Immunosenescence in Cerebral Small Vessel Disease

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Cerebral small vessel disease (CSVD) is one of the most important causes of vascular dementia. Immunosenescence and inflammatory response, with the involvement of the cerebrovascular system, constitute the basis of this disease. Immunosenescence identifies a condition of deterioration of the immune organs and consequent dysregulation of the immune response caused by cellular senescence, which exposes older adults to a greater vulnerability. A low-grade chronic inflammation status also accompanies it without overt infections, an “inflammaging” condition. The correlation between immunosenescence and inflammaging is fundamental in understanding the pathogenesis of age-related CSVD (ArCSVD). The production of inflammatory mediators caused by inflammaging promotes cellular senescence and the decrease of the adaptive immune response. Vice versa, the depletion of the adaptive immune mechanisms favours the stimulation of the innate immune system and the production of inflammatory mediators leading to inflammaging. Furthermore, endothelial dysfunction, chronic inflammation promoted by senescent innate immune cells, oxidative stress and impairment of microglia functions constitute, therefore, the framework within which small vessel disease develops: it is a concatenation of molecular events that promotes the decline of the central nervous system and cognitive functions slowly and progressively.

CSVD ArCSVD immunosenescence

1. Introduction

Deterioration of the central nervous system associated with age depends on different mechanisms related to chronic inflammation and the consequent decline in the immune response. With aging, the dysregulation of molecular mechanisms of the immune system promotes neurodegeneration and plays a crucial role in determining outcomes such as dementia and stroke. Cerebral small vessel disease (CSVD) is nowadays recognized as one of the most important causes of vascular dementia: immunosenescence and inflammatory response, with involvement of the brain’s vascular system, constitute the basis of this disease [1]. The definition of CSVD refers to all the pathological processes in which there is an involvement of small vessels of the brain: small arteries, capillaries, and small veins. This vascular disease is associated with the lacunar lesion, cortical atrophy, microbleeds, abnormal changes of white matter and expanded perivascular spaces. The etiopathogenic classification of cerebral small vessel disease identifies many types, but the most frequent forms are arteriolosclerosis-related, also known as age-related, and the cerebral amyloid angiopathy [2]. Age-related CSVD (ArCSVD) is the most important cause of brain infarct and vascular dementia. It strictly correlates to many risk factors such as aging, hypertension, smoking and diabetes [3][4][5].

2. The Role of Aging in Pathophysiology of ArCSVD

Aging is characterized by immune-related modifications that determine susceptibility to infectious diseases, increased risk of cancer and cardiovascular diseases, and reduction in the effectiveness of vaccines. These conditions depend on a decline in the immune system called “immunosenescence” [6].

Immunosenescence identifies a condition of deterioration of the immune organs and consequent dysregulation of the immune response caused by cellular senescence, which exposes older adults to vulnerability [7].

A low-grade chronic inflammation status also accompanies it without overt infections, a condition named “inflammaging”, inflammation is a valid mechanism to destroy micro-organisms and harmful substances entering the human body, but chronic subclinical inflammation status associated with senescence increases the risk of degenerative and metabolic disease [8].

Under normal conditions, the innate and adaptive immune systems recognize dangerous substances and harmful stimuli such as pathogens [9] (bacteria, viruses, fungi, and parasites considered nonself), endogenous damaged cells, and degradation products of molecules (self) or gut microbiota (quasi-self), and activate the correct inflammatory response to maintain homeostasis. However, with aging, the degeneration of sensors that trigger the immune response causes uncontrolled activation of immune receptors and therefore of molecular cascades: pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) 9 and NOD-like receptors lose their physiological functions and produce an aberrant inflammatory response that promotes chronic inflammation [9].

This mechanism produces cellular damage and accumulation of molecular debris in multiple tissues and organs of the human body, interfering with the repair processes [10].

Inflammaging is the final and long-term result of inexorable and incessant physiological stimulation of the immune system due to many cellular and molecular pathways, such as senescence of immune and non-immune cells, mitochondrial dysfunction, alteration of autophagy and metaflammation [11].

The recent scientific literature has shown that senescent cells (SCs) have adverse effects on tissue homeostasis by producing inflammation amplifiers. It seems that SCs promote inflammaging through a senescence-associated secretory phenotype (SASP), characterized by a broad series of inflammatory actors (interleukin-6, interleukin-8) and degradation products of extracellular matrix [12].

The presence of cellular debris and nondegradable products in the tissues triggers the innate immune response through the molecular cascade of “damage-associated molecular patterns” (DAMPs) that recognize self-signals and produce macrophage activation [13].

Innate immune activation promotes pro-inflammatory pathways through “nuclear factor kappa-light-chain enhancer of activated B cells” (NF-kB) and “signal transducer and activator of transcription” (STAT): the immune cells

produce a significant number of inflammatory mediators (cytokines and chemokines) that amplify immune involvement [14].

In the pathophysiology of ArCSVD, the state of chronic inflammation caused by cellular aging and dysregulation of the immune system leads to endothelial dysfunction and alteration of the blood–brain barrier: it seems that this process could be identified early through the detection of circulating biological markers [15] categorized as systemic inflammatory factors such as CRP and IL-6 or vascular/endothelial altered factors such as homocysteine and von Willebrand factor.

Moreover, many studies have underlined that the early identification of pathological modifications of the BBB through imaging techniques such as classical MRI or functional MRI could predict the cognitive impairment in aged patients [16].

BBB leakage and endothelial dysfunction are considered the progenitors in the development of ArCSVD. Early correction of the risk factors underlying these two alterations is considered the best treatment to halt cognitive decline.

The BBB dysfunction leads to the release of the central nervous system (CNS) antigens into the peripheral circulation and the infiltration of leukocytes into brain tissue [17][18].

The transit of serum proteins at the neurovascular unit due to BBB dysfunction leads to microglia activation. Macrophages of microglia can produce chemokines, which provoke the migration of peripheral inflammatory cells to the CNS, generating a perpetual inflammatory microenvironment and supporting activated lymphocytes to meet CNS antigens [19][20][21][22][23][24].

3. The Relationship between Immunosenescence and Inflammaging

Recent findings suggest that there is no one-way path in which immunosenescence produces inflammaging: indeed, there is a bidirectional pathway in which inflammaging induces and maintains immunosenescence and vice versa. This was understood by looking at what happens to T lymphocytes: in the elderly, there is an increase in memory of CD8+ T cells (in the past considered inert) characterized by the loss of naïve T cell surface markers, such as CD28 and CD27, and the appearance of new senescent markers such as KLRG1. Thus, the increase in the number of T memory cells, and consequently of B cells, with aging could be the expression of a chronic continuous antigenic stimulation analogous to the mechanism of inflammaging (for example, the trigger induced by CMV infection) [25].

The wide diffusion of CMV implies that the organism uses its immune energies to limit this specific infection in life. Thus, the T cell heritage is filled mainly by CMV-memory T cells. Previously, they were considered inactive and inert, but challenging data suggest that they are functionally active and contribute to inflammaging [26].

This chronic stimulation of the immune system causes the increase in the number of senescent T cells and the inflammageing; the consequence of chronic stimulation, however, is the appearance of exhausted cellular phenotypes with the remodeling of membrane receptors and the emergence of inhibitory receptors (PD-1, CTLA-4) [27].

Moreover, the B cell population is compromised and unable to fight against new harmful pathogens (altered clonal expansion, impaired antibody production), which is why there is a significant risk of developing infectious diseases and cancer [28].

This situation represents the dog biting its tail: the production of inflammatory mediators caused by inflammaging promotes cellular senescence and the decrease in the adaptive immune response; vice versa, the depletion of the adaptive immune mechanisms favours the stimulation of the innate immune system and the production of inflammatory mediators leading to inflammaging.

In this synoptic picture, it is possible to understand the physiopathological bases of the ArCSVD: inflammaging is recognized as an essential risk factor for vascular dementia and stroke by promoting the aging of the immune system and by acting synergistically with traditional risk factors (obesity, hypertension, diabetes mellitus, etc.) [29].

The progressive vascular damage of ArCSVD patients produces the release of central nervous system antigens in the peripheral circulation, generating the recruitment of lymphocytes in the brain tissue and the consequent dysfunctions [30].

In contrast, cerebral dysfunction is responsible for the progressive deterioration of the immune system, causing a continuous stimulation of the immune cells through the release of antigens and immunogenic molecules [31].

Pro-inflammatory molecules and activated immune cells are involved in the atherosclerotic process caused by inflammaging [32].

The correlation between immunosenescence and inflammaging is fundamental in understanding the pathogenesis of ArCSVD. With one-to-one correspondence, cellular aging and the loss of integrity of the blood–brain barrier favour the perpetual activation of the immune system, and the latter continuously worsens brain damage through a varied series of molecular alterations. Therefore, immunosenescence and inflammaging are two sides of the same coin and constitute a dynamic field of study and research to find therapeutic perspectives which interfere with these mechanisms [30][31][32].

4. Immunotarget of Aging in Early Diagnosis and Therapeutic Perspectives of Cerebral Small Vessel Disease

At the brain level, it has been studied how the dysregulation of vascular homeostasis and the balance between the processes of vascular dilation and constriction, with the release of inflammatory cytokines, derive from endothelial

dysfunction. These processes result from chronic inflammation, responsible at least partly for the onset of ischemic events. Endothelial dysfunction is a determinant key of vascular damage. Chronic inflammation induces the release of molecular mediators that trigger immunological reactions capable of stimulating and worsening brain damage, thus affecting the outcome of the disease [33].

Endothelial dysfunction is an early marker of cardiovascular disease: many studies showed the role of endothelial dysfunction and arterial stiffness as surrogate markers of vascular health.

Several works documented how, in diabetic patients suffering from microangiopathy, the indices of arterial stiffness (PWV and Aix) were higher than in the control group. In contrast, indices of endothelial function (RHI) and cognitive function (MMSE) were lower.

The researchers speculated a possible correlation between increased arterial stiffness and decreased endothelial function, and mild cognitive impairment in this population [34].

Another scientific work, instead, evaluated the correlation between type 2 diabetes mellitus complicated by diabetic foot and the presence of white matter hyperintensity (WMH), also associated with alteration of omentin levels, and endothelial and cognitive performance indices [35][36].

In patients with diabetic foot, there was evidence of alteration of small vessels, as documented by the finding of hyperintensity of the white matter. Furthermore, the higher frequency of WMH lesions in these patients could be due to the higher degree of arterial stiffness, endothelial dysfunction and reduced serum levels of Omentin-1. Because of that, more robust cardiovascular prevention with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins and aspirin, and the evaluation of the values of some adipokines could be necessary to identify the risk of brain-vessel dysfunction in the diabetic patient with organ complications [36].

It is essential to identify therapeutic targets and try to interfere with the mechanisms of immunosenescence. These therapeutic strategies could be specific or nonspecific. Concerning nonspecific therapies, it would be necessary to modify the risk factors that act by promoting chronic inflammation with consequent endothelial damage. Therefore, cardiovascular risk factors could be controlled (arterial hypertension, obesity, cigarette smoking, dyslipidemia, etc.), evaluating the possibility of introducing anti-platelet and anticoagulant therapy according to the individual patient's ischaemic and haemorrhagic risk [37].

The use of specific categories of drugs could have a dual role, on the one hand, to allow the control of cardiovascular risk factors and, on the other hand, to limit inflammatory damage. Some studies have shown that therapy with statins, cilostazol, and ACE-i could stabilize endothelial cells and reduce the chronic inflammatory process [38].

Additionally, in some clinical trials, statins have significantly reduced the risk of cerebrovascular events in patients with hypercholesterolemia [39]. ACE-I-therapy has shown a more active role in preventing the progression of WMH in ArCSVD [40].

Shuzhen et al. proposed that lipoprotein-associated phospholipase A2 (Lp-PLA2) and superoxide dismutase (SOD) are independently related to cognitive dysfunction and injury. This means that the white matter hyperintensity (WMH) of ArCSVD could be considered a therapeutic target [41].

Considering the role of chronic inflammation and immunosenescence in the pathogenesis of ArCSVD, it would be interesting to consider using drugs already used for other neuroinflammatory diseases such as multiple sclerosis (fingolimod, natalizumab, dimethyl fumarate, and rituximab) in order to interfere with the action of the cytokines and inflammatory mediators involved [30].

About individual drugs, fingolimod is a drug commonly used in relapsing/remitting multiple sclerosis; it reduces circulating lymphocytes and, consequently, prevents them from escaping from the lymph nodes during a stroke. Therefore, this drug could contribute to the prevention of early infiltration of lymphocytes in the brain and could reduce thromboinflammation [42].

Fingolimod was used during the acute phase of ischemic stroke, and it showed an improvement in microvascular permeability and secondary damage [43].

Further studies are still needed to understand its precise role. In addition, a recent study found that fingolimod could induce the expression of VEGF in astrocytes. It, therefore, could stimulate the molecule S1PR3, which plays a role in the breakdown of the BBB and would be followed by the entry of pathogenic lymphocytes into the brain [44].

Natalizumab is another drug used in multiple sclerosis, and it has the function of blocking α4-integrin, which regulates the presence of lymphocytes (mainly T cells) in the central nervous system. The ACTION study considered administering natalizumab within 9 h of the onset of the acute ischemic event symptoms, but it did not find the effects of natalizumab on infarct growth. However, patients who received natalizumab had excellent cognitive outcomes at 90 days, especially in the small ischemic lesion group [45].

Dimethyl fumarate is also used in the treatment of multiple sclerosis. It has been documented that this drug is more effective and has fewer side effects than the other drugs tested. Above all, it has an essential role in the process of oxidative stress cells. This mechanism allows for the transcription of genes downstream of the activation of the antioxidant nuclear factor Nrf2 [46].

Molecules that mediate pericyte-EC interactions, such as TGF-β, and platelet-derived growth factor-BB (PDGF-BB), have been proposed as targets for the treatment of neurological disorders. Pericytes play a vital role in regulating various microvascular functions, such as angiogenesis, preservation of BBB, capillary blood flow, and migration of immune cells to the brain [47].

Some works have shown how pericytes can differentiate into neurons, microglia, and vascular cells after brain lesions in ischemic disease and hypoxia [48].

A trial in mice investigated how implantation of pericytes in the brain increased cerebral blood flow and could reduce pathological deposition of Aβ122 [49].

Thus, this evidence suggests that pericytes transplantation may be a promising approach for treating ArCSVD.

Inflammation is increasingly recognized as a risk factor for dementia, stroke, and ArCSVD [50].

As life expectancy continues to rise worldwide, the number of individuals living in the community with age-related diseases will increase, especially ArCSVD [50].

Inflammation not only acts through the aging of the immune system, but it also promotes the main cerebrovascular risk factors (such as obesity, hypertension, and type 2 diabetes) to trigger their damaging effects. For example, in ArCSVD patients, recurrent injuries such as mild stroke lead to BBB loss, central nervous system antigens release into the peripheral circulation, and infiltration of lymphocytes into brain tissue and related brain dysfunction. Brain dysfunction can further damage the immune system, forming a vicious cycle [31].

For this reason, the study of the role of the immune response during aging in the development of small vessel disease and the corresponding brain damage is of fundamental importance.

The role of immunosenescence in endothelial dysfunction and blood–brain barrier disorder has led to exciting aspects. Therefore, it could be a possible candidate for further study [51][52][53][54][55][56][57].

Therefore, immunosenescence and the set of altered molecular mechanisms described above are the basis for understanding many diseases in older people: cellular aging damages the immune system both in its innate and adaptive compartments.

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