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Review article

Innate and adaptive immune response in stroke: Focus on epigenetic regulation

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ABSTRACT

Inflammation and immune response play a pivotal role in the pathophysiology of ischemic stroke giving their contribution to tissue damage and repair. Emerging evidence supports the involvement of epigenetic mechanisms such as methylation, histone modification and miRNAs in the pathogenesis of stroke.
Interestingly, epigenetics can influence the molecular events involved in ischemic injury by controlling the switch from pro- to anti-inflammatory response, however, this is still a field to be fully explored. The knowledge of epigenetic processes could to allow for the discovery of more sensitive and specific biomarkers for risk, onset, and progression of disease as well as further novel tools to be used in both primary prevention and therapy of stroke. Indeed, studies performed in vitro and in small animal models seem to suggest a neuroprotective role of HDAC inhibitors (e.g. valproic acid) and antagomir (e.g. anti-miR-181a) in ischemic condition by modulation of both immune and inflammatory pathways. Thus, the clinical implications of altered epigenetic mechanisms for the prevention of stroke are very promising but clinical prospective studies and translational approaches are still warranted.

Contents

1. Introduction

Ischemic stroke is a heterogeneous and multifactorial disease in which environmental and genetic factors play a pivotal role in its onset and outcome (Hajat et al., 2011). Mounting evidence suggests that immunity and inflammation are key elements involved in several

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steps of ischemic cascade such as acute events after blood flow reduction, brain tissue damage, progression of ischemic lesions and tissue repair (Kamel and Iadecola, 2012). Furthermore, the immune system is actively involved in the acute phase of stroke when thrombosis and hypoxia elicit the release from injured or dying cells of danger signals that activate components of the innate immune system such as resident cells, microglia, endothelial cells and recruitment of circulating leucocytes (Kamel and Iadecola, 2012). The presence of the blood–brain barrier (BBB) that prevents the entry of immune cells in the brain has led us to believe, for a long time, that the brain is an immunologically privileged organ (Keep et al., 2014). However, some studies showed that in several conditions such as stroke the brain and the immune system communicate bidirectionally (An et al., 2014; Kamel and Iadecola, 2012). The activation of innate immunity after stroke triggers an adaptive immune response employing T and B cells as well as antigen presenting cells (APCs) (Fig. 1). Atherosclerosis, autoimmune diseases, obesity and infections are associated with a dysregulated immune response that can contribute to vascular damage and inflammation and to an increased risk of stroke (Napoli et al., 1999a, 1999b; Grau et al., 2010; Schiano et al., 2015; Picascia et al., 2015). Although the inflammation represents a risk factor for stroke it is also involved in the brain injury occurring after the stroke (An et al., 2014). Indeed, randomized clinical trials suggest that the statins reduce the mortality and improve the outcome in acute stroke (Laloux, 2013). Inflammatory mechanisms may have also beneficial effects by contributing to regeneration and tissue repair. The failure of many therapies for ischemic stroke has emphasized the importance of clarifying novel mechanisms that may contribute to its onset as well as the roles of innate and adaptive immune responses (Chamorro et al., 2012; Kamel and Iadecola, 2012).

Many complex molecular and cellular pathways are regulated at epigenetic level and the identification of epigenetic mechanisms that could modulate the immune response at all different steps during ischemic damage could represent a promising future therapeutic approach.

Here, we will describe the different steps of innate and adaptive immune responses during an ischemic stroke focusing on their regulation mediated by epigenetic mechanisms.

2. Epigenetic evidence in stroke

Genome-wide studies have provided insights on the molecular events and epigenetic modifications such as methylation, histone modification and microRNAs (miRNAs) occurring during a stroke and, regulating several process related to neurogenesis and neural pathways.

Indeed, epigenetic changes measured in blood DNA of stroke patients and healthy subjects seem to predict the risk of common age-related diseases, such as coronary heart disease and stroke suggesting that blood repetitive-element hypomethylation can be a novel target to identify subjects with cardiovascular disease (Baccarelli et al., 2010; Grimaldi et al., 2015; Napoli, 2011). A recent study has reported an increase in the 5-hydroxymethylcytosine (5hmC) in blood of acute ischemic stroke patients associated with differentially hydroxymethylated regions in genes involved in cell junction or neuronal morphogenesis (Miao et al., 2015). Moreover, methylation of methylenetetrahydrofolate reductase significantly increases susceptibility risk for ischemic stroke by mediating serum folate and vitamin B12 levels but does not affect ischemic stroke severity (Wei et al., 2015). However, Soriano-Tarraga et al. have reported no global methylation differences in subjects with three different etiologies of stroke (Soriano-Tárraga et al., 2014).

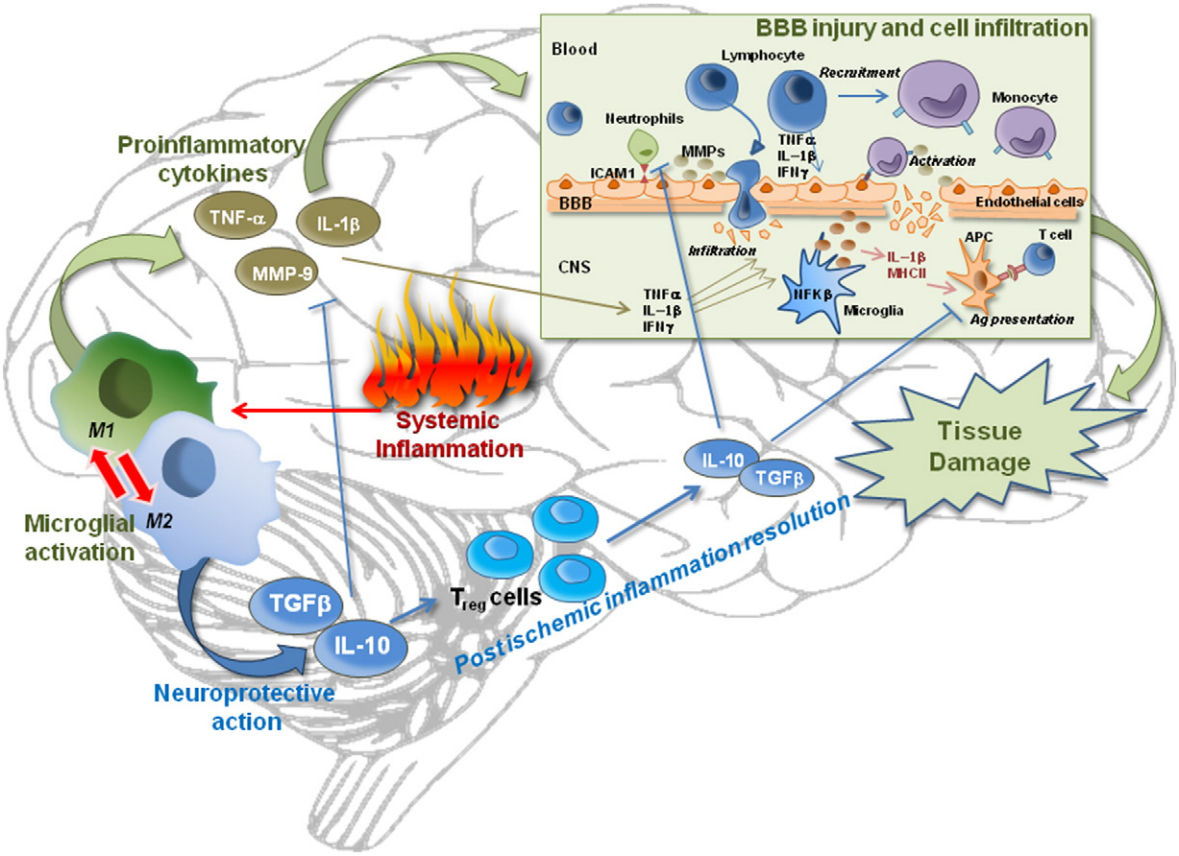

Fig. 1. Involvement of innate and adaptive immune responses in ischemic stroke. Pathways of microglial cell activation after brain injury with switch from M1 to M2 phenotype induce the release of proinflammatory cytokines or inflammation resolution. TNFα, IL-1β and MMP-9 cause BBB injury and stimulate leukocyte infiltration promoted by adhesion molecules expressed by inflamed endothelial cells. Increased accumulation of APCs, related to expression of MHC class II molecules in the ischemic brain causes proliferation, differentiation and lymphocyte infiltration resulting in tissue damage. TGFβ and IL-10 promote the T-reg cell activation that modulates the immune response and alleviates the ischemic brain injury.