Naunyn-Schmiedeberg's Archives of Pharmacology
https://doi.org/10.1007/s00210-023-02657-5

REVIEW

Aging and age-related diseases with a focus on therapeutic potentials of young blood/plasma

Leila Hosseini[1] · Parviz Shahabi[2] · Ali Fakhari[1] · Hamid Soltani Zangbar[3] · Fatemehsadat Seyedaghamiri[3] · Jafar Sadeghzadeh[3] · Nasrin Abolhasanpour[4]

Received: 6 July 2023 / Accepted: 31 July 2023

Abstract

Aging is accompanied by alterations in the body with time-related to decline of physiological integrity and functionality process, responsible for increasing diseases and vulnerability to death. Several ages associated with biomarkers were observed in red blood cells, and consequently plasma proteins have a critical rejuvenating role in the aging process and age-related disorders. Advanced age is a risk factor for a broad spectrum of diseases and disorders such as cardiovascular diseases, musculoskeletal disorders and liver, chronic kidney disease, neurodegenerative diseases, and cancer because of loss of regenerative capacity, correlated to reduced systemic factors and raise of pro-inflammatory cytokines. Most studies have shown that systemic factors in young blood/plasma can strongly protect against age-related diseases in various tissues by restoring autophagy, increasing neurogenesis, and reducing oxidative stress, inflammation, and apoptosis. Here, we focus on the current advances in using young plasma or blood to combat aging and age-related diseases and summarize the experimental and clinical evidence supporting this approach. Based on reports, young plasma or blood is new a therapeutic approach to aging and age-associated diseases.

Keywords Aging · Young plasma · Blood · Regeneration · Inflammation · Blood factors

Introduction

The aging process is related to a loss of physiological functions across all organ systems within the body through disrupted homeostatic and regenerative mechanisms (Liu and Rando 2011). It is a driving factor of numerous age-associated diseases, including neurodegenerative diseases, cardiovascular disease and liver, immune system disorders, and musculoskeletal disorders. No effective treatment was identified for most of these disorders, and despite several decades of research and clinical investigation, aging has declined the effectiveness of treatment (Castellano 2019; Kim et al. 2020a; Zhavoronkov 2020). To enhance the quality of life for aged people, strategies that combat aging-associated dysfunctions are necessary.

The proper model to identify and study the aging process is red blood cells (RBCs) (Antonelou et al. 2010). Several biomarkers related to aging and senescence were observed in RBCs, such as the ferric-reducing ability of plasma (FRAP), cysteine influx, level of malondialdehyde, protein carbonylation, and activity of the plasma membrane redox system (PMRS) (Kumar and Rizvi 2014; Tanase et al. 2016; Wang et al. 2015). Following the aging process, a remarkable decline has been seen in metabolic activity and the structure of RBCs (Bratosin et al. 1998). Different metabolomics data from human plasma showed that aging influences plasma metabolite levels, so abundant metabolites are connected with age (Chaleckis et al. 2016; Darst et al. 2019; Lehallier et al. 2019; Tanaka et al. 2018). Several studies notion that all the pro-aging and rejuvenating factors exist in the circulation, and a board range of research with different methods

✉ Leila Hosseini
leilahosseini337@gmail.com

✉ Nasrin Abolhasanpour
nasrin.a64@gmail.com

[1] Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

[2] Department of Physiology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, IR, Iran

[3] Department of Neurosciences, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

[4] Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Published online: 08 August 2023

efforts to recognize these factors (Katsimpardi et al. 2014; Loffredo et al. 2013; Sinha et al. 2014). Plasma proteins have a critical role in aging and age-related diseases (Baht et al. 2015; Katsimpardi et al. 2014; Villeda et al. 2014). Moreover, various plasma proteins have been recognized as crucial rejuvenating factors, which showed beneficial effects in various tissues (de Magalhães et al. 2017). Appropriate using of these factors and accurate medical implementation into the bloodstream permit transporting signals to the internal systems of the body that regularly monitor aging (Vaiserman et al. 2018).

A large body of studies have showed that young plasma or blood has favorable effects in protecting against aged-associated diseases in various tissues through restoring autophagy, increasing neurogenesis, and reducing oxidative stress, inflammation, and apoptosis. A rejuvenating effect of young blood/plasma has been shown in many organs, including the spinal cord (Ruckh et al. 2012), brain (Villeda et al. 2014), kidney (Huang et al. 2018), heart (Loffredo et al. 2013), liver (Liu et al. 2018), bone (Baht et al. 2015), and hair follicles (Keyes et al. 2013). Hence, the administration of young plasma or blood can be considered a potential strategy for prevention and treatment of age-associated deterioration of organs. So, in this review, we attempt to explain the effect of young plasma/blood on aging-related diseases and role of it as a therapeutic approach to combat aging and age-associated diseases.

Blood anti-aging/pro-aging factors

Interestingly, blood plasma is strongly identified as a potential and essential additive to increase in vitro progression and also survival of systems related to intracellular models (Greiner et al. 2011; Vogel et al. 2006; Walenda et al. 2011). So, it was observed that injection of young mice's blood or derivate in it to the blood flow of old mice has led to increased tissue-protective effects and regeneration of the organism related to aging (Loffredo et al. 2013; Villeda et al. 2014). The interest in the rejuvenation of old tissues following the application of young blood lies in identifying specific factors like cytokines, chemokines, hormones, or miRNAs (Kang and Yang 2020).

Apelin

Apelin is a hormone, a 13-amino acid peptide, declining with age in humans and mice, which was firstly known as an endogenous ligand with the obligation of regulating gastric acid production via a G-protein-coupled receptor, APJ (Tatemoto et al. 1998; Vinel et al. 2018). Both, apelin and APJ are broadly present in most of the body parts, and also have essential roles in various organs. Interestingly, apelin alleviates the symptoms of different illnesses such as hypertension (Zhang et al. 2009), metabolic disorders (Dray et al. 2008), neurological dysfunctions (Duan et al. 2019), hepatic diseases (Melgar-Lesmes et al. 2011), and also gastrointestinal diseases (Ge et al. 2018). A significant reduction in the circulating levels of apelin is reported in aged mice (Vinel et al. 2018). Despite the healthy appearance, the Apln − / − and Aplnr − / − mice undergo accelerated aging in several organs. However, pharmacologic or genetic inhibition of apelin-mediated signaling caused progressive cellular senescence, and a reduction in age-related pathologies was observed following the systemic restoration of apelin in mice (Rai et al. 2017). Cellular senescence is defined as a highly stable cell cycle arrest in response to several stressors, such as exposure to genotoxic agents, hypoxia, mitochondrial dysfunction, deprivation of nutrients, and oncogene activation. It arises throughout the lifespan and can have harmful effects on tissue function because of the numerous proteins they secrete. Cellular senescence contributes to tissue regenerative potential and function decline, inflammation, and tumorigenesis in old organisms (Chaib et al. 2022).

Myofibers have a role in the production of apelin, and robust production of apelin is stimulated by muscle contraction during exercise. Still, a remarkable decrease in apelin synthesis in the skeletal muscles and plasma was reported in old mice and humans (Vinel et al. 2018). Also, a reduction in the expression levels of apelin receptors was reported in muscle stem cells of aged mice (Vinel et al. 2018). So, using apelin supplements could restore skeletal muscle function by increasing the biogenesis of mitochondria (Vinel et al. 2018).

Beta 2–macroglobulin (β2M)

All nucleated cells can produce β2M; under normal physiological conditions, it is present in circulation. Enhanced plasma rates of β2M were reported in aged mice, while intrahippocampal or intravenous injection of β2M in young mice progressively led to impairment in neurogenesis process and cognitive dysfunction (Smith et al. 2015). Smith et al. reported a significant elevation of β2M in human cerebrospinal fluid (CSF) who have high age (Smith et al. 2015), although an association has been observed between β2M and frailty in the elderly (Liu et al. 2017). Recently, Althubiti and colleagues showed an elevation of β2M protein level in the human blood serum of aged persons, which could also have an association with the oxidative stress status of samples (Althubiti et al. 2021). The research on single-cell transcriptomic data proposes the β2M secretion by cardiomyocytes that stimulate cardiac fibroblast following ischemia–reperfusion injury (Molenaar et al. 2021), likely

demonstrating a tissue-specific role and function of β2M (Höving et al. 2022).

Cadherin-13

Another circulating factor that decreases with age is cadherin-13, which regulates cellular functions by cooperating with membrane-bound molecules. Despite attaching to the cell membrane, cadherin-13 is identified in the blood. A correlation was observed between decreased levels of circulating cadherin-13 and coronary artery disease (Pfaff et al. 2015). Its expression level is high in developing and mature brains (Takeuchi et al. 2000), and is also identified as a gene with risk of ADHD (Rivero et al. 2015). In the study tried by Yang and colleagues, they detected a reduction in plasma rates of cadherin-13 in old mice. In contrast, intraperitoneal injection of cadherin-13 resulted in a delay in bone loss following aging (Yang et al. 2020). Cadherin-13 is considered an age-associated bone factor and has a crucial role in osteoporosis/osteopenia during the aging process, so it could be considered a novel therapeutic molecule to bone loss treatment (Kang and Yang 2020).

Matrix metalloproteinase 9 (MMP9) and monocyte chemotactic protein 1 (MCP1)

In the multi-analyte research conducted by Chiao and colleagues, they revealed high levels of MMP9 and MCP1 in both plasma and in tissue of the left ventricle in old mice. So, they suggested MMP9 and MCP1 as potential biomarkers for heart aging (Chiao et al. 2011). In a recent clinical research, authors verified a high level of MMP9 in serum and saliva fluid of patients who suffer from cardiovascular disease (Isola et al. 2021). Furthermore, enhanced cardiac protection was observed in MMP9 knockout mice following the ischemia–reperfusion-induced myocardial infarction (Romanic et al. 2002), while MCP1 likely has a key role at the beginning of cardiovascular disease (Niu and Kolattukudy 2009). Later, progressive studies reported both MCP1 and MMP9 as potential biomarkers for aging in systemic level in the body (Kim et al. 2016).

Eotaxin 1

The chemokine Eotaxin 1, identified as C–C motif chemokine 11 (CCL11), showed a significant elevation with increasing age (Hoefer et al. 2017). It was showed that there is a negative association between increased plasma levels of Eotaxin 1 and neurogenesis (Villeda et al. 2011). Also, a study has shown a positive association between the Eotaxin 1 concentration and chronologic age by measuring the plasma levels of Eotaxin 1 in healthy humans (Villeda et al. 2011). Following the injection of CCL11 into young mice, the symptoms of aging in hippocampus, such as elevation of microglial activation and reduction in synapses, were observed (Das et al. 2019). Previous research also showed the negative association of CCL11 in plasma on the memory function of patients who have Alzheimer's dementia and elderly individuals living in rural communities (Bettcher et al. 2016; Butcher et al. 2018). However, a recently published clinical trial study measured the CCL11 plasma level in individuals with preclinical symptoms of Alzheimer's disease (AD) and healthy aged persons and did not find any significant changes among both groups (Prins et al. 2022). The most potential target of CCL11 in cardiovascular disease is the specific endothelial cells in the coronary arteries which led to increased vascular permeability and consequent activation of pathways such as p38-MAPK, STAT3, and NF-kappaB (Wu et al. 2013), but so far, no connection has been found between plasma levels of CCL11 and age-related cardiovascular disease (Höving et al. 2022).

Oxytocin

The hormone oxytocin is another factor related to the aging process (Höving et al. 2022). In the study tried by Elabd and coworkers, they reported an age-related decline in plasma oxytocin and its relationship with defects in muscle regeneration. In addition, it was observed that oxytocin has a crucial role in rejuvenating the muscle stem cells through promoting their proliferation following muscle damage. Furthermore, premature sarcopenia was shown in the aged $Oxt^{-/-}$ mice (Elabd et al. 2014). Mice and rhesus macaques observed an age-related decline in circulating oxytocin levels (Elabd et al. 2014; Parker et al. 2010). A remarkable reduction in the oxytocin level was also observed in postmenopausal women with osteoporosis (Breuil et al. 2011). Interestingly, oxytocin has a protective effect on cardiomyocytes by exerting anti-apoptotic and anti-inflammatory properties (Jankowski et al. 2020). An animal model study showed the increased level of oxytocin and its receptor expression in the heart of developing rats, which its amount decreased to lower levels postnatally (Jankowski et al. 2004).

Osteocalcin (OCN)

Bone-derived hormone OCN is another hormone that has been shown to decrease with age in all primates (Khrimian et al. 2017; Mera et al. 2016; Smith 2020). ELISA assays used by Mera and coworkers identified a remarkable decline in the plasma levels of OCN with advanced age in both male

and female mice (Mera et al. 2016). In addition, an association between a decline in plasma levels of OCN and a decline in cognitive functions was reported. Furthermore, applying the young plasma OCN into old mice could partially reverse the beneficial effects on cognitive function, while improvement in the cognitive abilities of aged mice was observed by systemic administration of OCN (Khrimian et al. 2017). In humans, a sex-specific effect of OCN was observed, so declining in the serum levels of OCN led to a default in left ventricular systolic function in men but was not observed in women (Zhang et al. 2019).

Growth differentiation factor 11 (GDF11)

Besides the contradictory findings in the literature, GDF11, which is also identified as bone morphogenetic protein 11 (BMP-11), is considered an age-related protein (Kang and Yang 2020). Loffredo and colleagues identified GDF11 as an anti-aging factor that reverses age-related cardiac hypertrophy (Loffredo et al. 2013). Besides its anti-aging effect in the heart, GDF11 has a protective role in reversing skeletal muscle aging so that, following systemic delivery of GDF11 protein, genomic integrity in aged muscle stem cells is restored and improved both muscle physiology and also physical functions (Sinha et al. 2014). Moreover, GDF11 plays an effective role in improving the aged brain via promoting vascular remodeling and, also in neurogenesis (Katsimpardi et al. 2014). In contrast to the protective role of GDF11 in aging, some follow-up studies showed the negative effect of GDF11 in aged tissues. GDF11 resulted in impaired muscle regeneration in mice by inhibiting myoblast differentiation (Egerman et al. 2015). In addition, Hinken and colleagues showed GDF11 did not have an influential role in the outgrowth of muscle stem cells (Hinken et al. 2016); indeed, skeletal and cardiac muscle atrophy was observed following the systemic overexpression of GDF11 (Hammers et al. 2017). GDF11 has a negative impact on bone formation; thus, inhibition of GDF11 functions could effectively prevent age-related osteoporosis (Liu et al. 2016). In line with the controversial result, in a recently published study by Peng and colleagues, after measurement of human serum GDF8 and GDF11, no age-related alteration was observed in GDF8 or GDF11 in the serum sample of healthy men between 20 and 90 years (Peng et al. 2022).

Tissue inhibitor of metalloproteinases 2 (TIMP2)

TIMP2 is another circulating factor that declines with age (Kang and Yang 2020). Castellano and colleagues reported a notable decrease in plasma and hippocampus levels of TIMP2 in aged mice. They showed an improvement in the hippocampus function after enriching the plasma of the human umbilical cord with TIMP2. Most importantly, systemic supplementation with TIMP2 increased cognition and plasticity of synapses in old mice. They conclude that plasma TIMP2 is key in reversing age-related neuronal dysfunction (Castellano et al. 2017). It is suggested that TIMP2 is implicated in the homing mechanisms of mesenchymal stem cells (Ries et al. 2007). In addition, TIMP2 deficiency led to inhibition in cardiac remodeling processes in mice following myocardial infarction, which occurs through the inhibition of membrane type 1 matrix metalloproteinase (Kandalam et al. 2010). In contrast, Kelly and colleagues in a clinical cohort with 1313 patients showed an association between the increased plasma levels of TIMP1, TIMP2, and TIMP4 and a high risk of adverse cardiovascular events following the acute myocardial injury (Kelly et al. 2010).

Human serum albumin (HSA)

HSA is the most rich protein in blood serum and possesses various functions in the maintenance of the colloidal osmotic pressure of the blood, and most prominently, in the transportation of ions, cell toxins, or cytokines (Yang et al. 2014). Furthermore, effective anti-oxidative properties of serum albumin were reported in the literature (Roche et al. 2008). Also, previous literature has showed a slight decline in serum HAS during the aging process (Greenblatt 1979; Weaving et al. 2016). The study by Costa and Páez summarized present knowledge about the therapeutic approach for patients with Alzheimer's disease by using plasma exchange with albumin replacement (Costa and Páez 2021). The meta-analysis study result of Wang and colleagues revealed a correlation between decreasing HSA and the elevation of atrial fibrillation risk (Wang et al. 2021). Recently, the protective effect of HSA has been showed against oxidative stress in mouse hippocampal slice cultures and adult human stem cell–derived neurons (Ruiz-Perera et al. 2021).

Exosomes

Exosomes are mediators of serum-induced effects and have a role in transporting anti-aging/pro-aging factors in circulating blood. Recently, several studies focused on the potential role of young plasma exosomes or exosomes derived from stem cell culture supernatants in different aspects of regenerative medicine (Jayaraman et al. 2021; Sun et al. 2021). In the animal study on the murine model, significant improvement in cardiac repair was observed following both intramyocardial and intravenous infusion of stem cell–derived exosomes (Ju et al. 2018; Zhao et al. 2019). The data of the

survey conducted by Xu and colleagues showed exosomes derived from mesenchymal stem cells remarkably reduced apoptosis after hypoxic injury (Xu et al. 2020). Moreover, the study by Bobis-Wozowicz and colleagues reported the potential of induced pluripotent stem cell–derived exosomes in the induction of proliferation. Also, they increased the cardiac and endothelial differentiation potential of human heart–derived mesenchymal stromal cells (Bobis-Wozowicz et al. 2015). In recent research, Lee and colleagues evaluated the effects of young mice serum samples of exosomes in Huntington's disease (HD). In the in vitro model, they showed an improvement in the pathological markers of HD (Lee et al. 2021).

Thrombospondin-4 (THBS4) and SPARC-like protein 1 (SPARCL1)

In the investigation of identifying rejuvenating factors present in the blood, Gan and colleagues, using mass spectrometry of plasma, found various proteins enhanced in old or young blood (Gan and Südhof 2019). From the proteins abundant in young plasma, THBS4 and SPARCL1 were more prominent. These two proteins have a crucial role in increasing synaptic density, responses, and induction of branching in dendrites of neurons that are trans-differentiated from human embryonic stem cells (Yang et al. 2020). Interestingly, both proteins are synaptogenic factors secreted from astrocytes, and they are extracellular matrix-associated proteins (Banker 1980). Proteins THBS1 and 2 are secreted from astrocytes and induce synaptogenesis, while THBS4 improves neurite adhesion and outgrowth (Arber and Caroni 1995). SPARCL1 has a role in regulating CNS synaptogenesis (Kucukdereli et al. 2011). Despite the achievement of this knowledge that THBS4 and SPARCL1 both are enriched in young mouse blood and in in vitro studies elevate synapse formation, their effects on process of rejuvenation in the brain remain unknown in animal models (Fig. 1) (Kang and Yang 2020).

The effect of young blood/plasma in aging and aged-related diseases

Alzheimer's disease

AD is the common form of dementia among the older people, and prevalence of it rises with age (Jiao et al. 2015). The neuropathological hallmarks of AD include accumulation of amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles formation, hyperphosphorylated tau protein, and neuronal loss (Gong et al. 2018). Recent studies have shed light on the therapeutic effects of young blood for aging-related diseases. Xia and colleagues observed that exogenous young blood serum administration could attenuate hippocampal learning and memory impairments, reduce Aβ plaque load, restore synaptic plasticity and synapse formation, and repair cholinergic circuit in aged AD model. They found that neuroprotective effects of young blood serum were mediated by activating repressor element 1-silencing transcription factor (REST)/Forkhead box protein O1 (FOXO1) signaling. Also, they revealed that pharmacological blockage of cholinergic activity abolished the neuroprotective actions of young blood in AD animals (Xia et al. 2019). It has been showed REST/FOXO1 signaling mediates stress resistance against toxic injuries related to AD and maintains neuronal physiology (Lu et al. 2014). Another study revealed that young blood improved working and associative memories in a transgenic mouse model of AD (Middeldorp et al. 2016). It has been reported that young plasma administration for

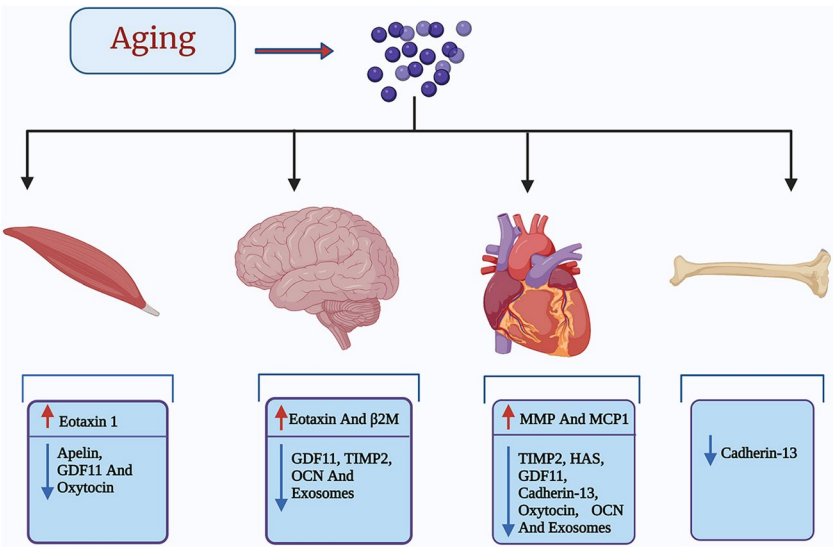

Fig. 1 The effects of aging on blood factors in organs. β2M, beta 2–macroglobulin; MMP9, matrix metalloproteinase 9; MCP1, monocyte chemotactic protein 1; OCN, osteocalcin; GDF11, growth differentiation factor 11; TIMP2, tissue inhibitor of metalloproteinases 2; HSA, human serum albumin

5 weeks restored the synaptic proteins (synaptophysin and calbindin) in the dentate gyrus, without changing amyloid plaques and microglial activation. This treatment could reverse the abnormal expression of the extracellular Signal-Regulated Kinase (ERK) and the p38 Mitogen-Activated Protein Kinase (MAPK) (Middeldorp et al. 2016).

Young plasma transfusion to 3×Tg-AD mice improved the spatial learning and short-term memory and diminished both tau and Aβ pathologies, in the mouse brain. Moreover, young plasma reduced Iba 1 level, a microglia marker, in the hippocampus, showing inhibition of neuroinflammation. However, there were not any significant changes in levels of synaptic proteins (synapsin 1, synaptophysin, postsynaptic density protein 95, cyclic AMP response element-binding protein (CREB), and phosphorylated CREB (p-CREB), and neurogenesis in dentate gyrus after treatment with young plasma (Zhao et al. 2020). It has been shown that infusion of plasma from young exercised mice attenuated cognitive deficits through increasing hippocampal neuroplasticity and mitochondrial functions and apoptosis suppression in AD mice (Kim et al. 2020b). The findings of this study showed that decreased protein level brain-derived neurotrophic factor (BDNF) was reversed by treatment with plasma from young exercised mice. However, this treatment failed to reduce tau hyperphosphorylation.

Aged brain

Aging drives cognitive dysfunction and susceptibility to neurological disorders in the healthy adult brain (Bishop et al. 2010). Given the increase in the percentage of old humans, it is essential to identify a means to preserve cognitive integrity by protecting or counteracting the aging process (Andrews-Hanna et al. 2007). In another study on aged mice, young blood can improve age-associated cognition deficits in both contextual fear conditioning and spatial learning and memory and rejuvenating synaptic plasticity by activating the CREB in the aged hippocampal (Villeda et al. 2014). Remyelination is a spontaneous regenerative process in the adult central nervous system (CNS) to restore saltatory conduction, impede axonal degeneration, and promote functional recovery (Edgar and Nave 2009). With advancing age because of changes in the environmental signals regulating remyelination and also alternations in epigenetic within oligodendrocyte precursor cells, remyelination reduces (Shen et al. 2008). The findings of Ruckh et al. explained that, in the aging CNS, exposure to a young systemic milieu increases activity of remyelination (Ruckh et al. 2012).

GDF11 is a youth factor that belongs to the transforming growth factor β (TGFβ) family. It is founded in various tissues, including the brain and the myocardium and its level diminishes with advanced age in both the blood circulation and tissues (Loffredo et al. 2013). Injection of young plasma (three times per week, for 4 weeks) to old rats protected from oxidative stress (Tripathi et al. 2021). It reduced generation of reactive oxygen species (ROS) and increased the ferric-reducing ability of plasma levels (antioxidant ability of plasma), and also upregulated levels of reduced glutathione. In addition, increased protein carbonyl and malondialdehyde levels as well advanced oxidation of protein product (AOPP) content were reversed by young plasma treatment in old aged animals (Tripathi et al. 2021).

Cognitive dysfunction is commonly observed in the elderly patients who underwent anesthesia and surgery, which manifests changes in CNS function that persist for several days to years and affect the quality of life (Yuan et al. 2019). It has been reported that anesthesia and surgery suppress synaptic function via activating mammalian target of rapamycin and inhibiting autophagy (Gao et al. 2021). Recently, young plasma can reverse anesthesia and surgery-induced cognitive decline through activation of the TrkB/ERK/CREB signaling pathway and improvement in hippocampal synaptic plasticity (Li et al. 2022).

Cerebrovascular diseases

The incidence of stroke enhances significantly with advancing age (Ramirez-Lassepas 1998). Experimental and clinical stroke studies have showed that age associates with poor histologic outcome and worsened neurobehavioral impairments after ischemic stroke (Miao et al. 2013; Umehara et al. 2018). Up to now, no effective treatment has been introduced to cope with stroke post-complications.

Pan et al. used an animal model of ischemic stroke injury to investigate the effect of young plasma on infarct volume and neurobehavioral tests. They showed that administration of young plasma into aged rats reduced infarct volume and improved motor impairment after ischemic stroke (Pan et al. 2017). Cerebral amyloid angiopathy (CAA) is characterized by the deposition of Aβ in the walls of pial arteries and cortical perforators. CAA is a major cause of spontaneous intracerebral hemorrhage (ICH) in old people and plays an important role in age-associated cognitive decline (Jäkel et al. 2022). A study conducted by Li et al. showed that administration of young plasma ameliorated cognition and learning and memory impairments, and diminished anxiety in CAA model mice. It inhibited neuronal apoptosis and promoted neurogenesis in APP/PS1 mice. This treatment did not diminish the Aβ level in the cortex and hippocampus of APP/PS1 mice. Besides, they demonstrated that young plasma decreased the area of cerebral hemorrhage in APP/PS1 mice (Li et al. 2021).

A study has reported that administration of young plasma plays obviously therapeutic roles in the diminution of acute brain injury induced by ICH in aged rodents. In this study, the treatment with young plasma decreased

the mortality rate and neurological deficit score in aged ICH rats, which might be because of the reduction of brain water content and increased survival neurons around the peri-hematoma brain tissues. Interestingly, this treatment enhanced brain IGF-1 level, whereas the mRNA level was not altered (Yuan et al. 2019).

Depression

Late-life depression is the most mental disorder among old people and is related to cognitive deficits and executive dysfunction (Bulut 2009). It has been shown that young plasma eases depression-like behaviors in chronic unpredictable mild stress old rats through decreasing apoptosis in prefrontal cortex area (Ghaffari-Nasab et al. 2021). They also found that administration of young plasma can increase the sucrose consumption ratio in the sucrose preference test and the decrease in immobility time in the forced swimming test, indicating improved depression-like behaviors. Additionally, young plasma noticeably decreased the levels of interferon-gamma (IFN-γ), indoleamine 2,3-dioxygenase, kynurenine (Kyn), and Kyn to tryptophan (Kyn/Trp) ratio in the prefrontal cortex area. Also, the expression of the serotonin transporter and growth-associated protein (GAP)-43 was downregulated following chronic mild stress, which was reversed by young plasma therapy (Ghaffari-Nasab et al. 2022).

Liver

Aging is commonly related to defective autophagy and reduction of the liver function and restoration of autophagy promotes longevity and improves age-related anomalies. A reduced autophagy in an aged cell leads to harmful substances accumulation and finally apoptosis (Luo et al. 2013). Liu et al. (2018) found that young plasma can reverse age-dependent changes in hepatic function through the restoration of autophagy. Administration of young plasma significantly reduced serum levels of aspartate aminotransferase and alanine transaminase in old rats. Increased steatosis and fibrosis in aged livers were decreased by young plasma treatment. Moreover, young plasma-treated rats showed less senescence-associated b-galactosidase (SA-b-gal) activity and accumulation of lipofuscin (an autofluorescent compound), as well 16 and p21 protein levels, which are cellular senescence markers. Also, they showed that young plasma diminishes aged-induced endoplasmic reticulum stress and increased ability of liver regeneration (Liu et al. 2018). In aged livers, activity of autophagy is downregulated, whereas the autophagy restoration improves cellular maintenance and hepatic function (Schneider et al. 2015). Also, young serum substantially attenuated age-dependent liver ischemia–reperfusion injury via restoration of autophagy through activation of AMPK/ULK1 axis (Liu et al. 2019). Brack and coworkers revealed that young blood diminished age-dependent increase in tissue fibrosis through suppression of the Wnt signaling pathway in aged myogenic progenitors (Brack et al. 2007).

Kidney

In a study, it has been shown that a young blood environment could enhance the autophagy and ease apoptosis and inflammation in aged kidneys in a heterochronic parabiosis animal model (Huang et al. 2018). Furthermore, some studies have been revealed that renal fibrosis is associated with enhanced NF-κB expression which can activate fibroblasts and renal tubular cells to secrete cytokines, and exert a positive feedback effect on angiotensin, promoting renal fibrosis via several pathways (Chung et al. 2017; Woods et al. 2001). Plasminogen activator inhibitor-1 (PAI-1) inhibits the degradation of the extracellular matrix by reducing plasmin generation and induced by angiotensin and is essential in remodeling of renal fibrosis (Yamamoto et al. 2014). The level of angiotensin and PAI-1 enhanced with increasing age, and aged mouse parabiose to young mouse has restored the ability of antifibrosis via downregulation of PAI-1, angiotensin, and pNF-κB expression (Huang et al. 2018).

Bone

With aging, the capacity tissues to repair and regenerate decrease. Hence, bone repair and associated processes, such as an osseous integration of implants, happen at a slower speed in old patients relative to young patients (Nilsson and Edwards 1969). Baht et al. (2015) examined the role of young plasma in fracture repair and osteogenic potential in aged animals. They found that young plasma reversed the aged fracture repair phenotype and reduced osteoblastic differentiation capacity of aged mice through modulate β-catenin signaling (Baht et al. 2015).

Adipose tissue

Cellular senescence is an essential aging mechanism that contributes to age-associated chronic inflammation and organ dysfunction such as visceral adipose tissue. The phenomenon of cellular senescence is characterized by the increased expression of cyclin-dependent kinase inhibitor genes: p16 (Cdkn2a) and p21 (Cdkn1a/ Cip1), accompanied by an exhibition of aged-related secretary phenotype (Tchkonia et al. 2010). A study examined young plasma in cellular senescence phenotypes in the visceral adipose tissue of aged mice. They found that expression of pro-inflammatory cytokines (Mcp-1 and Il-6), p16, and p21 reduced in the presence of young serum (Ghosh et al. 2019). It is

Table 1 The effects of young plasma/blood in aging animals

Treatment	Dose/time	Species	Organ	Main findings	References
Young blood	100 lL per injection, 10 times over 30 days, IV	Male APP/PS1 mice	Brain	Reduced learning and memory and Ab plaque, restored synapse formation and synaptic plasticity, repaired the hippocampal cholinergic circuit, activation of REST/FOXO1 signaling	Xia et al. (2019)
Young plasma	150μL/injection, twice a week for 4 weeks, IV	Female APP mice	Brain	Improved working memory and associative memory, restoration of levels of synaptic and neuronal proteins	Middeldorp et al. (2016)
Young plasma	150 μL twice a week for 8 weeks, IV	Female 16–17-month-old 3 × Tg-AD mice	Brain	Improved short-term memory and spatial learning and memory, decreased both tau and Aβ pathologies, as well as neuroinflammation	Zhao et al. (2020)
Young plasma	100 μL,10 times at 3-day intervals, IV	12-month-old 3xTg-AD mice	Brain	Improved neuroplasticity, mitochondrial function, and cognitive function, suppressed apoptosis	Kim et al. (2020b)
Young blood	5 weeks, parabiosis	Mice	Brain	Improved age-related cognitive impairments in both contextual fear conditioning and spatial learning and memory, Rejuvenated synaptic plasticity, activation of CREB	Villeda et al. (2014)
Young plasma	1 mL, 4 weeks, IV	Rat	Brain	Reduced oxidative stress	Tripathi et al. (2021)
Young plasma	100 μL, once every 3 days	Rat	Brain	Activation of the TrkB/ERK/CREB signaling pathway, improved synaptic plasticity, alleviated cognitive dysfunction and dendritic and spine deficits	Li et al. (2022)
Young plasma	150 μL, 3 days, IP	Male rat	Brain	Reduced infarct volume and motor impairment, improved neurobehavioral deficit	Pan et al. (2017)
Young plasma	100 μL, twice a week for 4 weeks, IV	Mice	Brain	Improved cognition, learning and memory impairment, and anxiety, prevented neuronal apoptosis, and enhanced neurogenesis, reduced the area of cortical hemorrhage	Althubiti et al. (2021)
Young plasma	500 μL, 30 min after the ICH, IV	Rat	Brain	Reduced neurological deficit, alleviated severity of edema, the degree of necrosis, and inflammatory cell infiltration around the hematoma site, and reduced apoptosis	Yuan et al. (2019)
Young plasma	1 mL, times per week for four weeks, IV	Rat	Brain	Reduced neuronal apoptosis and increased locomotor activity	Ghaffari-Nasab et al. (2021)
Young plasma	1 mL, times per week for 4 weeks, IV	Rat	Brain	Reduced the levels of interferon-gamma (IFN-γ), IDO, Kyn, and Kyn to tryptophan (Kyn/Trp) ratio, as well immobility	Ghaffari-Nasab et al. (2022)
Young plasma	1 mL, times per week for 4 weeks, IV	Rat	Liver	Restored aging-impaired autophagy activity, ameliorates aging-induced hepatic injury, steatosis, and fibrosis, reduced aging-induced hepatic senescence and endoplasmic reticulum stress	Liu et al. (2018)

Table 1 (continued)

Treatment	Dose/time	Species	Organ	Main findings	References
Young plasma	1 mL, times per week for four weeks, IV	Rat	Liver	Restored age-impaired autophagy, via AMPK/ULK1 signaling. Reduced hepatocellular necrosis	Liu et al. (2019)
Young blood	4 weeks, parabiosis	Mice	kidney	Enhanced the autophagy of aged kidneys, mitigated apoptosis and inflammation, and reduced expression of aging-related protein p16 and SA-β-gal	Huang et al. (2018)
Young blood	4 weeks, parabiosis	Mice	Bone	Rejuvenated aged bone healing, modulated b-catenin signaling	Baht et al. (2015)
Young blood	4 weeks, parabiosis	Mice	Adipose Tissue	Reduced adipose tissue inflammation, diminished abundance of SEN-promoting ADKs, reduced p16 and p21 expression, reduced expression of senescence-associated and pro-inflammatory genes	Ghosh et al. (2019)

well known that impaired autophagy results in inflammation in aging visceral adipose tissue. So, the beneficial effect of circulating factors in young blood can be mediated through the restoration of autophagy activity (Ghosh et al. 2016). The effects of young blood/plasma in aged-related diseases reported in studies are summarized in Table 1.

Side effects of blood transfusion

Blood transfusion (RBCs, plasma, or platelets) has some critical risks, and certain complications are more probable with plasma than other kinds of blood components. Experimental and clinical research on the patients confront reactions after infusion of fresh-frozen plasma and blood demonstrated the etiology and pathogenesis of adverse effects (Pandey and Vyas 2012). The list of side effects following the transfusion is well recognized and includes (1) transfusion-related circulatory overload, (2) allergic and anaphylactic responses, and (3) transfusion-associated acute lung injury. Besides, less common risks contain hemolytic transfusion reactions, transmission of infections, post-transfusion purpura, febrile nonhemolytic transfusion reactions, and RBC alloimmunization (Menis et al. 2015). Although most of these adverse effects are not lethal and can be treated, developing new approaches for plasma and blood transfusion will raise transfusion safety by diminishing inappropriate.

Conclusion

Young blood has rejuvenating effects on aged animals. Numerous emerging studies show the potential of young blood in treating a variety of pathologies after aged-related diseases. Young blood can be effective in the control of inflammation, apoptosis, autophagy, neurogenesis, synaptic plasticity, and myelination following aged-associated diseases. So numerous proteins, hormones, and chemokines were discovered in plasma that have pro-aging or anti-aging effects. More investigations into identifying other effective agents and functions of young blood will help to develop novel strategies for combat with aging and age-related diseases.

Authors Contributions L. H and N.A: conceptualization, methodology, writing—original draft preparation and prepared figure. P. S, A. F, H. S, F. S, and J. S: writing—reviewing and editing. All authors read and approved the final manuscript. The authors confirm that no paper mill and artificial intelligence was used.

Data Availability Not applicable.

Declarations

Ethical approval Not required.

Consent to participate This is review article.

Consent for publication All authors declare that they have seen and approved the submitted version of this manuscript.

Competing interests The authors declare no competing interests.

References

Althubiti M et al (2021) Beta 2 microglobulin correlates with oxidative stress in elderly. Experiment Gerontol 150:111359

Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL (2007) Disruption of large-scale brain systems in advanced aging. Neuron 56:924–935

Antonelou MH, Kriebardis AG, Papassideri IS (2010) Aging and death signalling in mature red cells: from basic science to transfusion practice. Blood Transfus 8:s39

Arber S, Caroni P (1995) Thrombospondin-4, an extracellular matrix protein expressed in the developing and adult nervous system promotes neurite outgrowth. J Cell Biol 131:1083–1094. https://doi.org/10.1083/jcb.131.4.1083

Baht GS et al (2015) Exposure to a Youthful Circulation Rejuvenates Bone Repair through Modulation of β-Catenin. Nat Commun 6:1–10

Banker GA (1980) Trophic interactions between astroglial cells and hippocampal neurons in culture. Science 209:809–810. https://doi.org/10.1126/science.7403847

Bettcher BM et al (2016) MCP-1 and eotaxin-1 selectively and negatively associate with memory in MCI and Alzheimer's disease dementia phenotypes. Alzheimers Dement (Amst) 3:91–97. https://doi.org/10.1016/j.dadm.2016.05.004

Bishop NA, Lu T, Yankner BA (2010) Neural mechanisms of ageing and cognitive decline. Nature 464:529–535

Bobis-Wozowicz S et al (2015) Human induced pluripotent stem cell-derived microvesicles transmit RNAs and proteins to recipient mature heart cells modulating cell fate and behavior. Stem Cells 33:2748–2761. https://doi.org/10.1002/stem.2078

Brack AS, Conboy MJ, Roy S, Lee M, Kuo CJ, Keller C, Rando TA (2007) Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science 317:807–810

Bratosin D et al (1998) Cellular and molecular mechanisms of senescent erythrocyte phagocytosis by macrophages. A Rev Biochimie 80:173–195

Breuil V et al (2011) Oxytocin and bone remodelling: relationships with neuropituitary hormones, bone status and body composition. Joint Bone Spine 78:611–615. https://doi.org/10.1016/j.jbspin.2011.02.002

Bulut S (2009) Late Life Depression: a Literature Review of Late-Life Depression and Contributing Factors. Anales De Psicología 25:21–26

Butcher L et al (2018) Association between plasma CCL11 (eotaxin-1) and cognitive status in older adults: differences between rural and urban dwellers. Exp Gerontol 113:173–179. https://doi.org/10.1016/j.exger.2018.10.004

Castellano JM (2019) Blood-Based Therapies to Combat. Aging Gerontol 65:84–89. https://doi.org/10.1159/000492573

Castellano JM et al (2017) Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. Nature 544:488–492. https://doi.org/10.1038/nature22067

Chaib S, Tchkonia T, Kirkland JL (2022) Cellular senescence and senolytics: the path to the clinic. Nat Med 28:1556–1568

Chaleckis R, Murakami I, Takada J, Kondoh H, Yanagida M (2016) Individual variability in human blood metabolites identifies age-related differences. Proc Natl Acad Sci 113:4252–4259

Chiao YA et al. (2011) Multi-analyte profiling reveals matrix metalloproteinase-9 and monocyte chemotactic protein-1 as plasma biomarkers of cardiac aging. Circulation: Cardiovasc Genet 4:455–462

Chung KW et al (2017) Involvement of NF-κBIZ and Related Cytokines in Age-Associated Renal Fibrosis. Oncotarget 8:7315

Costa M, Páez A (2021) Emerging insights into the role of albumin with plasma exchange in Alzheimer's disease management. Transfus Apher Sci 60:103164. https://doi.org/10.1016/j.transci.2021.103164

Darst BF, Koscik RL, Hogan KJ, Johnson SC, Engelman CD (2019) Longitudinal Plasma Metabolomics of Aging and Sex. Aging (Albany NY) 11:1262

Das MM et al (2019) Young Bone Marrow Transplantation Preserves Learning and Memory in Old Mice. Commun Biol 2:73. https://doi.org/10.1038/s42003-019-0298-5

de Magalhães JP, Stevens M, Thornton D (2017) The Business of Anti-Aging Science Trends. Biotechnol 35:1062–1073. https://doi.org/10.1016/j.tibtech.2017.07.004

Dray C et al (2008) Apelin stimulates glucose utilization in normal and obese insulin-resistant mice. Cell Metab 8:437–445

Duan J et al (2019) Neuroprotective effect of Apelin 13 on ischemic stroke by activating AMPK/GSK-3β/Nrf2 signaling. J Neuroinflamm 16:1–16

Edgar JM, Nave K-A (2009) The role of CNS glia in preserving axon function. Curr Opin Neurobiol 19:498–504

Egerman MA et al (2015) GDF11 increases with age and inhibits skeletal muscle regeneration. Cell Metab 22:164–174. https://doi.org/10.1016/j.cmet.2015.05.010

Elabd C et al (2014) Oxytocin is an Age-Specific Circulating Hormone That is Necessary for Muscle Maintenance and Regeneration. Nat Commun 5:4082. https://doi.org/10.1038/ncomms5082

Gan KJ, Südhof TC (2019) Specific factors in blood from young but not old mice directly promote synapse formation and NMDA-receptor recruitment. Proc Natl Acad Sci 116:12524–12533

Gao S et al (2021) Role of mTOR-regulated autophagy in synaptic plasticity related proteins downregulation and the reference memory deficits induced by anesthesia/surgery in aged mice Frontiers in Aging. Neuroscience 13:628541

Ge Y et al (2018) Adipokine apelin ameliorates chronic colitis in Il-10−/− mice by promoting intestinal lymphatic functions. Biochem Pharmacol 148:202–212

Ghaffari-Nasab A, Badalzadeh R, Mohaddes G, Javani G, Ebrahimi-Kalan A, Alipour MR (2022) Young plasma induces antidepressant-like effects in aged rats subjected to chronic mild stress by suppressing indoleamine 2, 3-dioxygenase enzyme and kynurenine pathway in the prefrontal cortex. Neurochem Res 47:358–371

Ghaffari-Nasab A, Badalzadeh R, Mohaddes G, Alipour MR (2021) Young plasma administration mitigates depression-like behaviours in chronic mild stress-exposed aged rats by attenuating apoptosis in prefrontal cortex. Exp Physiol 106:1621–1630

Ghosh AK, Mau T, O'Brien M, Garg S, Yung R (2016) Impaired Autophagy Activity is Linked to Elevated ER-Stress and Inflammation in Aging Adipose Tissue. Aging (Albany NY) 8:2525–2537. https://doi.org/10.18632/aging.101083

Ghosh AK, O'Brien M, Mau T, Qi N, Yung R (2019) Adipose tissue senescence and inflammation in aging is reversed by the young milieu. J Gerontol: A 74:1709–1715

Gong C-X, Liu F, Iqbal K (2018) Multifactorial hypothesis and multitargets for Alzheimer's disease. J Alzheimers Dis 64:S107–S117

Greenblatt DJ (1979) Reduced serum albumin concentration in the elderly: a report from the Boston Collaborative Drug

Surveillance Program. J Am Geriatr Soc 27:20–22. https://doi.org/10.1111/j.1532-5415.1979.tb01715.x
Greiner J et al (2011) Efficient animal-serum free 3D cultivation method for adult human neural crest-derived stem cell therapeutics. Eur Cell Mater 22:403–419
Hammers DW, Merscham-Banda M, Hsiao JY, Engst S, Hartman JJ, Sweeney HL (2017) Supraphysiological levels of GDF11 induce striated muscle atrophy. EMBO Mol Med 9:531–544. https://doi.org/10.15252/emmm.201607231
Hinken AC, Powers JM, Luo G, Holt JA, Billin AN, Russell AJ (2016) Lack of evidence for GDF11 as a rejuvenator of aged skeletal muscle satellite cells. Aging Cell 15:582–584. https://doi.org/10.1111/acel.12475
Hoefer J, Luger M, Dal-Pont C, Culig Z, Schennach H, Jochberger S (2017) The "aging factor" eotaxin-1 (CCL11) is detectable in transfusion blood products and increases with the donor's age. Front Aging Neurosci 9:402
Höving AL, Schmidt KE, Kaltschmidt B, Kaltschmidt C, Knabbe C (2022) The role of blood-derived factors in protection and regeneration of aged tissues. Int J Mol Sci 23:9626
Huang Q et al (2018) A young blood environment decreases aging of senile mice kidneys. J Gerontol: A 73:421–428
Isola G, Polizzi A, Ronsivalle V, Alibrandi A, Palazzo G, Lo Giudice A (2021) Impact of matrix metalloproteinase-9 during periodontitis and cardiovascular diseases. Molecules 26:1777
Jäkel L, De Kort AM, Klijn CJ, Schreuder FH, Verbeek MM (2022) Prevalence of cerebral amyloid angiopathy: a systematic review and meta-analysis. Alzheimers Dement 18:10–28
Jankowski M, Broderick TL, Gutkowska J (2020) The Role of Oxytocin in Cardiovascular Protection. Front Psychol 11:2139. https://doi.org/10.3389/fpsyg.2020.02139
Jankowski M et al (2004) Oxytocin in cardiac ontogeny. Proc Natl Acad Sci U S A 101:13074–13079. https://doi.org/10.1073/pnas.0405324101
Jayaraman S, Gnanasampanthapandian D, Rajasingh J, Palaniyandi K (2021) Stem cell-derived exosomes potential therapeutic roles in cardiovascular diseases. Front Cardiovasc Med 8:723236. https://doi.org/10.3389/fcvm.2021.723236
Jiao S-S et al (2015) Edaravone alleviates Alzheimer's disease-type pathologies and cognitive deficits. Proc Natl Acad Sci 112:5225–5230
Ju C et al (2018) Transplantation of cardiac mesenchymal stem cell-derived exosomes promotes repair in ischemic myocardium Journal of Cardiovascular. Transl Res 11:420–428
Kandalam V et al (2010) TIMP2 deficiency accelerates adverse post-myocardial infarction remodeling because of enhanced MT1-MMP activity despite lack of MMP2 activation. Circ Res 106:796–808. https://doi.org/10.1161/circresaha.109.209189
Kang JS, Yang YR (2020) Circulating Plasma Factors Involved in Rejuvenation. Aging (Albany NY) 12:23394–23408. https://doi.org/10.18632/aging.103933
Katsimpardi L et al (2014) Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science 344:630–634. https://doi.org/10.1126/science.1251141
Kelly D et al (2010) Usefulness of plasma tissue inhibitors of metalloproteinases as markers of prognosis after acute myocardial infarction. Am J Cardiol 106:477–482. https://doi.org/10.1016/j.amjcard.2010.03.060
Keyes BE et al (2013) Nfatc1 orchestrates aging in hair follicle stem cells. Proc Nat Acad Sci 110:E4950–E4959
Khrimian L et al (2017) Gpr158 mediates osteocalcin's regulation of cognition. J Exp Med 214:2859–2873. https://doi.org/10.1084/jem.20171320
Kim S et al (2016) Differential matrix metalloprotease (MMP) expression profiles found in aged gingiva. PloS one 11:e0158777
Kim DH et al (2020a) Senoinflammation: a major mediator underlying age-related metabolic dysregulation. Exp Gerontol 134:110891. https://doi.org/10.1016/j.exger.2020.110891
Kim T-W, Park S-S, Park J-Y, Park H-S (2020b) Infusion of plasma from exercised mice ameliorates cognitive dysfunction by increasing hippocampal neuroplasticity and mitochondrial functions in 3xTg-AD mice. Int J Molec Sci 21:3291
Kucukdereli H et al (2011) Control of excitatory CNS synaptogenesis by astrocyte-secreted proteins Hevin and SPARC. Proc Natl Acad Sci U S A 108:E440-449. https://doi.org/10.1073/pnas.1104977108
Kumar D, Rizvi SI (2014) Markers of oxidative stress in senescent erythrocytes obtained from young and old age rats. Rejuvenation Res 17:446–452
Lee M, Im W, Kim M (2021) Exosomes as a potential messenger unit during heterochronic parabiosis for amelioration of Huntington's disease. Neurobiol Dis 155:105374. https://doi.org/10.1016/j.nbd.2021.105374
Lehallier B et al (2019) Undulating changes in human plasma proteome profiles across the lifespan. Nat Med 25:1843–1850
Li N, Zhang X, Gu Z, Su C, Lian H (2021) Young plasma attenuates cognitive impairment and the cortical hemorrhage area in cerebral amyloid angiopathy model mice. Ann Transl Med 9(2):147. https://doi.org/10.21037/atm-20-8008
Li Y et al (2022) Young plasma reverses anesthesia and surgery-induced cognitive impairment in aged rats by modulating hippocampal synaptic plasticity. Front Aging Neurosci. 14:996223. https://doi.org/10.3389/fnagi.2022.996223
Liu A et al (2018) Young plasma reverses age-dependent alterations in hepatic function through the restoration of autophagy. Aging Cell 17:e12708
Liu A et al (2019) Young plasma attenuates age-dependent liver ischemia reperfusion injury. FASEB J 33:3063–3073
Liu L, Rando TA (2011) Manifestations and mechanisms of stem cell aging. J Cell Biol 193:257–266
Liu W et al (2016) GDF11 decreases bone mass by stimulating osteoclastogenesis and inhibiting osteoblast differentiation. Nat Commun 7:12794. https://doi.org/10.1038/ncomms12794
Liu Z-Y, Shen Y-Y, Ji L-J, Jiang X-Y, Wang X-F, Shi Y (2017) Association between serum β2-microglobulin levels and frailty in an elderly Chinese population: results from RuLAS. Clin Intervent Aging 12:1725
Loffredo FS et al (2013) Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. Cell 153:828–839. https://doi.org/10.1016/j.cell.2013.04.015
Lu T et al (2014) REST and stress resistance in ageing and Alzheimer's disease. Nature 507:448–454
Luo L et al (2013) Chronic resistance training activates autophagy and reduces apoptosis of muscle cells by modulating IGF-1 and its receptors, Akt/mTOR and Akt/FOXO3a signaling in aged rats. Experiment Gerontol 48:427–436
Melgar-Lesmes P et al (2011) Hypoxia and Proinflammatory Factors Upregulate Apelin Receptor Expression in Human Stellate Cells and Hepatocytes. Gut 60:1404–1411
Menis M et al (2015) Posttransfusion purpura occurrence and potential risk factors among the inpatient US elderly, as recorded in large M edicare databases during 2011 through 2012. Transfusion 55:284–295
Mera P et al (2016) Osteocalcin signaling in myofibers is necessary and sufficient for optimum adaptation to exercise. Cell Metab 23:1078–1092. https://doi.org/10.1016/j.cmet.2016.05.004
Miao J et al (2013) Overexpression of Adiponectin Improves Neurobehavioral Outcomes after Focal Cerebral Ischemia in Aged Mice. CNS Neurosci Therapeut 19:969–977
Middeldorp J et al (2016) Preclinical Assessment of Young Blood Plasma for Alzheimer Disease. JAMA Neurol 73:1325–1333

Molenaar B et al (2021) Single-cell transcriptomics following ischemic injury identifies a role for B2M in cardiac repair. Commun Biol 4:1–15

Nilsson B, Edwards P (1969) Age and fracture healing: a statistical analysis of 418 cases of tibial shaft fractures. Geriatrics (Basel, Switzerland) 24:112–117

Niu J, Kolattukudy PE (2009) Role of MCP-1 in cardiovascular disease: molecular mechanisms and clinical implications. Clin Sci 117:95–109

Pan M et al (2017) Aging Systemic Milieu Impairs Outcome after Ischemic Stroke in Rats. Aging Dis 8:519

Pandey S, Vyas GN (2012) Adverse Effects of Plasma Transfusion. Transfusion 52:65S-79S

Parker KJ, Hoffman CL, Hyde SA, Cummings CS, Maestripieri D (2010) Effects of age on cerebrospinal fluid oxytocin levels in free-ranging adult female and infant rhesus macaques. Behav Neurosci 124:428–433. https://doi.org/10.1037/a0019576

Peng L et al (2022) Age trends in growth and differentiation factor-11 and myostatin levels in healthy men, and differential response to testosterone, measured using liquid chromatography-tandem mass spectrometry. J Gerontol A Biol Sci Med Sci 77:763–769. https://doi.org/10.1093/gerona/glab146

Pfaff D, Schoenenberger AW, Dasen B, Erne P, Resink TJ, Philippova M (2015) Plasma T-Cadherin Negatively Associates with Coronary Lesion Severity and Acute Coronary Syndrome. Eur Heart J: Acute Cardiovasc Care 4:410–418

Prins S, de Kam ML, Teunissen CE, Groeneveld GJ (2022) Inflammatory Plasma Biomarkers in Subjects with Preclinical. Alzheimer's Dis Alzheimers Res Ther 14:106. https://doi.org/10.1186/s13195-022-01051-2

Rai R et al (2017) Downregulation of the apelinergic axis accelerates aging, whereas its systemic restoration improves the mammalian healthspan. Cell Reports 21:1471–1480

Ramirez-Lassepas M (1998) Stroke and the aging of the brain and the arteries. Geriatrics (Basel, Switzerland) 53:S44-48

Ries C, Egea V, Karow M, Kolb H, Jochum M, Neth P (2007) MMP-2, MT1-MMP, and TIMP-2 are essential for the invasive capacity of human mesenchymal stem cells: differential regulation by inflammatory cytokines. Blood 109:4055–4063. https://doi.org/10.1182/blood-2006-10-051060

Rivero O et al (2015) Cadherin-13, a risk gene for ADHD and comorbid disorders, impacts GABAergic function in hippocampus and cognition. Translat Psychiatry 5:e655–e655

Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E (2008) The antioxidant properties of serum albumin. FEBS Lett 582:1783–1787. https://doi.org/10.1016/j.febslet.2008.04.057

Romanic AM et al (2002) Myocardial protection from ischemia/reperfusion injury by targeted deletion of matrix metalloproteinase-9. Cardiovasc Res 54:549–558

Ruckh JM, Zhao J-W, Shadrach JL, van Wijngaarden P, Rao TN, Wagers AJ, Franklin RJ (2012) Rejuvenation of Regeneration in the Aging Central Nervous System. Cell Stem Cell 10:96–103

Ruiz-Perera LM et al (2021) Neuroprotection mediated by human blood plasma in mouse hippocampal slice cultures and in oxidatively stressed human. Neurons Int J Mol Sci 22:9567. https://doi.org/10.3390/ijms22179567

Schneider JL et al (2015) Loss of Hepatic Chaperone-Mediated Autophagy Accelerates Proteostasis Failure in Aging. Aging Cell 14:249–264

Shen S, Sandoval J, Swiss VA, Li J, Dupree J, Franklin RJ, Casaccia-Bonnefil P (2008) Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. Nat Neurosci 11:1024–1034

Sinha M et al (2014) Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. Science 344:649–652. https://doi.org/10.1126/science.1251152

Smith C et al (2020) Osteocalcin and its forms across the lifespan in adult men. Bone 130:115085. https://doi.org/10.1016/j.bone.2019.115085

Smith LK et al (2015) β2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis. Nat Med 21:932–937

Sun S-J, Wei R, Li F, Liao S-Y, Tse H-F (2021) Mesenchymal Stromal Cell-Derived Exosomes in Cardiac Regeneration and Repair. Stem Cell Reports 16:1662–1673

Takeuchi T, Misaki A, Liang SB, Tachibana A, Hayashi N, Sonobe H, Ohtsuki Y (2000) Expression of T-cadherin (CDH13, H-Cadherin) in human brain and its characteristics as a negative growth regulator of epidermal growth factor in neuroblastoma cells. J Neurochem 74:1489–1497

Tanaka T et al (2018) Plasma Proteomic Signature of Age in Healthy Humans. Aging Cell 17:e12799

Tanase M et al (2016) Role of Carbonyl Modifications on Aging-Associated Protein Aggregation. Sci Rep 6:1–14

Tatemoto K et al (1998) Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem Biophys Res Commun 251:471–476

Tchkonia T et al (2010) Fat tissue, aging, and cellular senescence. Aging Cell 9:667–684

Tripathi SS, Kumar R, Arya JK, Rizvi SI (2021) Plasma from young rats injected into old rats induce antiaging effects. Rejuvenation Res 24:206–212

Umehara T et al (2018) Can the amount of interventions during the convalescent phase predict the achievement of independence in activities of daily living in patients with stroke? A Retrospective Cohort Study. J Stroke Cerebrovasc Dis 27:2436–2444

Vaiserman A, Koliada A, Lushchak O (2018) Developmental programming of aging trajectory. Ageing Res Rev 47:105–122. https://doi.org/10.1016/j.arr.2018.07.007

Villeda SA et al (2011) The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 477:90–94

Villeda SA et al (2014) Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med 20:659–663

Vinel C et al (2018) The exerkine apelin reverses age-associated sarcopenia. Nat Med 24:1360–1371

Vogel JP, Szalay K, Geiger F, Kramer M, Richter W, Kasten P (2006) Platelet-rich plasma improves expansion of human mesenchymal stem cells and retains differentiation capacity and in vivo bone formation in calcium phosphate ceramics. Platelets 17:462–469

Walenda T et al (2011) Serum after Autologous Transplantation Stimulates Proliferation and Expansion of Human Hematopoietic Progenitor Cells. PloS One 6:e18012

Wang Y, Du P, Xiao Q, Li J, Liu X, Tan J, Zhang X (2021) Relationship between serum albumin and risk of atrial fibrillation: a dose-response meta-analysis. Front Nutr 8:728353. https://doi.org/10.3389/fnut.2021.728353

Wang Z, Wang Y, Liu H, Che Y, Xu Y (2015) Age-related variations of protein carbonyls in human saliva and plasma: is saliva protein carbonyls an alternative biomarker of aging? Age 37:1–8

Weaving G, Batstone GF, Jones RG (2016) Age and sex variation in serum albumin concentration: an observational study. Ann Clin Biochem 53:106–111. https://doi.org/10.1177/0004563215593561

Woods LL, Ingelfinger JR, Nyengaard JR, Rasch R (2001) Maternal protein restriction suppresses the newborn renin-angiotensin system and programs adult hypertension in rats. Pediatr Res 49:460–467

Wu JM, Hsieh TC, Yang CJ, Olson SC (2013) Resveratrol and its metabolites modulate cytokine-mediated induction of eotaxin-1 in human pulmonary artery endothelial cells. Ann N Y Acad Sci 1290:30–36. https://doi.org/10.1111/nyas.12151

Xia E et al (2019) Young blood rescues the cognition of Alzheimer's model mice by restoring the hippocampal cholinergic circuit. Neuroscience 417:57–69

Xu H, Wang Z, Liu L, Zhang B, Li B (2020) Exosomes derived from adipose tissue, bone marrow, and umbilical cord blood for cardioprotection after myocardial infarction. J Cell Biochem 121:2089–2102. https://doi.org/10.1002/jcb.27399

Yamamoto K, Takeshita K, Saito H (2014) Plasminogen activator inhibitor-1 in aging. Seminars Thromb Hemostasis 40:652–659. https://doi.org/10.1055/s-0034-1384635

Yang F, Zhang Y, Liang H (2014) Interactive association of drugs binding to human serum albumin. Int J Mol Sci 15:3580–3595. https://doi.org/10.3390/ijms15033580

Yang YR et al (2020) Plasma proteomic profiling of young and old mice reveals cadherin-13 prevents age-related bone loss. Aging (Albany NY) 12:8652

Yuan JJ et al (2019) Young plasma ameliorates aging-related acute brain injury after intracerebral hemorrhage. Biosci Rep 39(5):BSR20190537. https://doi.org/10.1042/BSR20190537

Zhang Q, Yao F, Raizada MK, O'Rourke ST, Sun C (2009) Apelin gene transfer into the rostral ventrolateral medulla induces chronic blood pressure elevation in normotensive rats. Circ Res 104:1421–1428

Zhang XL, Shen Y, Ma XJ, Lu ZG, Xu YT, Xiong Q, Bao YQ (2019) Low serum osteocalcin levels are correlated with left ventricular systolic dysfunction and cardiac death in Chinese men. Acta Pharmacol Sin 40:486–491. https://doi.org/10.1038/s41401-018-0080-0

Zhao J et al (2019) Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization. Cardiovasc Res 115:1205–1216

Zhao Y, Qian R, Zhang J, Liu F, Iqbal K, Dai C-L, Gong C-X (2020) Young blood plasma reduces Alzheimer's disease-like brain pathologies and ameliorates cognitive impairment in 3× Tg-AD mice. Alzheimer's Res Ther 12:1–13

Zhavoronkov A (2020) Geroprotective and senoremediative strategies to reduce the comorbidity, infection rates, severity, and lethality in gerophilic and gerolavic infections. Aging (Albany NY) 12:6492–6510. https://doi.org/10.18632/aging.102988