have focused on age-related functional changes of astrocytes[32,33]. With age, astrocytes become more 'reactive', characterized by upregulation of gene sets associated with synapse elimination, neurotoxicity and oligodendrocyte toxicity[32–34]. Both microglia and astrocytes are also thought to co-regulate, in part, synaptic pruning during aging through changes in molecular signals, such as complement[29,30]. There is growing appreciation for the functional heterogeneity of microglia and astrocytes across brain regions and developmental and adult time points. More broadly, neuroinflammatory changes may also be regulated by additional cell types such as border-associated macrophages and the diverse repertoire of immune cells residing in niches in the brain borders, raising the question of their roles as drivers of brain aging and cognitive decline[35,36].

Vascular and blood–brain barrier changes

The vasculature in the brain forms a specialized blood–brain barrier (BBB), which regulates transport of nutrients, molecules and cells from the blood to the brain. Aging of brain vasculature is characterized by changes in vascular morphology and stiffness, dysregulation in cerebral blood flow (CBF) and tissue oxygenation[37,38]. Traditionally, it was considered that the BBB begins to break down with age, allowing leakage of molecules that can drive cognitive dysfunction[39–41]. Recently, advances in single-cell RNA-sequencing technologies have begun to elucidate more nuanced age-related changes in brain endothelial cells (BECs) and other cellular components of the brain vasculature[42–44]. BECs display region- and segment-specific increases in inflammatory and stress-response markers with age[42,43,45], a reduction in density and volume and decreased pericyte coverage[10,45]. Experiments with labeled whole-blood plasma proteome in young animals revealed an astonishing amount of protein uptake by BECs, as well as by neurons and glia residing in the brain parenchyma[44]. This uptake of bulk plasma proteins was surprisingly reduced in aged mice, driven by pronounced changes in BEC transcytosis[44]. Although the exact composition of these transcytosed plasma factors remains unknown, the age-related changes coincide with a shift from ligand-specific receptor-mediated transport toward nonspecific caveolar transcytosis[44]. Age-related vascular and BBB changes fundamentally alter how signals from blood may be relayed to the brain; moreover, new findings focused on the choroid plexus (CP) blood–cerebrospinal fluid (CSF) barrier (Box 1) open new avenues to explore in our understanding of drivers of brain aging.

Bloodborne signals and the aging brain

Over the last decade, experiments using heterochronic parabiosis or heterochronic blood exchange from old to young animals have shown that these approaches induce a broad range of accelerated aging phenotypes in young animals[8,10,46] (Fig. 2), positing components in aged blood as major drivers of dysfunction in the aging brain. Young mice exposed to blood factors and cells from the aged systemic milieu have decreased adult hippocampal and SVZ neurogenesis and reduced long-term potentiation (LTP), an indicator of synaptic transmission and a neuronal correlate of learning and memory[8,10]. Interestingly, administration of aged blood plasma alone similarly decreases neurogenesis, increases inflammatory states of microglia and BECs and impairs hippocampus-dependent cognitive functions in young recipient mice[8,42,43]. Recent work has begun to decode individual components in aged blood, including cells and soluble factors in plasma, which can recapitulate some of the detrimental effects of an aging systemic environment on the brain[8,42,47–49].

Box 1: The blood–CSF interface

The CP is a specialized, highly vascularized epithelium in the brain ventricles that forms a tightly controlled interface between the blood and CSF, referred to as the blood–CSF barrier. Ependymal cells in the CP are the primary producers of CSF, which fills the ventricular system and subarachnoid space in and surrounding the brain and spinal cord. The CSF contains factors derived from both the CP and the brain parenchyma and serves important homeostatic functions such as trophic support and waste removal from the brain[146]. Owing to the lack of a barrier between the parenchyma and CSF, factors in CSF can have wide-ranging effects in the CNS. The CP is home to a dynamic repertoire of immune cells and may serve as an entry site for immune cells to the CSF and parenchyma during aging and disease states[53,56]. The CP responds to both peripheral and brain-derived signals[147]. As such, it is considered an exquisite sensor of inflammatory signals and serves as a potential site to relay peripheral inflammatory signals to the CNS.

With age, the CP undergoes drastic morphological and functional changes, including an increased inflammatory state, decreased barrier integrity and reduced production and altered composition of CSF[146,148]. Aging-associated inflammatory changes in the CP epithelium, in part mediated by the systemic milieu and $CD4^+$ T cells in the CP, result in altered CSF composition. These alterations have been shown to include changes in interferon signaling and increased pro-inflammatory cytokine production[58,147]. The aged CP has been shown to upregulate expression of the pro-aging factor chemokine C–C motif ligand (CCL)11, and an age-associated increase in CCL11 levels has also been reported in human CSF[8,58]. Functionally, changes in the aged CP and CSF have been linked to a decline in regenerative capacity, increased glial activation and impaired cognitive function[149]. As such, CSF derived from old mice has been shown to negatively regulate NSC functions in the SVZ, in part owing to a decrease in IGF1 and bone morphogenetic protein 5 (BMP5) in aging CSF[149]. Conversely, a recent study using heterochronic infusion of young CSF into the lateral ventricles of aged mice reported enhanced proliferation and differentiation of OPCs in the hippocampus, as well as cognitive improvements[150]. Fibroblast growth factor 17 (FGF17) was identified as a neuron-derived factor that decreases in the CSF with age and administration of which into the CSF of aged mice recapitulates the benefits of heterochronic CSF infusion[150]. These findings establish the blood–CSF barrier as an important sensor of the systemic milieu and a potential relay station for blood-to-brain communication.

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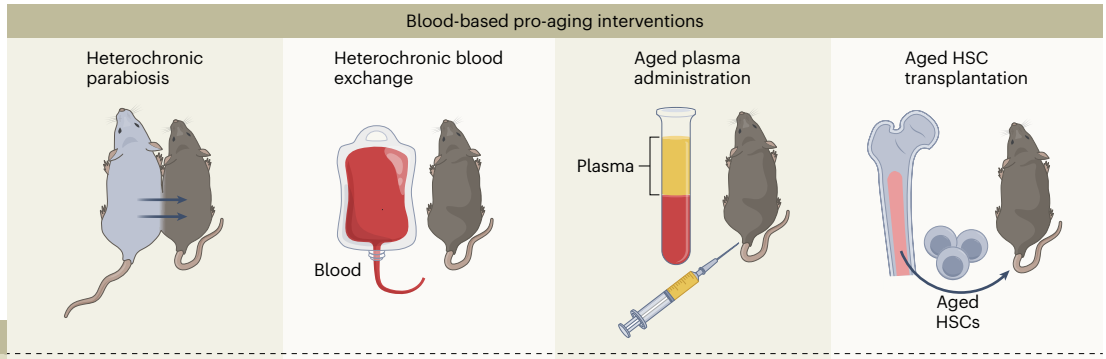

Hallmarks of brain aging	Heterochronic parabiosis	Heterochronic blood exchange	Aged plasma administration	Aged HSC transplantation
Neuronal and cognitive functions	↓ IEG expression (hipp) ↓ LTP (hipp) (Ref. 8)	↓ IEG expression (hipp) ↓ Cognition (hipp) (Ref. 46)	↓ IEG expression (hipp) ↓ Cognition (hipp) (Ref. 8)	↓ Synaptic proteins/IEG ↓ Spine density (hipp) ↓ Cognition (hipp) (Ref. 49)
Regenerative functions	↓ Neurogenesis (hipp) ↓ Neurogenesis (SVZ) (Refs. 8,10,48)	↓ Neurogenesis (hipp) (Ref. 46)	↓ Neurogenesis (hipp) (Refs. 8,42)	↓ Neurogenesis (hipp) (Ref. 49)
Neuroinflammation	(Not assessed)	↑ Neuroinflammation? (hipp) (Ref. 46)	↑ Microglia activation (hipp) (Ref. 42)	(Not assessed)
Vasculature	↔ CBF (SVZ) ↔ Vessel volume (SVZ) (Ref. 10)	(Not assessed)	↑ Vascular inflammation (hipp) (Refs. 42,43)	(Not assessed)

Fig. 2 | Pro-aging interventions. Young mice are illustrated with brown coats, and aged mice are shown with gray coats. In heterochronic parabiosis, two mice are surgically connected for 4–6 weeks, so that a young animal is exposed to an aged systemic environment. In heterochronic blood exchange, approximately 50% of the blood (both cells and plasma) of a young mouse is replaced with an equal amount of blood derived from an aged mouse. The mice are not surgically connected. In aged plasma administration, plasma is collected from aged donor mice and intravenously delivered over the course of 3–4 weeks into young recipient mice. In aged HSC transplantation, the hematopoietic system of young recipient mice is reconstituted with HSCs derived from aged donor mice. Pro-aging effects have been assessed on neuronal, regenerative, neuroinflammatory and/or vascular functions in young mice. Abbreviations: ↔, no change; hipp, hippocampus. A question mark indicates limited supporting data.

Circulating immune cells and brain aging

The aging process leads to drastic changes in immune cell compositions and functions, resulting in increased local and systemic inflammation[35]. Under adult homeostatic conditions, the brain parenchyma is considered mostly devoid of peripheral immune cells. By contrast, the central nervous system (CNS) barrier regions, including the CP, meninges and skull bone marrow, are populated with a diverse repertoire of innate and adaptive immune cells[36].

Aging myeloid cells display substantial cellular and functional changes associated with a maladaptive pro-inflammatory state and may be a potent source of pro-aging factors in the periphery and the CNS. In particular, prostaglandin E2 signaling through the EP2 receptor was demonstrated to be elevated in myeloid cells, impairing metabolic homeostasis and exacerbating pro-inflammatory signaling[50]. Conversely, inhibition of EP2 signaling selectively in peripheral myeloid cells was sufficient to reverse pro-inflammatory cytokine levels in plasma, restore hippocampal LTP and rescue cognition in aged mice[50].

Parabiosis and bone marrow reconstitution trafficking studies indicate that only a limited number of infiltrating circulating immune cells are present in the aging brain parenchyma[8,49]. Similarly, post-mortem human histological analysis did not identify significant differences in the distribution and density of B cells and T cells in the cortex with age[51]. However, the possibility remains that small shifts in hematogenous immune cell populations within the brain may influence function during aging. Surprisingly, an increase in natural killer (NK) cells was recently reported in the hippocampus of aged humans and mice[52]. In aged rodents, it is suggested that NK cells expand locally in the DG and display elevated markers of cytotoxicity[52]. Conversely, ablation of NK cells enhanced neurogenesis and cognitive functions in aged mice[52].

T cells have emerged as potential contributors to age-related brain dysfunction (Table 1). $CD8^+$ T cells are increased in the SVZ of the lateral ventricle in aged mice and humans and drive impairments in adult neurogenesis through increased interferon-γ signaling[53]. Furthermore, T cells have been reported near sinuses and in the hippocampus of aged rodents[45,54], and an increase in perivascular and parenchymal T cells was observed in white matter of aged rhesus macaques[55]. Although aging-associated T cell changes are relatively modest in the brain parenchyma, marked increases in T cells have been reported in rodent models of neurodegeneration and in CSF of human individuals with AD[54,56]. The extent to which immune cell populations act directly in the brain versus indirectly through interactions with the brain vasculature or borders or secreted systemic factors requires further investigation in both aging and neurodegeneration.

Pro-aging blood factors as drivers of brain dysfunction

Experiments involving heterochronic parabiosis and aged plasma administration (Fig. 2) indicate that the detrimental effects of aged blood can, in part, be mimicked by circulating pro-aging blood factors. Using proteomic approaches, a series of blood factors in plasma have been identified, which increase with age and promote features of aging

Table 1 | Pro-aging blood factors and immune cells

Factor or cell	Model identified	Effects on hallmarks of brain aging	Translational findings in humans	CNS site of action	References
CCL11 (eotaxin-1)	Aging/parabiosis	↓ Hippocampal neurogenesis ↑ Microglial activation ↓ Spine density ↓ Hippocampus-dependent cognition	↑ In plasma/CSF with age ↑ Correlates with cognitive decline in AD/MCI.	Brain: NSC, microglia	8,58–60,63
CCL2 (MCP-1)	Aging/parabiosis	↑ Vascular inflammation KO: ↓ inflammation and restores hippocampal neurogenesis in injury	↑ Levels correlate with ↓ cognition in AD/MCI.	Vascular: BEC Brain: NSC, microglia?	8,62–64
B2M	Aging/parabiosis	↓ Hippocampal neurogenesis ↓ Hippocampus-dependent cognition	↑ In CSF/plasma with age ↑ In AD/HIV dementia	Brain: NSC	8, 36, 48, 65,66
TGF-β1	Aging	Inhibition of TGF-β1: ↑ Hippocampal neurogenesis		Brain: NSC, microglia?	47
VCAM1	Aging/aged plasma	Inhibition of VCAM1: ↓ Microglial activation ↑ Hippocampal neurogenesis ↑ Hippocampus-dependent cognition	↑ In plasma with age	Vascular: BEC	42, 73,74
ASM	Aging	Inhibition of ASM: ↓ BBB disruption ↑ Spine density ↑ Hippocampus-dependent cognition	↑ In plasma with age and AD	Vascular: BEC	75
CyPA (PPIA)	Aged HSC transplant	↓ Synaptic proteins ↓ Hippocampus-dependent cognition		Vascular: BEC?	49,72
$CD8^+$ T cells	Aging	↓ SVZ neurogenesis	↑ In human SVZ	Brain: NSC, microglia/ BEC?	53
NK cells	Aging	↓ Hippocampal neurogenesis NK depletion: ↑ Neurogenesis (DG) ↑ Hippocampus-dependent cognition	↑ In human DG	Brain: NSC	52
Myeloid cells (peripheral)	Aging	Inhibition of myeloid cell EP2 receptor: ↓ Inflammation in periphery and brain ↑ LTP/hippocampus-dependent cognition	↑ EP2 expression in macrophages with age	Brain: microglia/neurons	50

List of pro-aging factors and cell types, the experimental model that they were identified in and their effects on brain aging in animal models as well as potential mechanisms of action. Potential translational findings were assessed in human brain aging and degeneration. KO, knockout; MCI, mild cognitive impairment. A question mark indicates limited supporting data.

in the brain. Here, we highlight pro-aging blood factors that recapitulate age-related cellular and cognitive dysfunction when administered to young individuals (Table 1).

Cytokines and chemokines

Cytokines and chemokines (secreted proteins that broadly regulate immune responses and cell trafficking) have emerged as prominent pro-aging factors with neuro-modulatory properties[57]. Several members of the C–C chemokine family were shown to be increased in blood plasma of aged rodents and in young heterochronic parabionts exposed to an aged systemic environment. CCL11 or eotaxin-1 increases in plasma and CSF of rodents and humans[8,58]. Systemic treatment with CCL11 was shown to reduce hippocampal neurogenesis, activate microglia and impair cognitive function in mice[8,59,60]. Radiolabeling experiments indicate that CCL11 can cross the BBB in rodents[61]. Moreover, the negative effects of systemic CCL11 on neurogenesis can be blocked with central delivery of a neutralizing antibody, suggesting that CCL11 acts locally in the hippocampus[8]. Interestingly, the *CCL11* gene is located in a genomic region with additional C–C motif genes including *CCL2* (MCP-1), the product of which is similarly elevated in blood plasma of aged mice and young heterochronic parabionts[8]. CCL2 has been suggested to contribute to BBB dysfunction and permeability[62]. In humans, the levels of CCL11 and CCL2 are associated with cognitive decline in individuals with mild cognitive impairments or AD and negatively correlate with memory functions[63,64], suggesting that their detrimental effects on cognition may be conserved across species.

Components of MHC-I

Systemic levels of β2-microglobulin (B2M), the soluble light chain of major histocompatibility complex class I (MHC-I) molecules, are elevated in aged mice and in the plasma and CSF of older humans[8,48]. Mimicking this aging-associated increase through systemic administration of B2M decreases adult hippocampal neurogenesis and impairs cognitive functions in mice. In humans, B2M levels are increased in patients with AD and human immunodeficiency virus (HIV)-associated dementia[65,66], indicating a conserved association with impaired cognition. Interestingly, *B2M* and MHC-I genes are upregulated in various cell types in the aged brain[32,43,67], and direct delivery of B2M into the

hippocampus also impairs neurogenesis and cognition. These detrimental effects were abrogated in mice that lack surface expression of classical MHC-I, indicating that its molecular effect may depend on the specific repertoire of MHC-I molecules expressed on individual cell types in the brain[67–69]. Aged mice lacking B2M display increased neurogenesis and enhanced cognition, suggesting that targeting B2M may be a viable therapeutic avenue to restore function to the aged brain[48]. Notably, transforming growth factor (TGF)-β1 was identified as a potential regulator of B2M expression in both the periphery and the CNS[47]. Systemic inhibition of TGF-β1 signaling reduced B2M levels and enhanced adult neurogenesis in aged mice. Thus TGF-β1 and B2M may act through converging pathways to promote regenerative decline in the aging brain[47].

Hematopoietic system-induced factors

Aging-associated changes of the immune system together with the role of pro-aging immune factors in promoting brain dysfunction point to the aging hematopoietic system as a driver of brain aging. Inflammatory insults have been shown to induce a persistent increase in markers of hematopoietic stem cell (HSC) aging even in young mice[70,71]. Moreover, heterochronic HSC transplantations (in which the bone marrow of young mice is reconstituted with old HSCs) reduced synaptic density, decreased hippocampal neurogenesis and impaired cognitive functions in adult recipient mice[49] (Fig. 2). Mass spectrometry analysis identified several putative pro-aging plasma factors associated with an aging hematopoietic system in the heterochronic HSC transplantation model. Secreted cyclophilin A (CyPA) was negatively correlated with cognitive performance in mice. Elevating systemic levels of CyPA impaired cognition in young mice, whereas neutralizing antibody treatment enhanced neuronal and cognitive functions in aged mice[49]. These findings suggest that neutralization of individual components of aging blood may provide a viable therapeutic strategy to rejuvenate the aged brain. Although the cellular source of systemic CyPA in aging remains unknown, systemic administration of CyPA has been shown to act on BECs, suggesting that it may indirectly modulate brain functions by targeting the brain vasculature and BBB integrity[72].

Vasculature-derived factors

Several recent discoveries establish the brain vasculature as a potential source of pro-aging factors. Vascular cell adhesion molecule 1 (VCAM1) is a membrane protein that is predominantly expressed on BECs in venous and arterial segments of the brain vasculature[42]. VCAM1 expression is upregulated in response to inflammatory stimuli such as an aging systemic milieu and facilitates interactions of leukocytes with the vasculature[42,43]. As a result of shedding, soluble VCAM1 levels are elevated in the plasma of aged mice and humans[42]. Additionally, circulating VCAM1 is elevated in patients with AD, and elevated VCAM1 levels are associated with cognitive impairments[73,74]. Treatment of aged mice with a VCAM1-neutralizing antibody or genetic ablation of *Vcam1* selectively in BECs increased hippocampal neurogenesis, reduced microglial activation and enhanced cognitive function[42]. Thus, endothelial VCAM1 is, at least in part, involved in relaying certain aging-associated signals from the periphery to the brain parenchyma.

Acid sphingomyelinase (ASM) is a sphingolipid-metabolizing enzyme secreted by endothelial cells[75]. Similar to VCAM1, ASM expression is elevated in the aging brain vasculature and the levels of secreted ASM are increased in mouse and human plasma with age. Normalizing ASM levels through genetic or targeted knockdown approaches restored vessel density and caveolar transcytosis toward youthful levels, increased synaptic spine number in the hippocampus and improved cognitive function in aged mice. Together, VCAM1 and ASM point to BECs as a critical source of systemic pro-aging factors and further establish the brain vasculature as a critical nexus in blood-to-brain communication during aging.

Risk factors, co-morbidities and the aging brain

Risk factors and co-morbidities linked to neurodegenerative diseases, including obesity, diabetes, hypertension, cardiovascular disease and chronic inflammation, are associated with decreased cognitive performance in older people and in animal models[38,76,77]. For example, animal models of obesity display impaired synaptic plasticity, increased neuroinflammation and reduced hippocampal neurogenesis[77,78]. Similarly, chronic and acute inflammatory conditions, such as long coronavirus disease 2019 (COVID-19) with brain fog and animal models of respiratory COVID-19 infections, were shown to recapitulate neuroinflammatory, regenerative and cognitive changes that mirror the previously described hallmarks of brain aging[60]. Moreover, the levels of plasma CCL11, originally described as a pro-aging factor in heterochronic parabiosis, are elevated in animal models and humans with COVID-19 (ref. 60). The link between risk factors, co-morbidities and memory impairments suggests a complex pathophysiology that may potentiate cellular and functional changes associated with brain aging and warrants further investigations. Thus, therapeutic or lifestyle interventions targeting risk factors and co-morbidities may directly or indirectly restore function to the aged brain by engaging pro-aging systemic drivers.

Systemic rejuvenating interventions

A growing body of work has investigated the effect of 'young blood' on the aging brain and whether a more youthful systemic milieu can ameliorate age-related brain dysfunction[8–10]. Similarly, lifestyle interventions, including exercise and caloric restriction, rejuvenate the aged brain[3,5,7,79]. These systemic and lifestyle interventions demonstrate that there is latent plasticity in the aged brain that can be harnessed to improve cognitive function late in life. Here, we summarize the various rejuvenating effects ascribed to each systemic intervention (Fig. 3).

Blood-based interventions

Heterochronic parabiosis has been shown to rejuvenate aged muscle, liver, heart, pancreas, bone, spinal cord and brain, ultimately leading to an extension of life and healthspan[9,10,80–84]. In the brain, it ameliorates multiple cellular hallmarks of aging, resulting in increased synaptic plasticity and synaptic density[9], increased hippocampal and SVZ neurogenesis[9,10], increased vascular density and CBF[10] and attenuation of cellular senescence markers within the forebrain[85]. Likewise, restoring the cellular component of aged blood with young immune cells through heterochronic bone marrow transplantation increased synaptic density, attenuated microglial activation and enhanced hippocampus-dependent cognitive function in aged mice[59] (Fig. 3).

Multiple reports have shown systemic administration of the plasma component of young blood to be effective at reversing hippocampus-dependent cognitive and regenerative dysfunction in aged mice[9,71,86] (Fig. 3), at least in part by enhancing synaptic plasticity through activation of the transcription factor cAMP response element-binding protein (CREB)[9]. Similarly, diluting plasma of aged mice by approximately 50% with a saline–albumin solution, through a procedure known as neutral blood exchange, enhanced regenerative capacity, mitigated microglial activation and improved cognition[87,88] (Fig. 3). Moreover, dilution of aged blood by neutral blood exchange enabled elevation of plasma factors known to promote brain health and function, suggesting that the aging systemic milieu may dampen the abundance of potential pro-youthful factors[88]. Young blood and plasma exchange-based approaches are now being tested in pre-clinical and clinical studies for aging-associated neurodegenerative diseases such as AD[89,90]. Collectively, these blood-based rejuvenating interventions highlight the importance of both administering pro-youthful factors and blocking or diminishing pro-aging factors as complementary potential therapeutic approaches to reverse age-related dysfunction in the brain.

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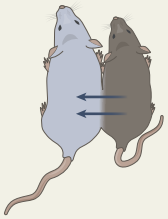
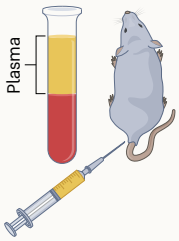
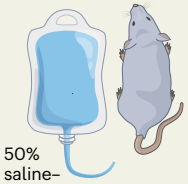
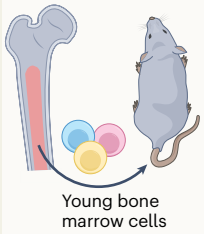
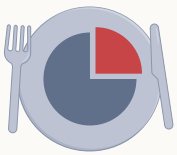
	Blood-based interventions				Lifestyle interventions	
	Heterochronic parabiosis	Aged plasma administration	Neutral blood exchange	Young bone marrow transplantation	Exercise	Caloric restriction
						
Hallmarks of brain aging						
Neuronal and cogntitive functions	↑ IEG/pCREB ↑ Synaptic plasticity (hipp) ↑ Olfaction (Refs. 9,10)	↑ pCREB (hipp) ↑ Cognition (hipp) (Refs. 9,86)	↑ Cognition (hipp) (Ref. 88)	↑ Synaptic density ↑ Activity ↑ Cognition (hipp) (Ref. 59)	↑ Synaptic plasticity ↑ BDNF ↑ Cognition (hipp) (Refs. 3,41,95)	↑ Synaptic plasticity ↓ Anxiety ↑ Cognition (hipp) (Refs. 79,98,103)
Regenerative functions	↑ Neurogenesis (hipp + SVZ) ↑ Remyelination (Refs. 9,10,82)	↑ Neurogenesis (hipp) (Ref. 71)	↑ Neurogenesis (hipp) (Ref. 87)	↓ Neurogenesis due to irradiation (hipp) (Ref. 59)	↑ Neurogenesis (hipp) (Refs. 3,91)	↑ Neurogenesis (hipp) ↑ White matter integrity (Ref. 104)
Neuro-inflammation	(Not assessed)	(Not assessed)	↓ Microglia activation (thalamus) (Ref. 88)	↓ Microglia/astrocyte activation (hipp) (Ref. 59)	↓ Microglia/astrocyte activation (Refs. 41,91,96)	↓ Microglia/astrocyte activation (Refs. 103,105)
Vasculature	↑ Vascular density (SVZ) ↑ CBF (Ref. 10)	↓ Expression of vascular inflammatory genes (Ref. 43)	(Not assessed)	(Not assessed)	↑ Vascular density ↑ Pericyte coverage ↓ Vascular leakage (Refs. 41,94)	↑ CBF (Refs. 101,102)

Fig. 3 | Rejuvenating interventions. Interventions are categorized into blood-based and lifestyle interventions. Young mice are illustrated with brown coats, and aged mice are shown with gray coats. Blood-based interventions: in heterochronic parabiosis, an aged mouse is surgically connected to a young mouse for 4–6 weeks and is exposed to a youthful systemic environment. In young plasma administration, the plasma fraction is collected from young donor mice and intravenously delivered to aged recipient mice over the course of 3–4 weeks. In neutral blood exchange, approximately 50% of the plasma is removed from aged mice and replaced with saline and albumin. In young bone marrow transplantation, the immune system of aged recipient mice is reconstituted with bone marrow cells derived from young donor mice. Lifestyle interventions: physical exercise paradigms can be of different duration and intensity. Caloric restriction paradigms are dietary interventions in which caloric intake is decreased by 10–50% without malnutrition. Rejuvenating effects have been assessed on neuronal, regenerative, neuroinflammatory and/or vascular functions in aged mice.

Physical activity and exercise

Physical activity and aerobic exercise mitigate age-related cognitive dysfunction in rodents[3,7,91], non-human primates[92] and humans[4,93]. Broad cellular and molecular hallmarks of brain aging are improved by exercise (Fig. 3). Several groups have reported benefits on vascular aging, including increased vascular density[94] and pericyte coverage of BECs, as well as reduced vascular leakage[41]. The benefits of exercise extend to cell types residing in the parenchyma. Exercise has been shown to increase synaptic plasticity[41,95], enhance adult hippocampal neurogenesis[3,7,91] and mitigate neuroinflammation by reducing microglial and astrocytic reactivity[41,91,96]. Furthermore, recent work has demonstrated that blood plasma from 'exercised' mice can transfer the beneficial effect of exercise on the brain and cognitive function to young and aged mice and mouse models of AD pathology[7,96]. Many of these positive exercise-induced effects observed in the brain have been suggested to be mediated, at least in part, by induction of the neurotrophin brain-derived neurotrophic factor (BDNF)[97].

Caloric restriction

Caloric restriction, in which caloric intake is decreased by 10–50% without malnutrition, has been demonstrated to enhance learning and memory of aging rodents[79,98], non-human primates[99] and humans[100]. Caloric restriction paradigms have been shown to maintain white and gray matter integrity in the aging brain while preserving CBF[79,101,102]. In the parenchyma, caloric restriction of aged individuals promoted synapse formation and other markers of synaptic plasticity[98,103], increased neurogenesis[104] and attenuated markers of neuroinflammation[103,105] (Fig. 3). Many of these beneficial effects of caloric restriction on the aged brain have been credited to advantageous metabolic alterations, protection from oxidative stress, neurotrophic factor production and increased autophagy. Additionally, caloric restriction may also have indirect benefits on the aged brain by reducing risk factors and co-morbidities associated with cognitive impairments[98,102,106].

Bloodborne factors as drivers of brain rejuvenation

Following the discovery that administration of plasma derived from young or 'exercised' animals rejuvenates the aged brain[7,9,86], multiple groups have attempted to identify a pro-youthful factor responsible for the effect of 'young blood' and lifestyle interventions on the aged brain by assessing changes in the composition of blood. The multifaceted effects of blood on the aged brain are highlighted by the growing number of beneficial factors identified and by the varied mechanisms by which they exert their rejuvenating effects, discussed below (Table 2).

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Table 2 | Pro-youthful blood factors

Factor	Model identified	Effects on hallmarks of brain aging	Translation to human aging	Cell or tissue source	CNS site of action	References
GDF11	Young plasma?	↑ Vascular density ↑ Neurogenesis in SVZ and hippocampus ↑ Neuronal/synaptic plasticity (hippocampus)		–	Vascular: BEC	10,109
Osteocalcin	Young plasma	↑ BDNF in hippocampus ↑ Excitatory neuron firing frequency ↑ Hippocampus-dependent cognition		Bone	Brain: neuron	86,111
TIMP2	Human umbilical cord plasma	↑ Synaptic plasticity in hippocampus ↑ Hippocampus-dependent cognition		–	Brain: neuron	112
CSF2 (GM-CSF)	Human umbilical cord plasma	↑ Synaptic plasticity in hippocampus ↑ Hippocampus-dependent cognition		–	Brain: neuron	112,114
THBS4	Young serum	In vitro: ↑ synaptogenesis and dendrite arborization in induced human neurons In vivo: unknown	↓ Associated with ↓ long-term recall in asymptomatic fAD	–	In vitro: neuron	115,116
SPARCL1	Young serum	In vitro: ↑ synaptogenesis and dendrite arborization in induced human neurons In vivo: unknown		–	In vitro: neuron	115
α-klotho	Longevity gene/ factor	↑ Synaptic plasticity ↑ Hippocampal neurogenesis ↑ Hippocampus-dependent cognition		–	Peripheral: possibly CP?	118,120
GnRH	Young hypothalamus	↑ Hippocampal neurogenesis ↑ Hippocampus-dependent cognition		Hypothalamus	Brain: neuron, NSCs Peripheral: targets possible, unknown	19
IGF1	Acute exercise	Young mice: ↑ BDNF and synaptic plasticity ↑ Neurogenesis Aged mice: ↑ hippocampus-dependent cognition		Liver and other tissue	Brain: neuron, NSCs	122–127
GPLD1 (GPI-PLD)	Exercise training	↑ Hippocampal neurogenesis ↑ Hippocampus-dependent cognition	↑ In plasma of active older people	Liver	Peripheral: targets unknown	7,128
SEPP1/selenium	Acute exercise	↑ Hippocampal neurogenesis ↑ Hippocampus-dependent cognition		Liver (SEPP1), diet (selenium)	Vascular: BECs (SEPP1); brain: NSCs (selenium)	129
Clusterin (ApoJ)	Exercise training	AD mouse model/LPS treatment (young): ↓ hippocampal BEC inflammation	↑ In plasma of individuals with MCI after 6 months of exercise	Liver	Vascular: BECs; brain: unknown	96
Irisin/FNDC5	Exercise training	Young mice: ↑ BDNF and markers of synaptic plasticity AD mouse model: ↑ Synaptic plasticity ↓ Glial activation ↑ Hippocampus-dependent cognition	↑ In plasma of aerobic exercise-trained adults	Muscle	Brain: neuron	132, 134,135
VEGF	Acute exercise	Young mice: ↑ angiogenesis and CBF ↑ Hippocampal neurogenesis ↑ Synaptic plasticity (hippocampus) ↑ Hippocampus-dependent cognition		Muscle	Vascular: BECs; brain: NSCs and neurons	136
Lactate	Acute exercise	Young mice: ↑ brain VEGF, ↑ angiogenesis Lactate transport across BBB is necessary for exercise-induced increase in hippocampal BDNF and hippocampus-dependent cognition ↑ Hippocampal BDNF ↑ Hippocampus-dependent cognition		Muscle	Vascular: fibroblast and pericyte-like cells; brain: neuron	137
PF4 (CXCL4)	Acute exercise	Young mice: ↑ hippocampal neurogenesis		Platelets	Brain: NSCs	140
CTSB	Exercise training	In vitro: ↑ neurotrophin and Dcx expression but not proliferation or survival of NPCs In vivo: unknown	↑ In plasma of aerobic exercise-trained adults, correlated with recall	Muscle?	Brain: NSCs?	138
Ketone bodies/β-hydroxybutyrate	Caloric restriction	↑ CBF ↑ Neuronal metabolism ↓ Systemic inflammation and ROS ↑ Neuroprotective macrophages ↑ Hippocampus-dependent cognition	↑ Memory in aging and MCI	Liver	Multifunctional: vascular and brain	79,141–145

List of pro-youthful factors, the experimental model that they were identified in and their effects on brain aging in animal models as well as the potential mechanism of action. Potential translational findings were assessed in human brain aging and degeneration. Dcx, doublecortin; fAD, familial forms of AD; LPS, lipopolysaccharide. A question mark indicates limited supporting data.

Young bloodborne rejuvenating factors

One of the first reported rejuvenating factors in young blood was growth differentiation factor 11 (GDF11)[83]. As a member of the activin–TGF-β superfamily of growth and differentiation factors, GDF11 was originally identified as a mediator of skeletal patterning during embryogenesis[107]. Although the age-related dynamics of its abundance in blood are under debate[83,108], GDF11 reproduced some of the beneficial effects of heterochronic parabiosis on the aged brain by increasing vascular density and CBF, ultimately leading to enhanced adult neurogenesis in the SVZ and the DG and increased markers of neuronal activity in the hippocampus and cortex[10,109]. Surprisingly, increased GDF11 expression within the adult hippocampus inhibits neurogenesis[110]. These disparate findings were reconciled when biotinylation experiments determined that circulating GDF11 is unable to cross the BBB[109], suggesting that systemic GDF11 exerts its rejuvenating effect on the aged brain by signaling through BECs.

By contrast, a second young blood-derived rejuvenating factor, the bone-derived hormone osteocalcin, is capable of crossing the BBB[111]. When administered systemically, it can bind to neurons, increase BDNF levels, promote action potential in excitatory neurons and enhance learning and memory in aged mice[86,111]. Interestingly, antibody-based depletion of osteocalcin demonstrated its necessity for the beneficial effect of young blood plasma on hippocampal cognitive function in aged mice[86].

To identify potential human rejuvenating factors, others discovered that systemic administration of human umbilical cord plasma rejuvenates the brain of aged immunodeficient mice[112]. Within human umbilical cord plasma, tissue inhibitor of metalloproteinases 2 (TIMP2) and colony-stimulating factor 2 (CSF2 or granulocyte–macrophage colony-stimulating factor (GM-CSF)) were identified as two factors that decrease by early adulthood[112]. Autoradiographic labeling of TIMP2 (ref. [112]) and CSF2 (ref. [113]) revealed both factors to be BBB permeable. When injected systemically, both factors were sufficient to enhance synaptic plasticity and hippocampus-dependent memory in aged mice[112]. CSF2 also restored cognition in a mouse model of AD pathology[114].

Additional work attempted to screen for potential pro-youthful factors capable of acting on human neurons by treating human induced neurons in vitro with factors found to be downregulated with age in mouse serum[115]. This work revealed two factors capable of promoting synaptogenesis and dendrite arborization: the secreted matricellular proteins thrombospondin 4 (THBS4) and SPARC-like protein 1 (SPARCL1)[115]. Interestingly, lower plasma levels of THBS4 were found to be associated with impaired long-term recall in asymptomatic middle-aged humans from families with autosomal dominant AD[116]. However, it is unknown whether THBS4 or SPARCL1 are beneficial when administered systemically or whether they can cross the BBB to act directly on neurons.

Complementary approaches have also been used to identify circulating factors that can rejuvenate the aged brain. Circulating levels of the pro-longevity factor α-klotho do not change with age[117]; however, peripheral administration of a fragment of α-klotho enhances synaptic plasticity and cognition in aged mice[118]. Although α-klotho does not seem to cross the BBB, as shown in tagging experiments[119], one report suggests that it may be regulating inflammation at the CP blood–CSF barrier[120]. Along similar lines, inflammation within the aged hypothalamus has been shown to inhibit expression of gonadotropin-releasing hormone (GnRH), a hypothalamic neuropeptide responsible for regulating reproductive biology, and drive aging phenotypes in mice[19]. Interestingly, peripheral administration of GnRH is sufficient to enhance hippocampal neurogenesis and restore cognitive function in aged rodents[19]. Systemic GnRH may be targeting the CNS through the circumventricular organs, specialized parts of the brain vasculature lacking a canonical BBB[19].

Physical activity and exercise-induced factors

It has long been appreciated that, in response to acute and/or chronic aerobic exercise, humoral factors termed exerkines[121] are released from skeletal muscle and other metabolically active tissues such as liver and adipose tissue and are able to mediate some of the beneficial effects of exercise (Table 2).

One of the first exerkines shown to enhance brain function in aged animals was insulin-like growth factor 1 (IGF1). Plasma IGF1 levels increase acutely during aerobic exercise[122], and radiolabeling experiments revealed that IGF1 is able to cross the BBB via receptor-mediated transport[123]. Systemic IGF1 promotes markers of synaptic plasticity[124] and neurogenesis[125] and ameliorates age-related cognitive dysfunction[126]. Moreover, systemically blocking the receptor for IGF1, at least in young rats, was sufficient to abolish the effect of voluntary running on BDNF production in the hippocampus and spatial memory[127], suggesting that some of the beneficial effects of exercise on the brain are promoted by systemic IGF1.

Recent work has begun to highlight a liver-to-brain axis by which liver-derived blood factors transfer the benefits of exercise to the aged brain. Both aged mice exposed to exercise for 6 weeks and physically active older humans have elevated blood levels of glycosylphosphatidylinositol (GPI)-specific phospholipase D1 (GPLD1 or GPI-PLD), a liver-derived protein that cleaves GPI-anchored proteins from the plasma membrane[7]. Additionally, liver and plasma GPLD1 levels were recently reported to be elevated in long-lived mutant mouse strains and mice treated with lifespan-extending drugs[128]. Increasing liver-derived systemic GPLD1 levels in aged mice recapitulated the benefit of exercise on hippocampal neurogenesis and cognitive function[7]. HiBiT-tagged bioluminescence experiments indicate that GPLD1 does not readily cross the BBB, and mass spectrometry analysis implicates changes in coagulation and complement signaling cascades downstream of GPI-anchored substrate cleavage as possible mediators of the rejuvenating effects[7]. Another predominantly liver-derived protein, selenoprotein P (SEPP1), is also upregulated in blood of mice after 4 d of voluntary wheel running[129]. SEPP1 transports selenium across the BBB by binding LDL-like receptor 8 (LRP8), and both SEPP1 and LRP8 are required for the exercise-induced increase in hippocampal neurogenesis[129]. Additionally, selenium supplementation was found to increase hippocampal neurogenesis and reverse cognitive dysfunction in aged mice[129]. This emerging body of work highlights the liver as a potential hub of exercise-induced rejuvenation, capable of influencing the systemic milieu to ameliorate age-related brain dysfunction.

Recently, clusterin (or apolipoprotein J (ApoJ)), also an LRP8 ligand and predominantly expressed in hepatocytes and cardiomyocytes[96,130], was identified as an exerkine following 4 weeks of exercise with implications for neuroinflammation and AD. Clusterin is a multifunctional apolipoprotein that acts as an inhibitor of apoptosis, inflammation and complement activation[96,131]. Systemically administered clusterin binds to LRP8 on BECs and reduces inflammation following lipopolysaccharide treatment in young mice as well as in a mouse model of AD pathology[96]. Additional exercise-induced blood factors have also been demonstrated to improve brain function in the context of AD. Skeletal muscle-derived circulating levels of irisin, a BBB-permeable protein[132] released upon cleavage from the transmembrane protein fibronectin type III domain-containing protein (FNDC5), are increased in response to 3 weeks of wheel running in mice[133] and 12 weeks of high-intensity aerobic training in humans[134]. Interestingly, levels of FNDC5 and irisin are decreased in the brains of individuals with AD. In mouse models of AD pathology, both peripheral and central overexpression of *Fndc5* or irisin has been shown to enhance synaptic plasticity, reduce glial activation and improve cognitive performance, whereas antibody-mediated blockade of FNDC5 diminishes the beneficial effect of voluntary wheel running on synaptic plasticity and memory[132,135]. Although levels of FNDC5 and irisin have been reported to be increased in the aged CSF, it is

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still unknown whether the benefits of irisin extend to aging-associated cognitive deficits[135].

A number of additional exerkines, including vascular endothelial growth factor (VEGF)[136], lactate[137], cysteine protease cathepsin B (CTSB)[138], platelets and platelet factor 4 (PF4)[139,140], have been identified in young animals, but their effect on the aged or degenerating brain has yet to be investigated (Table 2).

Caloric restriction signals

In contrast to young blood and exercise interventions, potential systemic mediators of the rejuvenating capacity of caloric restriction on the aged brain have not been extensively examined. However, a number of studies have reported an increase in ketone body levels in calorically restricted animals[79,141]. Ketone bodies, consisting of acetone, acetoacetate and β-hydroxybutyrate, are metabolites produced during fatty acid metabolism in the liver, can be transported throughout the body and serve as a glucose-sparing energy source. Supplementation with ketone esters and dietary manipulations to augment endogenous ketone production attenuate memory loss in aging[142–144] and in mouse models of neurodegenerative diseases[145]. Further exploration is needed to understand the capacity of ketone bodies to reverse hallmarks of brain aging. Likewise, work identifying additional circulating blood factors capable of conferring the benefits of caloric restriction to the aged brain could have a profound effect on developing therapies for age-related brain dysfunction.

Conclusions and future directions

Applying cutting-edge molecular technologies to investigate effects of systemic and lifestyle interventions has yielded insight into the cellular and molecular targets and tissues of origin of pro-aging and pro-youthful factors in blood. A number of these circulating factors have been posited for future therapeutic applications to enhance cognitive resilience and reduce risk for dementia-related neurodegenerative diseases. However, to achieve this promise, it is critical for the burgeoning field of brain rejuvenation to tackle a series of important questions that remain unanswered.

To what extent do pro-aging and pro-youthful factors act through convergent or divergent mechanisms? With respect to a common tissue of origin, the hematopoietic system and inflammatory processes emerge as a source of pro-aging factors. Nevertheless, in many cases, the cell type or tissue sources remain obfuscated. Although earlier work identified a series of muscle-derived myokines, the liver as a major secretory organ is rapidly emerging as an additional source of exercise-induced factors, with IGF1, GPLD1, SEPP1 and clusterin all being putative liver-derived exerkines (Fig. 4). Regarding mechanisms of action, numerous aging and rejuvenating factors exert similar effects on the brain; therefore, it is important to understand whether each factor acts through the same or parallel cellular targets and molecular pathways. Given the predominant immune nature of pro-aging factors in old blood, microglia appear an obvious first target. However, several recent studies are highlighting BECs as a potential nexus by which pro-aging factors, including VCAM1, ASM, CyPA and CCL2, regulate brain aging. Conversely, pro-youthful factors identified across interventions, such as GDF11, clusterin, GPLD1 and α-klotho, may likewise

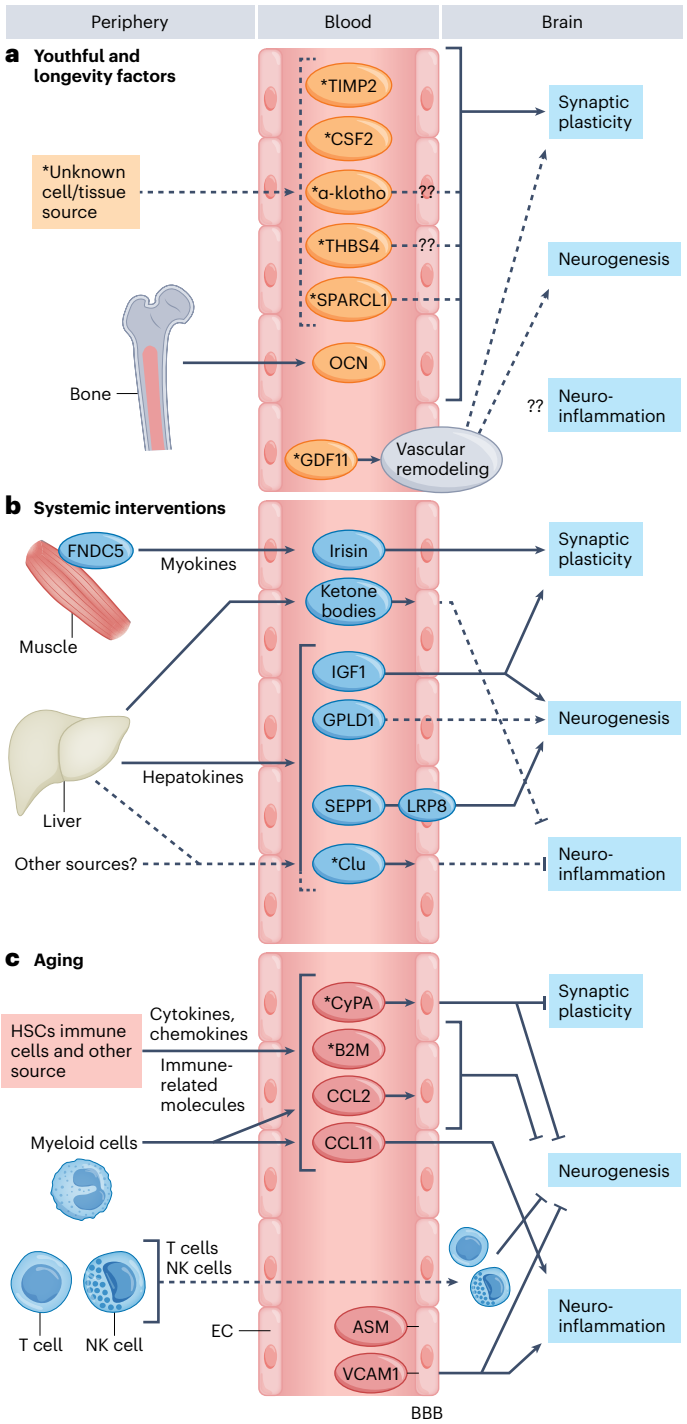

Fig. 4 | Intertissue communication in brain aging and rejuvenation. Systemic factors and cell types, their potential tissue of origin and direct versus indirect mechanisms of action on functional hallmarks of brain aging are divided into three main categories: youthful and longevity factors (**a**), factors associated with systemic (or lifestyle) interventions such as exercise and caloric restriction (**b**) and pro-aging factors (**c**). **a**, Youthful and longevity factors (indicated in brown) are of undetermined origin. TIMP2, CSF2, α-klotho, THBS4, SPARCL1 and osteocalcin (OCN) enhance synaptic and/or regenerative functions directly in the aged brain. GDF11 and α-klotho act through potentially indirect mechanisms (for example, by enhancing brain vascular function). THBS4 and SPARCL1 enhance neuronal functions in vitro but have not been tested in vivo. The effect of pro-youthful factors on neuroinflammation has not been tested. **b**, Exercise-induced factors (exerkines, indicated in blue) are predominantly derived from muscle (myokines: FNDC5 and irisin) and liver (hepatokines: IGF1, GPLD1, SEPP1, clusterin (Clu)) and enhance synaptic and regenerative functions during old age. **c**, Pro-aging factors (indicated in red) are predominantly immune-related molecules, such as cytokines and chemokines (CCL11, CCL2, B2M) and immune cells (T cells and NK cells). Pro-aging factors drive maladaptive neuroinflammatory changes, inhibit neurogenesis and impair synaptic plasticity in the brain. A question mark indicates unknown effect or limited supporting data; a dashed line indicates a potentially indirect mechanism; an asterisk indicates an unknown tissue or cell source; an arrowhead indicates a promotion; and a flathead represents inhibition of a cellular process in the brain.

exert their rejuvenating effects indirectly on the aged brain by restoring function to the aging vasculature and additional peripheral targets. Additionally, a series of pro-youthful factors, including TIMP2, osteocalcin, SPARCL1 and THSB4, appear to selectively enhance synaptic or cognitive functions; whereas others, such as FGF17 and SEPP1, have been demonstrated to regulate regenerative and stem cell functions. Collectively, these findings indicate that brain function can be restored through several parallel targets as well as direct and indirect mechanisms with relevance for future therapeutic approaches.

How broad ranging are the effects of pro-aging and pro-youthful factors throughout the brain? Apart from GDF11, most pro-aging and pro-youthful factors have been investigated in a single brain area or in the context of specific cellular hallmarks of brain aging, such as neurogenesis or synaptic plasticity. Considering the differential effects of aging on different brain regions and a growing understanding of the cellular and regional heterogeneity of neurons, microglia and astrocytes, it is essential that the effect of each circulating blood factor be examined across a wider range of brain regions and cellular hallmarks of brain aging.

Are there additional unidentified blood factors? Identification of pro-aging and pro-youthful blood factors has been challenging, as both mass spectrometry and antibody- or aptamer-based technologies have their own limitations in the total number of factors that can be surveyed, as well as biases in the factors that are enriched for by each platform. One such confound is that the protein content in blood plasma is often obscured by highly abundant proteins such as albumin and globulins, often requiring depletion methods for downstream analyses and detection of the larger number of the less-abundant blood protein components. Additional rejuvenating blood factors may be membrane bound or located within microvesicles, exosomes or platelets and released only in specific cellular contexts. This highlights the need for new tools to detect potential unidentified blood factors, for example, bioorthogonal labeling approaches. This will enable broader and more refined assessment of intertissue communication between peripheral signaling hubs, such as the liver, and the aging or rejuvenated brain. Additionally, unidentified blood factors could be of a completely different nature from those reported thus far, including lipids and metabolites. This consideration will be important as research begins to address whether the effects of other interventions, such as hormetic stresses and caloric restriction, can be transferred through systemic administration of circulating blood factors.

What would potential therapeutic strategies leveraging pro-youthful and pro-aging factors look like? It is unlikely that a single factor drives aging or that a single therapeutic intervention would be sufficient to restore function to a whole organism across all tissues. Because individuals appear to progress along different aging trajectories, future therapies would probably necessitate a combination of biomarker analyses to decode the unique aging profile in combination with a personalized treatment regimen composed of lifestyle interventions, pro-youthful factors and inhibition of pro-aging factors. For example, treatment may consist of mimetics of pro-youthful factors that decrease with age (for example, GDF11 or osteocalcin) and inhibition of pro-aging factors that increase with age (for example, CCL11 or B2M). These interventions may be synergistically combined with aging-independent pathways, such as exerkine mimetics (for example, GPLD1 or SEPP1) that enhance cognitive function but with levels that do not change with age[7,118]. Furthermore, identification of convergent mechanisms may point to future molecular targets, activation of which may provide additive benefits of multiple systemic factors.

Ultimately, rapid advances in our understanding of the tissues, cells and circulating blood factors involved in mitigating drivers of brain aging or transferring the benefits of systemic and lifestyle interventions bring hope that one day the memories typically lost with age can instead remain grounded in the rejuvenated plasticity that is unlocked through the intricate communication between blood and brain.

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Competing interests

The authors declare no competing interests.

Additional information

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