Review Article

The NLRP3 inflammasome and stroke

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Abstract: Inflammasome pattern recognition receptors, which belong to the family of multi-meric proteins, play an important role in innate immunity, including NLRPs, NLRC, and NAIP. Among these receptors, NLRP3 (nucleotide-binding domain (NOD)-like receptor protein 3) inflammasome may activate the inflammation and participate in atherosclerosis, pathophysiology of myocardial infarction, resultin ischemia/reperfusion injury and stroke and other cardiovascular diseases. Effective regulation of NLRP3 may help prevent or even treat stroke. In recent years, the role of inflammation in stroke has attracted much attention, and the in-depth study of its mechanism of action is gradually clear. This mini-review focuses on the association of regulatory mechanisms of NLRP3 inflammasome with the development of stroke, which may supply some clues for future therapies and novel drug targets for stroke.

Keywords: NLRP3, inflammasome, inflammation, stroke

Introduction

Stroke in the world

Stroke, one of the most frequent causes of death and disability worldwide, account for about 6.2 million deaths every year in the world, and is caused by the interruption of the blood supply to the brain [1-3]. Ischemic stroke is a common neurological disease with a variety of etiologies, which is a leading cause of severe disability and death in both developed and developing countries. Ischemic is by far the most common kind of stroke, accounting for 85 to 90% [3, 4]. It is well known that IS are affected by environmental risk factors and genetic profiles. And environmental risk factors for stroke include old age, high blood pressure, previous stroke or transient ischemic attack (TIA), diabetes, high cholesterol, tobacco smoking and atrial fibrillation [1, 5]. Overall, high blood pressure is the most important modifiable risk factor of stroke. However, the full range of contributory genes is yet to be determined [6-8]. Due to the ageing population in the world, the increasing of diseases burden will be a great public concern in the next 20 years, especially in developing countries. Like many other developing countries, China is facing the heaviest burden resulting from stroke [9, 10].

Inflammation and stroke

Cerebral ischemia and inflammation are closely interrelated. Ischemia is a robust stimulus for potentially damaging inflammation, while infection and the associated inflammation are known risk factors for IS [11-14]. In addition, Hypertension, hyperlipidemia, diabetes, obesity, smoking, cholesterol and others are known common risk factors promoting inflammation in the blood vessel wall. These risk factors are associated with endothelial cell inflammatory markers, which can increase the tumor necrosis factor alpha (TNF-a) levels, thereby making the lymphocytes in vitro to cerebrovascular endothelial migration [15-17]. Indeed, they may increase inflammation cells and the levels of
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Currently, there are three kinds of persuasive NLRP3 activation model: (1) Instability of macrophages lysosomes improves the release of protease and activates NLRP3 [28]; (2) ROS induces the dissociation of thioredoxin and activates NLRP3 [29]; (3) lower K + concentrations improve purine P2X7 and activate NLRP3 [29]. With the activation of NLRP3, the expression of caspase-1 will be improved and thus promote the release of interleukin-1β and interleukin-18, and further develop the pro-inflammatory effects [30]. NLRP3 involved in human acute immune and inflammatory response, and inadequate or excessive reaction will cause damage to the human body. Innate immunity

Activation of NLRP3

Figure 1. The structure of NLRP3; Apoptosis speck protein (ASC); Pyrin domains (PYD); Caspase activation and recruitment domain (CARD); NACHT domain (NACHT); Leucine-rich repeats (LRRs).

Figure 2. The pathways for NLRP3 inflammasome activation.

Methods (methodology)

Structure of NLRP3 inflammasome

Innate immunity is the body’s first defense against pathogens infection, which may be through pattern recognition receptors (PRRs) to recognize pathogen-associated molecular patterns (PAMPs), can activate the downstream signaling pathways and lead to the body’s inflammatory response and immune response. Inflammasome, one of the typical PRRs, has been found play a key role in the inflammation, including nucleotide-binding oligomerization domain (NOD), NOD leucine-rich repeats, and NOD effectors. Inflammasome can be divided into three categories, NLRPs, NLRC and NAIP [22-24]. And NLRP3 is a typical representative of NLRPs for the most studied inflammasome. NLRP3 are known to serve as a key mediator of the innate immune response to danger-associated molecular pattern molecules (DAMPs) and danger signals activate exogenous environment [25-27]. The structure of NLRP3 was described in the Figure 1.

Inflammatory markers in endothelial cells as well as the expression of nuclear factor kappa B (NF-κB), and thus involve in the NF-κB pathway. In the meantime, this pathway mechanistically links in the biology of the artery wall, which gives rise to atherosclerosis and stroke. Endothelial dysfunction caused by inflammation is a key initiating event in atherosclerotic plaque formation. And atheroemboli, resulting from ruptured carotid plaques, is a major cause of stroke. Also, Inflammation contributes to ischemic events through the promotion of atherosclerosis [18]. Inflammatory genes may thereby influence the incidence and outcome of IS. Anti-inflammation treatment maybe suggested as a promising therapeutic possibility for Atherosclerosis and stroke [19-21].
plays an important role in inflammation-related neuronal injury, which is associated with ischemic stroke. Since the brain has a very high glucose and oxygen demand, rapid disturbances in the blood supply to the brain lead to the development of an ischemic infarct with accompanying necrosis of neurons and generation of DAMPs. Thus, NLRP3 activation, expression levels, and abnormal gene mutation encoding components of the components can affect NLRP3-mediated inflammatory response, thereby affecting the immune balance of internal environment and development of ischemic stroke [31-33]. The activation signal of NLRP3 was described in Figure 2.

The role of NLRP3 in the development of stroke

NLRP3 plays an important role in early atherosclerosis, while Low-density lipoprotein promotes the deposition of cholesterol crystals in blood vessel wall. Macrophage could be transformed into foam cells, and Foam cells activated NLRP3 through the following mechanisms: (1) ROS contained in the ruptured lysosomes activates NLRP3 [34]. (2) TLR-12/TLR-4 identify minimally oxidized LDL and free fatty acids, and raise myeloid differentiation primary response gene 88 (MyD88) and then interferon TIR-domain-containing adapter-inducing interferon-β (TRIF) to induce the expression nuclear factor-κB (NF-κB). NF-κB further promotes the production of NLRP3 and IL-1β and enhances inflammation [35-37]. (3) Pro-inflammatory cytokines further induce the infiltration and activation of macrophages, neutrophils, lymphocytes, vascular smooth muscle cell, leading to cell death and rupture of macrophages [38-40]. (4) IL-1β recruited monocytes and activated platelets to promote the release of IL-1β [41-43]. (5) The activation of macrophages may generate more IL-18 to induce vascular smooth muscle cell necrosis and release tissue metalloproteinases to trigger plaque stability [44-46]. The above cyclic reaction mechanism activate NLRP3 and aggravate atherosclerosis, thereby resulting to the development of stroke [47].

Association of NLRP3 with treatment and prevention of stroke

NLRP3-mediated inflammatory response involved in atherosclerosis and the development of stroke. Regulation of inflammation level may play critical role in the prevention and treatment of stroke. NLRP3 mainly activated by ROS, K+ efflux or elevated extracellular ATP concentration. Antioxidants inhibit ROS production, reduce Caspase-1 generation and release of IL-1β [48-50]. Inflammasome initiate inflammation, inhibition of NLRP3 can regulate inflammation. But NLRP3 can be activated by a variety of signaling systems; each detailed molecular mechanism remains unclear [51]. To date, for NLRP3 drug development is still in the initial stage. Currently there are some applications: ① IL-1 receptor antagonists, such as anakinra hormone [52], ② Anti-IL-1βantibody, such as canakinumab [53-55], ③ NLRP3 inhibitor drugs such as atorvastatin [56], ④ Inhibition Caspase-1 drugs such as ritonovir which can also reduce the level of IL-18 [57], ⑤ P2X7 receptor antagonists inhibit the activation of the inflammasome and IL-1β levels [58, 59]. The combination of these types of drugs will help promote the long-term effect. The inflammation has a two-phase effect in the development of stroke: Early inflammation could remove necrotic tissue and promote granulation tissue formation. However, excessive inflammation can cause damage to the brain stem tissues surrounding area and expand the area of the brain stem. Therefore, the implementation of anti-inflammatory treatment should consider how to determine the timing of the use of anti-inflammatory drugs and how to determine the degree of inflammation in the brain stem and how to use anti-inflammatory drugs after cerebral infarction and how to determine the duration of anti-inflammatory drugs appropriately [60-63].

In terms of drug use directions, however, A randomized, double-blind, placebo-controlled and multi-center trial have suggested that the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage [64].

Summary and outlook

In summary, these previous results have a number of therapeutic implications. NLRP3 inflammasome can identify a large number of bacteria, viruses, and some endogenous signals that activate caspase-1 and induce production and secretion of IL-1β and IL-18.
Numerous studies have confirmed that the NLRP3 plays an important role in the atherosclerosis and occurrence of stroke. Based on the activation mode of NLRP3, inhibiting NLRP3 inflammasome activation may have beneficial effects in preventing the damage mediated by the sterile inflammatory response in diseases such as IS. Preventing pathological inflammasome from activation may provide some insight into the future prevention and treatment of stroke [65-67]. Currently the most promising treatments for inhibiting NLRP3 are anti-IL-1, inhibition of caspase-1 and P2X7 receptors antagonist [68, 69]. Further research on the NLRP3 activation mechanism and more sophisticated animal experiments as well as clinical trials of molecular targeted agents on NLRP3 are needed to better shed light on the association with NLRP3 and IS, as well as the complicated role of inflammation in IS precisely.

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Disclosure of conflict of interest

None.

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