



HAEMORRHAGE AND STROKE: IMMUNITY AND INFLAMMATION

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ABSTRACT

In ischemic stroke, microglia and the blood-brain barrier (BBB) are activated. This phenomenon leads to the activation of immune cells such as monocytes/macrophages, lymphocytes, mast cells (MCs), and neutrophils. The recruitment of these cells to the site of tissue damage leads to the release of pro-inflammatory cytokines, while in normal tissue, these cells are beneficial for the brain's physiological activity. The BBB protects brain tissue and can be disrupted after stroke, an effect mediated by pro-inflammatory cytokines. However, the relationship between the BBB, microglia and pro-inflammatory compounds in hemorrhagic stroke still needs to be determined.

KEYWORDS: *haemorrhage, stroke, immunity, inflammation, cytokines, microglia, BBB*

INTRODUCTION

Ischemic stroke is characterized by decreased blood flow in the brain tissue and the activation of microglia, which are macrophage-like immune cells resident in the central nervous system (CNS) (1). Microglia are brain cells adjacent to the microvasculature in the basal ganglia, substantia nigra, and hippocampus. These cells, like activated peripheral blood monocytes, produce inflammatory cytokines and chemokines but can also release activated mast cells (MCs), producing proteases and reactive oxygen species (ROS) (2). The release of these pro-inflammatory compounds in stroke recruits immune cells to the site and exacerbates brain damage, resulting in neuronal destruction (3). In addition, the recruitment of immune cells from the bloodstream into the damaged CNS leads to the upregulation of adhesion molecules and cytokine/chemokine receptors with traumatic brain injury (4).

Conversely, the arrival of immune cells occludes vessels after ischemia, causing neuroprotection (5). These cellular dynamics are still unclear and can be the subject of future studies. Ischemic brain tissue produces damage-associated molecular patterns (DAMPs) with immune and inflammatory responses contributing to stroke (6).

DISCUSSION

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Immune cells, including T cells, macrophages, microglia, MCs, and neutrophils, are present after stroke and cause damage by worsening ischemic brain damage (7). Cytokines such as IL-1 and TNF are upregulated in stroke and participate in brain inflammation. The secretion of pro-inflammatory cytokines, including IL-1, IL-6, and tumor necrosis factor (TNF) produced by macrophages and microglia, causes brain inflammation (8).

Microglia, which mediate their effect through the CD36 receptor and other molecules, also produce high levels of ROS, which together with pro-inflammatory cytokines, characterize ischemic stroke. These reactions mediate the acute phase of stroke (9). However, it is not yet clear whether microglia influence neurogenesis (10). Non-activated microglia protect the CNS, but on the contrary, after activation, they polarize in M1 cells through TLR4, interferon gamma ($\text{IFN}\gamma$) or granulocyte-monocyte-colony stimulating factor (GM-CSF) receptors, with generation of pro-inflammatory cytokines and arachidonic acid products (11) (Fig. 1).

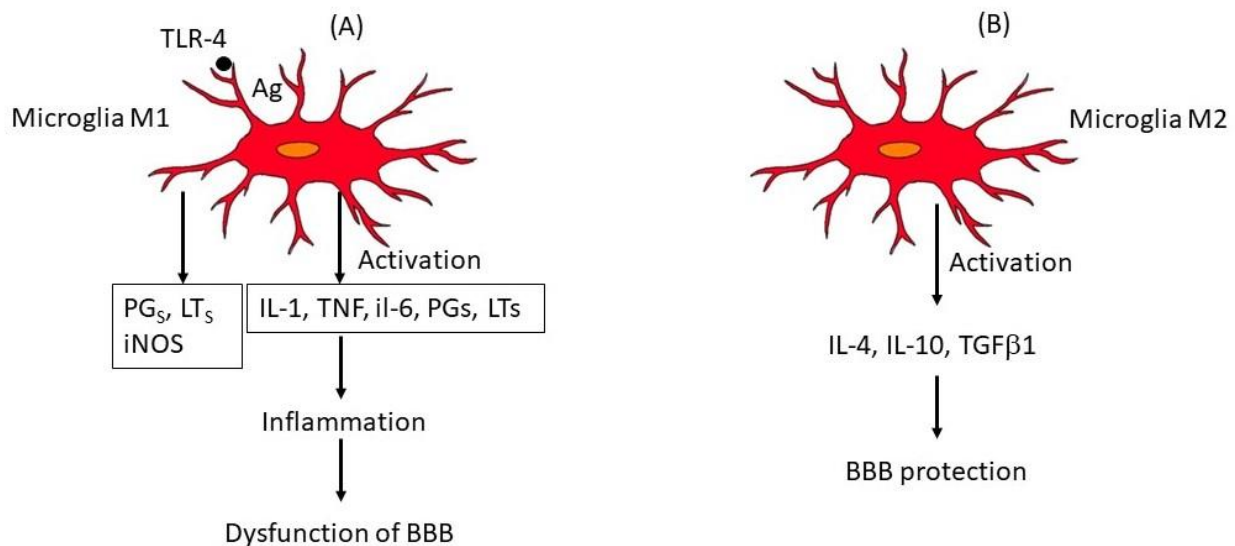


Fig. 1. In panel A we show that the antigen binds TLR4 in Microglia M1 which activates the generation of prostaglandins (PGs) leukotrienes (LTs), and Inducible Nitric Oxide Synthase (iNOS) causing inflammation and dysfunction in the Blood-Brain Barrier (BBB). In panel B the activation of microglia (M2) leads to secretion of anti-inflammatory cytokines which protect the BBB. PGs: Prostaglandins; LTs: Leukotrienes; TLR: Toll-like receptor.

These effects cause a breakdown of the BBB with brain damage. The M2 microglia cells, producing anti-inflammatory cytokines such as IL-10, IL-4, TGFβ₁ and probably IL-37 and IL-38, tend to dump inflammation with the benefit of the brain system (12) (Table I). The disruption of the BBB can lead to the activation of microglia which are physiologically responsible for the protection and repair of the CNS. The production of IL-10 by the M2 microglia phenotype allows the recruitment of Treg cells, with increased expression of CD86 and MHC-II, counteracting inflammation (13).

Table I. Activation of microglia in response to pathological stressor.

Pro-inflammatory receptors: TLR4, $\text{IFN}\gamma\text{R}$, GM-CSFR
Compounds: TNF, IL-1, IL-6, CCL2, CXCL10, Inos
Anti-inflammatory receptors: IL-4R, IL10R, VEGFR2, Compounds: IL-10, TGF-b1, IL-37, IL-38

We know that immunological processes contribute to hypertensive phenomena. In particular, activated T cells and macrophages arrive in abundance in the perivascular regions of the arteries and release cytokines such as IL-1, TNF, IL-6, IL-17, and interferon gamma ($\text{IFN}\gamma$), causing vascular resistance and renal fibrosis (14). By causing inflammation, both the innate and adaptive immune systems can provoke damage and malfunction of the organs with the possible consequence of cerebral stroke (15). Microglia, astrocytes, and oligodendrocytes are part of the brain system and play an

important role in the formation and healing of ischemic stroke. Thus, they can mediate both harmful and healing effects (16). Oligodendrocyte antigens implicated in neuronal inflammation activate T lymphocytes, involved in the tissue repair process. By producing inflammatory cytokines, active microglia damage the CNS, but in post-ischemic stroke they can generate anti-inflammatory cytokines such as IL-10, IL-37, and IL-38, which regulate the immune response with benefits and recovery of the tissue pathological state (17).

Microglial cells crosstalk with endothelial cells (ECs) contributing to the formation and functioning of the BBB. The CNS is separated from the peripheral circulatory system through the BBB which is composed of cells and biological reactions (18). The BBB, where ECs play a crucial role, protects brain tissue from external insults and keeps the neuronal system safe. Therefore, the BBB is important for the protection of the CNS and the proper functioning of neurons (19). The contact of the ECs of the CNS with other cells such as pericytes and astrocytes, constitutes the BBB and is critical for its efficient functioning. The BBB, with its vasculature, restricts the trafficking of immune cells in the brain, an effect that is impaired when the BBB is disrupted (20). ECs, together with neurons and microglia, form part of the BBB which, when disrupted or dysregulated, leads to the generation of neurological diseases (21). Activation of ECs in brain tissue induces expression of adhesion molecules ICAM-1 and VCAM-1. ICAM-1 and VCAM-1, and other adhesion molecules such as PECAM-1, participate in the migration of immune cells and, particularly, of CD4+ T cells (22).

Through the interaction with an integrin, the activated CD4+ T cells contribute to the inflammation by crossing the basement membrane of the ECs and in doing so, they can reach the brain tissue (23). The increase in expression of metalloproteins in the inflammatory process contributes to the migration of CD4+ T lymphocytes and neutrophils into the CNS with the secretion of cytokines and chemokines and damage to the glial system. In these biological dynamics, blood vessels play a crucial role in initiating CNS pathologies, including the inflammation that often accompanies these neuropathies such as ischemic stroke (24).

CONCLUSIONS

Therefore, resting microglia cells help to protect the brain tissue, however when they are activated, they can be detrimental to the CNS and may disrupt the BBB, mediating ischemic stroke and hemorrhage (25).

The study of cellular functioning in the BBB allows for better identification of new diagnostic and therapeutic elements which are very important in this field of medicine, where many points are still waiting to be clarified. After a stroke, there can be a loss of BBB that is measurable by various methods such as magnetic resonance imaging, computed tomography, etc (26). Accurate and early examination with these methodologies can prevent intracerebral hemorrhage in individuals presenting with an acute ischemic stroke. Failure of the BBB leads to an accumulation of immune cells in the brain with the secretion of numerous cytokines and growth factors such as VEGF, which are instrumental in causing vascular permeability and neuroinflammation (27).

Thus, after a stroke, the BBB breaks down and fails to function, resulting in the involvement of immune cells that contribute to inflammation and vascular damage. However, more studies are needed to clarify the exact role of pro and anti-inflammatory cytokines in stroke and haemorrhage (28).

Conflict of interest

The author declares that they have no conflict of interest.

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