Chapter

Aging, Cerebrovascular Burden, and Cognitive Decline

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Abstract

Brain function is supported by the cerebrovascular system, and changes in vascular phenotype and function through aging process make the brain more susceptible to neurodegenerative diseases, particularly cognitive decline. Correspondingly, the incidence of dementia and the prevalence of neurodegenerative diseases have also increased. In aging, the vessels have been exposed to the inflammatory state by harmful factors referred to as the senescence-associated secretory phenotype (SASP). Aging is a complex process that is associated with accumulated cellular stresses and an increased stress response. The aging in the brain includes structural and functional changes, which cause brain pathologies in the elderly. Particularly, damaged neurovascular event can be a consequent trigger in the pathology of vascular cognitive impairment. This chapter introduces the current knowledge on cognitive decline according to cerebrovascular aging relevant to endothelial senescence and the changes in the SASPs.

Keywords: aging, cerebrovascular, cognitive impairment, senescence-associated secretory phenotype, endothelial cells

1. Introduction

Aging is a complex process that is associated with an accumulation of the effects of cellular stresses and an increased stress response. The aging in the brain includes structural and functional changes, which together cause brain pathologies in the elderly. These changes are also thought to be critical risk factors in the development of cognitive disorders [1, 2]. It is well known that the cerebrovascular system supports brain function [3]. Vascular phenotypic and functional changes caused by aging make the brain more susceptible to neurodegenerative diseases, particularly to cognitive decline [4]. Dysregulation of cerebral blood flow (CBF) is one factor in the pathogenesis of vascular cognitive impairment (VCI) [5]. However, definition, diagnostic criteria, and treatments for VCI have not been firmly established. Thus, strategies in translational medicine and the clinical approach to VCI patients and the current aged society need to be established. This is because according to the World Alzheimer Report 2015, it was estimated that 46.8 million people worldwide suffer from dementia, and this number is expected to increase to 74.7 million by 2030 and 131.5 million by 2050 [6]. The report also stated that the incidence of dementia, including Alzheimer's disease (AD) and vascular dementia (VaD), will increase by 45%. As a result of the increase in the size of the aging population, the incidence of dementia and the onset or prevalence of neurodegenerative diseases

are increasing. These diseases have become important social concerns and represent both a current and a future social and economic burden.

In the aging process, age-related cerebrovascular dysfunction results from multiple pathophysiological changes. The first of them is oxidative stress and inflammation. Excessive oxidative stress is well known to contribute to vascular aging in both animals [4, 7–10] and humans [11, 12]. It is an overproduction of reactive oxygen species (ROS) rather than accumulation of ROS. In cellular senescence, inflammatory mediators such as chemokines and cytokines are secreted in an autocrine or paracrine manner. This is often referred to as the senescence-associated secretory phenotype (SASP) [13–15]. The second is the narrowing of the vascular lumen caused by atherosclerotic plaques, which is referred to as atherosclerosis in large vessels or arteriosclerosis in small vessels [16–18]. Technically a further factor is endothelial cell senescence induced by the SASP in the aging process. This arises as a result of the action of pro-inflammatory cytokines such as interleukin (IL)-1 and IL-6 [19]. Under aging, atherosclerotic plaques are prone to arise in the human aorta and coronary arteries, which contain senescent endothelial cells [20]. The senescent phenotypes of endothelial cells can be physiologically classified as having either an anti-inflammatory phenotype or a pro-inflammatory senescent phenotype [21]. Recently, numerous studies have focused on the status of the immune system during aging [22–24]. This chapter introduces the current knowledge about cognitive decline according to cerebrovascular aging relevant to cellular senescence and the changes in the SASPs. It also provides approaches on how senescent vessels exposed to the SASP enhance age-related cerebrovascular degeneration and vascular damage-derived cognitive impairment.

2. Aging and vessels

Cellular senescence is the state in which normal cells cease to divide. It can be thought of as a type of programmed cell cycle arrest. The senescent cells go through changes in gene expression and secretion of soluble factors in response to excessive stresses [25]. The secreted soluble factors from senescent cells are referred to as the SASP [26–28]. The SASP includes interleukins (IL) and chemokines such as IL-1, IL-6, IL-8, monocyte chemoattractant protein (MCP)-2, and macrophage inflammatory protein (MIP)-1 [29]. In addition, nitric oxide, growth factors, and several matrix metalloproteinases have also been identified in the SASP [14]. Several studies have reported that SASP factors have roles in inducing normal cells to acquire a senescent phenotype and can act in a paracrine manner to affect the activity of other nearby cells [30]. This might suggest that SASP factors do not merely arise as a result of cell senescence but could rather act to promote the senescence phenotype in normal cells.

Although it still remains equivocal whether neurodegenerative diseases arise as a result of, or from, aging-related changes, it is clear, however, that the prevalence of neurodegenerative diseases that show a cognitive decline is positively associated with aging. Increases in oxidative stress and inflammation in response to aging trigger cellular senescence and the appropriate downstream responses. A series of these insults can aggravate age-related or neurodegenerative pathogenesis with several vascular diseases [31].

2.1 Endothelium

The endothelium is one of the vessel constituents and is important in vascular structure because of its high versatility. The endothelium has multifunctional

roles in maintaining blood fluidity and metabolic homeostasis. The features are important in regulating the delivery of water and nutrients through the whole body [32]. The endothelium also plays an important role in the resolution of inflammatory responses. Morphological and functional changes in the endothelium are also involved in the development of numerous pathological disorders [33, 34]. Endothelial cells are located in the inner layer of the vasculature and can come into contact with blood-containing macrophages. Therefore, endothelial cells are the first target of cytokines circulating in the blood. Simultaneously, endothelial cells also secrete pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, IL-15, MCP-1, and tumor necrosis factor (TNF)-α [29]. In fact, endothelial cell-derived pro-inflammatory cytokines and chemokines are important in recruiting immune cells to the site and play a role in wound healing, angiogenesis, and inflammatory diseases. In addition to their inflammatory function, endothelial cells also produce pro-thrombotic mediators and cellular adhesion molecules (ICAM-1, intercellular adhesion molecule-1; PAI-1, plasminogen activator inhibitor-1) and enhance the adhesion and transmigration of immune cells into underlying tissues. It has also been reported that senescent endothelial cells have reduced expression levels of nitric oxide (NO) as well as reduced expression levels and phosphorylation of endothelial NO synthase (eNOS) [35, 36].

It is well accepted that senescence in vascular endothelial cells is a common factor in various age-related diseases. Associated with aging, endothelial cells dynamically change the inflammatory phenotype to SASP [21]. A recent study has demonstrated that alterations in toll-like receptor (TLR) and TLR ligands during aging might determine the state of the inflammatory process [29]. Since endothelial cells are not immune cells, they cannot recognize foreign antigens via TLRs or present antigens through MHC II molecules to T and B cells [37]. On the other hand, endothelial cells have been shown to upregulate the mRNA levels of TLR-2, TLR-4, TLR-7, TLR-8, TLR-9, and TLR-10 during aging [38]. Since aging is a chronic inflammatory condition in the lower level, nonimmune endothelial cells could play a role in controlling and maintaining immune homeostasis. Taken these reasons, endothelial cells could be a therapeutic target to allow for recovery of a disruption in immune homeostasis.

Endothelial cells derived from patients with severe coronary artery disease have also been shown to be mostly senescent endothelial cells with reduced levels of telomeric DNA-binding factor 1 (TRF1) and increased telomere oxidation [20]. When TRF1 was overexpressed in a cellular aging model, namely, human umbilical vein endothelial cells' (HUVECs) passage for a long period of time, the telomere-associated DNA damage foci and the SASP were decreased [39, 40]. These results suggest that telomere dysfunction and the SASP occur prior to cellular senescence and induce vascular dysfunction following cardiovascular disease (CVD) development.

2.2 Atherosclerosis

Atherosclerosis and its associated clinical outcomes such as vascular stiffness are initiated and progressed through dysfunction in senescent endothelial cells [29]. During oxidation in the vessel, there are changes in its physicochemical properties including lipid charge, size, and content. Oxidized low-density lipid (oxLDL) becomes different from natural LDL. The oxLDL stimulates endothelial cells to induce the expression of adhesion molecules such as E-selectin and vascular cell adhesion molecule-1 (VCAM-1) on the surface of the artery [41]. Numerous senescent endothelial cells are detected in the aorta of the human with atherosclerotic plaques [42, 43]. The formation of atherosclerotic plaques is initiated by macrophages that infiltrate into the arterial intima in response to oxLDL present in

the vessel [69]. Lipid-laden foam cells become pro-inflammatory, and macrophages secrete pro-inflammatory cytokines. The recruited macrophages move into the artery, and consequently, the atherosclerotic plaque size and complexity are getting larger [44].

Atherosclerosis occurs following chronic exposure to cellular stressors. It has been reported that SASP can be restrained simply by inhibiting TNF-α without any transmission of senescence signals in an autocrine or paracrine manner [45]. Anti-TNF-α treatment has been demonstrated to physiologically reduce the non-cell autonomous effects of SASP. In patients treated with adalimumab (Humira, a human monoclonal antibody against TNF-α), epigenetic modifications were triggered. The molecular mechanisms are identified as TNF-α signaling in senescent endothelial cells, which raises the possibility of therapeutic approaches for age-associated diseases. In senescent human umbilical vein endothelial cells (HUVECs), the levels of miR-146a-5p and miR-126-3p show higher than younger HUVECs. Additionally, the levels of miR-146a-5p are increased in both senescent and young HUVECs following lipopolysaccharide (LPS) exposure, whereas the level of miR-126-3p is decreased only in senescent HUVECs and is unchanged in young HUVECs [45]. This study also showed that changes in the levels of several microRNAs (miRNAs) do not arise as a result of just treatment with LPS or an anti-TNF-α antibody. These data suggest that some miRNAs work in an age-dependent manner in vessels and endothelial cells.

2.3 Vascular aging

From a classical perspective, the aged vasculature is viewed as having worsened vasodilation, arterial stiffness, remodeling of the extracellular matrix, intimal thickening, and endothelial cell dysfunction [46]. The effects of vascular aging have been explored extensively and have been attributed to the number of different causes with genome instability and mTOR being two of the major causes. Studies with mTOR-inhibiting drugs in vessels have shown that such drugs have a deleterious effect on endothelial function in patients who have advanced arterial aging and inserted coronary stents [47–49]. Compared to human studies, cultured endothelial cells have augmented anti-inflammatory effects to mTOR inhibitors with a dose-dependent manner and have increased cytostatic effect [50]. It also showed that rapamycin, an mTOR inhibitor, induces the expression of PAI-1 in mice as well as in cultured endothelial cells [51]. When the Atg7 gene, one of the mediators of the autophagic process, is deleted in mice, vascular aging is accelerated [52]. In a mouse model of Hutchinson-Gilford progeria, autophagy is activated by AMPK activation and inhibition of mTOR [53]. These results showed that the mTOR–AMPK signaling pathway might be a link to the regulation of autophagy in age-related diseases. Based on the results described above, it is hard to firmly establish that rapamycin plays a preventive role on cellular senescence.

Telomere shortening is known to be a hallmark of cellular senescence. Telomeres are significantly shorter in several endothelial cells and vascular smooth muscle cells (VSMCs), which is a clear marker of SASP in aged vasculature. The shortened telomeres in mouse vascular tissue have been shown to be sufficient to induce endothelial dysfunction [54], whereas human VSMCs still have a normal phenotype sustaining plaque stability regardless of telomere length [55]. Although telomere shortening is common in vascular aging and CVD, it remains unclear whether telomere shortening is sufficient to lead to cellular senescence and vascular degeneration in aged vessels [56].

In the patients with severe coronary artery disease, most of endothelial cells demonstrated the features of senescent endothelial cells that reduced levels of

telomeric DNA-binding factor 1 (TRF1) and increased telomere oxidation as mentioned above [20, 39, 40]. These results suggest that telomere dysfunction and the SASP occur prior to cellular senescence and induce vascular dysfunction following CVD development.

The causes of vascular aging and vascular aging-related phenotypes can be summarized as follows:

i. Oxidative DNA damage: during aging, the onset of CVD led by changes in vascular endothelial cells results in an impairment of endothelium-dependent vasodilation, an overproduction of pro-inflammatory and prothrombotic factors, and an increase in oxidative stress [57]. In the human population, age is an important and independent risk factor for CVD [58].

ii. Telomere shortening: an association between telomere shortening and CVD risk factors has been found in atherosclerosis, arterial stiffness, type 1 and type 2 diabetes, and obesity [59–62].

iii. Genome instability: a failure in DNA damage repair occurs in cells and tissues during the aging process [63].

3. Aging and cerebrovascular function

As aging progresses, cerebrovascular function declines which can increase the possibility for ischemic stroke, intracerebral hemorrhages (ICHs), microbleeds, and cognitive decline [64]. Healthy functional cerebral vessels can coordinate with CBF and appropriately supply blood to the brain [65]. However, cerebrovascular aging has the following features, which can lead to age-related cerebrovascular diseases: (i) endothelial senescence, (ii) oxidative stress and inflammation, (iii) microvascular rarefaction, (iv) arterial stiffness, (v) vascular lumen narrowness, and (vi) CBF reduction. Each feature according to cerebrovascular aging is described in detail in the following subsections.

3.1 Cerebral vasculature

Cerebral vessels play a critical role in mediating between the whole body and the brain by transporting molecules between the blood and brain [5]. The brain vasculature that supplies blood to the brain tissue consists of two blood supply systems. One is the internal carotid artery system. This system is responsible for approximately 70% of the total CBF. The other system is the vertebral artery system, which is responsible for approximately 30% of the total CBF. These two major blood systems converge at Willis' circle, which allows communication between the left and right brain hemispheres, and branch out into the whole brain through cerebral arteries [66]. The most common structural feature of cerebral vessels is the blood–brain barrier (BBB), which comprises tight junctions and adherens junctions [5]. These tight junctions exist between endothelial cells, the basal membrane, pericytes, and the astrocyte end feet [67].

The BBB is important because it prevents harmful molecules from entering the brain tissue from the systemic circulation. Accordingly, a malfunction in BBB permeability has been reported in neurodegenerative disorders and cognitive decline that leads to dementia [68–70]. CBF is regulated in response to blood pressure through cerebral autoregulation. It was demonstrated that there were minor differences between CBF and blood pressure (within 10 mmHg of blood pressure)

among healthy humans in the plateau region [71]. The report also suggested that hypertension and a higher pulsatile rate might disrupt cerebral autoregulation, which make subjects prone to neurodegenerative diseases because the aging brain is subject to hypoperfusion [71].

3.2 Cerebral vascular aging

Healthy functional cerebral vessels can coordinate with CBF and appropriately supply blood to the brain [65]. As aging progresses, however, cerebrovascular function declines, which can increase the possibility of ischemic stroke, intracerebral hemorrhages (ICHs), microbleeds, and cognitive decline [64]. Cerebrovascular aging has the following features, which can lead to age-related cerebrovascular diseases:

i. Endothelial senescence: many studies have shown the presence of senescent endothelial cells in aged cerebrovascular lesions, which is triggered by the accumulation of ROS [31] and modulated by inflammatory factors, as described above.

ii. Oxidative stress and inflammation: in vessels' walls, ROS increase nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity associated with aging [7, 72, 73]. These findings have been reported in both nonclinical and clinical studies. It is also well known that the vasculature can be easily damaged by vasculopathy, including atherosclerosis [74–76].

iii. Microvascular rarefaction: this is a condition where the microvascular network and its density are reduced. Rarefaction has been detected in some brain subregions, particularly in the hippocampus. Since the hippocampus is involved in memory, it could lead to memory loss [77, 78]. Circulating endothelial progenitor cells have been shown to be diminished by aging, which is linked to white matter changes and a decline in cognitive function [79, 80].

iv. Arterial stiffness: this is a major characteristic of vascular aging. Vascular stiffness increases blood flow velocity and blood pressure. Arterial stiffness results in an increase in systolic pressure and a decrease in diastolic pressure.

v. Vascular lumen narrowness: the accumulation of toxic molecules in the vessel walls makes the vascular lumen narrow. There have been clinical studies such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) that have examined Notch3 molecules in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. The high-temperature requirement A serine peptidase 1 (HTRA1) is also explored in cerebral autosomal recessive arteriopathy and leukoencephalopathy [81–83].

vi. CBF reduction: generally, hypoperfusion in the cerebral circulation is suggested to lead to cognitive impairment [84]. In cases of mild hypoperfusion, synaptic plasticity is impaired by a reduction in protein synthesis during learning and memory consolidation [2]. Under severe hypoperfusion, there is failure in the formation of the action potential, disruption in the acid–base balance, occurrence of neuronal edema, and accumulation of neurotic molecules [85].

With respect to neural activity, cerebrovascular reactivity (CVR) can be used to measure the response levels of brain blood vessels to various stimuli. Very recent evidence has shown that cerebral vessel contractility and dilation decrease as aging progresses and have effects on the neurovascular damage mediated by NO [86]. In addition, there is an induction of vasoconstrictive factors in the cerebral endothelium [87]. Since the vessel wall undergoes structural changes through the normal aging process, it is a natural and frequently found phenomenon that the basement membrane becomes thicker but smooth muscle cells and elastin layer are thinner [88]. These different responses between young and old adults have been demonstrated using blood-oxygen-level-dependent functional MRI (BOLD fMRI) data [89]. As a result of these collective findings, it is now considered that the vasculature plays a critical secondary cause in many neurodegenerative diseases, particularly in neurovascular dysfunction. Therefore, there needs to be an increase in recognition and a focus on cognitive decline after vascular damage to develop newer therapeutic approaches.

4. Aging and vessel-related cognitive decline

Dementia is an irreversible cognitive condition. According to a statistical report, 7.7 million people are newly diagnosed with dementia every year [90]. Among these, patients with vascular cognitive impairment and dementia (VCID) compose over 20% of the total dementia patient population [91]. By 2030, the number of older people (>60 years of age) is predicted to increase by 56% compared to the number in 2015, and it will continue to grow year by year. Finally, by 2050, our society will become a superaged society, and it is evident that the prevalence of neurodegenerative diseases will increase. Cognitive-related diseases, such as AD or VaD, will increase by 45% in 2050 compared to 2015 [92].

Mild cognitive impairment (MCI) is included as a cognitive-related disease in the older population. Although MCI is also considered as a pre-step proceeding to dementia, patients with MCI still fortunately have a chance of recovery or at least have a chance to delay the progression of the disease. Therefore, new strategies are urgently needed to diagnose and treat patients with MCI. Some blood factors such as MCP-1 or IL-6 have been suggested to be biomarkers for estimating the progression in cognitive decline because the vascular blood factors are modified in patients with MCI [93]. Some clinical studies have shown that VCID occurs in 25–30% of aged people who have had a previous stroke [94, 95]. Stroke is known to be the second leading cause of cognitive dysfunction. Furthermore, a clinical history of stroke increases the risk of cognitive dysfunction up to fivefold [96, 97]. Therefore, the symptoms of poststroke dementia could be related to the occlusion site, occlusion type, occlusion numbers, and lesion volume in the brain. There are studies that have shown that poststroke cognitive decline is related to the pathology of cerebrovascular disease and dementia, although the mechanisms involved in poststroke dementia are complex [90, 98].

Aging is complex and vulnerable to cognitive decline as well as brain disorders [99]. A recent study concluded that cognitive impairment in aged adults with depression is correlated with the SASP profile [100]. This study showed that the levels of the SASP were highest in participants with both late-life depression (LLD) and MCI (**Figure 1**). This study suggests that cognitive impairment in LLD is linked to an aging-specific molecular profile, which might be an indicator for aging people with LLD who develop dementia [100]. Recent clinical studies have reported that depression and cognitive impairment in aging are associated with the regulation of the SASP: immune-inflammatory response [101], proteostasis [102], signal transduction, and oxidative stress [103].

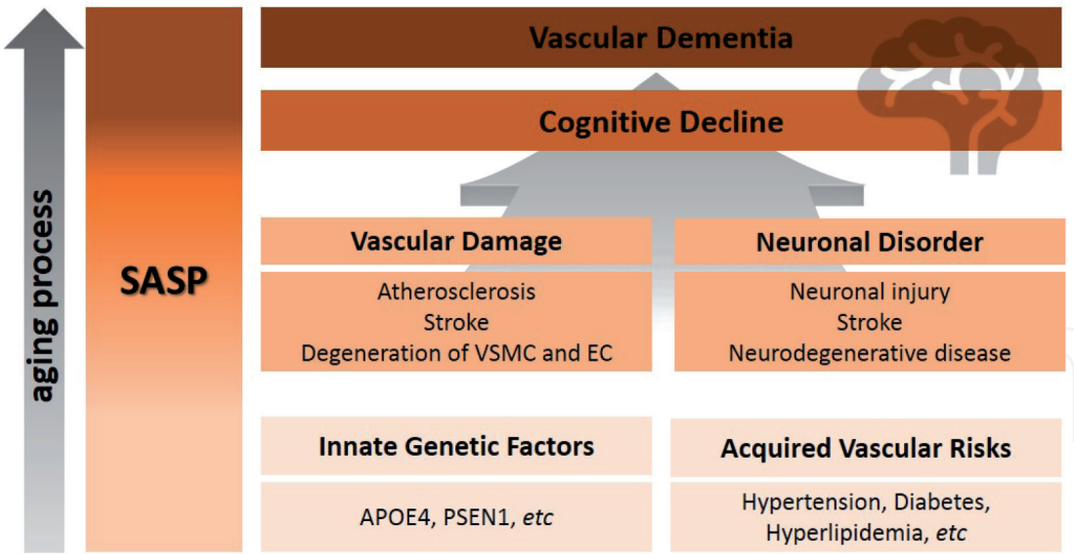

Figure 1.
Aging, cerebrovascular burden, and developing cognitive decline to vascular dementia. With aging, the number of resident senescent cells displaying SASP increases. The familial genetic backgrounds and vascular risk factors acquired through individual lifestyle or harmful habits, such as smoking, increase vulnerability to vascular damage and neuronal dysfunction. Combined with aging factors, such as SASP, during the aging process, vascular damage and neuronal diseases could lead to susceptibility to cognitive decline, which consequently contributes to the progression of vascular dementia. Abbreviations: SASP, senescence-associated secretory phenotype; APOE4, apolipoprotein E4; PSEN1, presenilin 1; VSMC, vascular smooth muscle cell; EC, endothelial cell.

5. Conclusions

Clinically and pathologically, vessel diseases including atherosclerosis are important diseases in a rapidly aging world. Age-related cerebrovascular dysfunctions result from multiple pathophysiological alterations. The clear one thing is that vascular aging and the aged brain vessels are vulnerable to damages and harmful factors such as the SASPs. Once the cerebral vessels have experienced insults, cognitive decline is eventually followed. The source of insults can be SASP particularly in the aging process. Despite efforts to develop therapeutic targets, it is not possible to identify the processes contributing to the onset of vascular disease and its progression of cognitive decline. Our aging society needed more fundamental approaches for treating aging-related neurodegenerative diseases containing dementia. Preferential treatment might be a preventive chance to neurodegenerative diseases. In the present time when dementia becomes an important issue in public heath, economics, social aspects, as well as the political fields, it should be possible to develop preventing and also therapeutic strategies against progressive dementia with a careful focus on treating vascular health by modulating the SASP.

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Conflict of interest

The authors declare no conflict of interest.

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