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Review article

Neuroinflammation responses after subarachnoid hemorrhage: A review

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ABSTRACT

Subarachnoid hemorrhage (SAH) is an important cause of stroke mortality and morbidity, especially in the young stroke population. Recent evidences indicate that neuroinflammation plays a critical role in both early brain injury and the delayed brain deterioration after SAH, including cellular and molecular components. Cerebral vasospasm (CV) can lead to death after SAH and independently correlated with poor outcome. Neuroinflammation is evidenced to contribute to the etiology of vasospasm. Besides, systemic inflammatory response syndrome (SIRS) commonly occurs in the SAH patients, with the presence of non-infectious fever and systematic complications. In this review, we summarize the evidences that indicate the prominent role of inflammation in the pathophysiology of SAH. That may provide the potential implications on diagnostic and therapeutic strategies.

1. Introduction

Subarachnoid hemorrhage (SAH) accounts for the second mortality in stroke patients. About 10 in 100,000 of the populations develop aneurysmal SAH. The mortality occurs in nearly half of SAH patients, including the pre-hospital death. Patients survive the initial ictus may damage from the secondary injury. 30% survivors develop the delayed neurological disability, which severely affect the quality of life of patients [1]. The current primary treatment, including hemodynamic augmentation and medically or surgically mediated intra-arterial vasodilation, mainly concentrated on the fatal attack [2]. However, these treatments provide relatively less effect on the delayed neurological decline. Neuroinflammation plays an important role in SAH pathogenesis. Current studies showed the evidences that inflammation response contributes to early brain injury, vasospasm, and delayed neurological deterioration after SAH. The inflammatory response with increased cytokines is detected in clinical SAH patients. Preclinical animal studies help to improve the understanding of the mechanism under neuroinflammation pathogenesis. Both cellular component and molecular components are involved in the inflammatory regulation. The characteristics of glial cell activation and the release of a variety of cytokines appear after SAH attack [3]. In addition, the inflammation related pathways, such as Toll-like receptor 4 (TLR4), are investigated for illustrating the potential causality linked to the poor outcome [4]. Along the increased evidences of the importance of neuroinflammation, the novel treatments targeting the neuroinflammation are being developed. The unclear clarity to the beneficial or detrimental role of inflammation after SAH may give a confusion on therapeutical target [5]. The inflammatory response at different time points with different protective or detrimental function may depend on the surrounding environment and type of cells recruited to the site [6]. Neuroinflammation act both protective and detrimental function after SAH. Thus, this review summarizes the current studies on neuroinflammation in SAH. The roles and effect of different components will be described and the underlying pathways are discussed over time along SAH pathogenesis. The neuroinflammation modulation in vasospasm and SIRS will be discussed as well.

2. Neuroinflammation in early brain injury

The first 72 h is a critical time for the SAH patient. The deaths mostly occur in this period. The key events arise including blood release, acute reactive hyperemia, and acute vasospasm. These events contribute to early brain injury (EBI) resulting in increased intracranial pressure, acute hydrocephalus, microvascular alterations and transient global ischemia [7]. Recent studies indicate the critical role of neuroinflammation and reactive oxygen stress in the pathogenesis of EBI. Inflammatory evolve over time and participate in the secondary brain injury after SAH.

SAH introduced blood into subarachnoid space. Red blood cells breakdown and degrade over time and the degraded products then deposit into the site of bleed area. The products mainly include hemoglobin, methemoglobin, oxyhemoglobin heme and hemin,

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which lead to the release of inflammatory factors and trigger the inflammation cascade pathways. Animal studies indicated hemin is related to the release of free radicals and lipid peroxidation, which increase oxidative stress for the brain tissue. The rupture of aneurysm interrupts the integrity of blood brain barrier (BBB). NO level is figured out increasing in CSF of SAH patient and also in animal model [8,9]. Oxyhemoglobin leads to the apoptosis of endothelial cells and necrosis of astrocytes [10,11].

Cellular component of inflammation on early stage involves microglia, astrocyte and endothelin. The cells of the immune system, such as neutrophils, are studied contributing to the inflammation response after SAH. Inflammation-modulatory cells in the CNS, including microglia and astrocyte, are activated after SAH [3]. These cells up-regulate the cell adhesion molecules within endothelial cells, which subsequently recruit the inflammatory cells from circulation, such as macrophages and neutrophils, and allow them to bind and enter the subarachnoid space. The peripheral inflammatory cells can clear hemoglobin. However, the trapped macrophages and neutrophils underwent degranulation and subsequently released a multitude of inflammatory factors, including endothelin and oxidative radicals. These factors release results in vasoconstriction, meningitis, and cerebritis [6]. Importantly, the inflammatory response causes the release of inflammatory cytokines, endothelial adhesion molecules, and activated complement over through the brain. The release of cytokine is associated with early edema as well [12].

Glial cell, as the prominent cellular inflammatory factors, is a double-blade sword in the modulation of neuroinflammation. Glial cells contribute to the microcirculatory blood flow controlling, synaptic plasticity pruning, and neuronal communication [3]. Microglia, as the immune cells in the CNS, effect both beneficially and detrimentally after SAH. Once activated, microglia gain morphology changes from ramified to amoeboid shape. The shorter process morphology suggests the macrophage-like cells. The activation of microglia is diffuse in the brain parenchymal besides the bleeding area, such as brain stem, cortex and hippocampus [13,14]. Microglia has two-dimensional spectrum comprising activation states in the central nervous system, according to the different expression profile [15]. M1 phenotype is related to the pro-inflammation, while the M2 phenotype is more related to anti-inflammation. Microglia also shows the ability to active astrocyte after SAH in rat model [13]. Microglia contributes to the neuronal damage after SAH [16]. On the other side, microglia also bear a neuroprotective function in SAH process. Microglia upregulate heme-oxygenase-1 (HO-1) in the brain parenchymal, which is a stress-response protein helping the blood clearance in SAH. In addition, SAH activated microglia leads to the expression of anti-inflammatories, such as IL-4 (Interlukin-4), IL-10 [17]. The release of the neuroglobin prevents neurons from oxidative stress [18]. Microglial interaction with synapse is observed modulating over 45 min after SAH. The neuronal circuitry is thus modified, which may affect the neurological functions [19].

Astrocyte connects with neurons by bodies, synapse and axons, and comprise the perivascular endfeet to BBB. Astrocyte maintains the homeostatic microenvironment and supplies the nutrition to neurons. In addition, astrocyte can communicate with endothelium and microglia. After the SAH attack, astrocytes are activated as a part of gliosis [3]. Similar to microglia, astrocyte has both positive and negative effect on neuronal survival. Reactive astrocytes decrease edema, preserve of the BBB and protect of neurons from oxidative stress. While reactive astrocytes have been indicated contributing to scar formation, decreasing the axonal regeneration and increasing the cytokine expression [14]. Glial fibrillary acidic protein (GFAP), the specific marker of the astrocyte, is highly expressed after SAH from first day up to three weeks [20–22]. Astrocytes can respond to neurotransmitters and regulate synaptic plasticity [23].

Acute mediators of inflammation and proinflammatory cytokines, adhesion molecules, P and S-selectins increase within several hours after SAH, including IL-1β, IL-6, tumor necrosis factor (TNF)-α, intercellular adhesion molecule (ICAM)-1 and others. Increase of the IL-1 beta and IL-6 levels in CSF of SAH patients during the first three days [24]. The similar increase of IL-1 receptor antagonist and TNF-α in CSF of SAH patient are found [25]. The changes of the molecules are associated with early brain injury. The soluble adhesion molecules are found elevating in both serum and CSF within 1–3 days after SAH. That changes are related with hyperthermia, vascular spasm, and poor outcome.

The original inflammatory response triggers the pathway cascade, which further amplifies the inflammatory modulation. The high expression of high-mobility group box 1 protein (HMGB1) in microglia triggers the expression of pro-inflammatory and actives Toll-like receptor 4 (TLR4). Neurons can also release the HMGB1 on the early stage after SAH [26]. The downstream target of TLR4 pathway factor MYD88 is unregulated on early stage after SAH. Hence the nuclear transcription factor NF-κB, controlling cytokines production, is activated. TNF-α and IL-1β expression are then increased. The TLR4 pathway can be also activated by the blood metabolite methemoglobin [27]. In addition, the neuronal apoptosis after SAH was largely TLR4-MyD88-dependent and microglial-dependent rather than TLR4 associated activator of interferon (TRIF)-dependent [4]. Therefore, TLRs/MyD88/NF-κB inflammatory pathway plays an important role in inflammatory response after SAH and it evolves in both early stage and late stage [28]. Activation of metabotropic glutamate receptor 5 (mGluR5) alleviates microglia activation on early stage and neuronal apoptosis after SAH. The neurological deficits and brain oedema are improved after blocking mGluR5. However, the downstream target is unclear [29]. The receptors for advanced glycation end-products (RAGE), a transmembrane receptor, have highest expression on 1 day after SAH induction in rat model. RAGE senses inflammatory molecules, such as HMGB1, S100 family of proteins, β-amyloid peptide, and macrophage antigen complex 1. After activation, the downstream nuclear transcription factors of p65 protein, the major subunit of nuclear factor kappa B, are activated and triggers the genes transcription. RAGE are detected a high expression in both neurons and microglia, which indicate RAGE may be directly involved in the inflammatory response and related to the neuronal death after SAH [30]. Activation of the MAPK-ERK1/2 pathway occurs in 24 h after SAH, which relates to the elevated TNF-α level [31]. STAT3, a member of signal transducer and activator of transcription (STAT) family, has been shown to mediate pro-inflammation in microglia, neuroprotection in neurons, and apoptosis in endothelial cells [32–34]. The accumulation of STAT3 is observed in the cerebral arteries and involves in the delayed vascular events in SAH animal model. According to our previous laboratory work, the phosphorylation of STAT3 is involved in the modulation of microglial activation. The activation of STAT3-dependent microglial activation may have both detrimental and beneficial effect on neuronal. A better understanding of early mechanisms and their timely prevention may provide potential strategies to improve clinical outcome in SAH patients.

3. Inflammation in delayed brain deterioration

30% patients, surviving from initial ictus of SAH, are attacked by delayed brain deterioration. Delayed brain deterioration generally appears 3–14 days later and is characterized by delayed cerebral ischemia (DCI) and delayed neurological deficits [35]. Delayed brain deterioration is initial described equal to DCI since vasospasm is