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Research Report

Complexity of the cell–cell interactions in the innate immune response after cerebral ischemia

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ABSTRACT

In response to brain ischemia a cascade of signals leads to the activation of the brain innate immune system and to the recruitment of blood borne derived cells to the ischemic tissue. These processes have been increasingly shown to play a role on stroke pathogenesis. Here, we discuss the key features of resident microglia and different leukocyte subsets implicated in cerebral ischemia with special emphasis of neutrophils, monocytes and microglia. We focus on how leukocytes are recruited to injured brain through a complex interplay between endothelial cells, platelets and leukocytes and describe different strategies used to inhibit their recruitment. Finally, we discuss the possible existence of different leukocyte subsets in the ischemic tissue and the repercussion of different myeloid phenotypes on stroke outcome. The knowledge of the nature of these heterogeneous cell–cell interactions may open new lines of investigation on new therapies to promote protective immune responses and tissue repair after cerebral ischemia or to block harmful responses.

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1. The immune response after brain ischemia, a complex network of cell–cell interactions

Inflammation is recognized as an important contributor to the pathophysiology of stroke. After stroke, a cascade of signals leads to the activation of resident glial cells – mainly microglia – perivascular macrophages, as well as to an influx of blood-derived cells recruited by cytokines, adhesion molecules, and chemokines (rev. in Chamorro et al., 2012; Iadecola and Anrather, 2011; Jin et al., 2010; Kriz, 2006). The release of damage- associated molecular patterns (DAMPs) because of stress or necrosis and of glutamate from damaged cells, and the loss of cell-to-cell interactions drive the initial activation of the innate immune system in the ischemic brain. After cerebral blood flow disruption, the increased expression of cell surface adhesion molecules in cerebral endothelial cells

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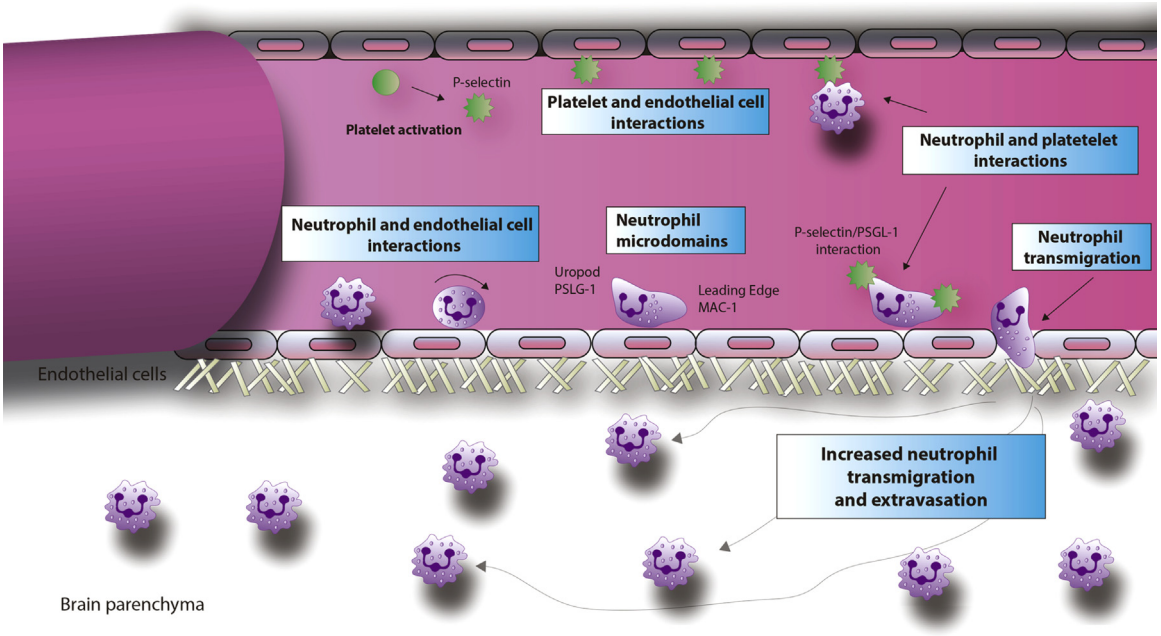

Fig. 1 – Neutrophil, endothelial cell and platelet interactions facilitate neutrophil recruitment and extravasation into brain parenchyma after stroke. After cerebral blood flow interruption, the increased expression of cell surface adhesion molecules in cerebral endothelial cells promotes the rolling and firm adhesion of both neutrophils and platelets. Neutrophil activation leads to the formation of two differentiated regions, the moving or "leading edge" and the uropod. This process involves morphological changes (from a round to an elongated shape) and the differential segregation and accumulation of molecules and surface receptors. At the same time, activated platelets increase the expression of P-selectin. In this scenario, neutrophils bind toactivated platelets through P-selectin/PSGL-1 interactions and this would facilitate neutrophil recruitment and transmigration during acute brain injury.

promotes the rolling and firm adhesion of both leukocytes and platelets. The recruitment of successive waves of leukocyte subsets including neutrophils, monocytes and lymphocytes to inflamed vessels and subsequently to the injured brain occurs over hours to days, and contributes to the pathogenesis of ischemic brain injury by inducing brain damage and blood brain barrier (BBB) disruption, which can lead to edema, cerebral hemorrhage and a vicious circle of sustained influx of myeloid cells (Iadecola and Anrather, 2011) mediating the release of reactive oxygen species (ROS), further BBB disruption and immune cell activation, and the subsequent cytotoxicity Figs. 1 and 2

The recruitment of leukocytes into the cerebral microvasculature could be considered as a rate-limiting step in cerebral ischemia-induced inflammation. In response to an ischemic event, endothelial cells begin to express high levels of adhesion molecules, which allow the interactions with activated leukocytes. This process implicates the coordinated expression and reorganization of specific adhesion molecules on the surface of endothelial cells and leukocytes, and also a cellular and molecular complex interplay between platelets, endothelial cells and leukocyte subsets (Yilmaz and Granger, 2008). The recruitment process and the dynamics of leukocyte recruitment after stroke may be differentially influenced by extrinsic and/or intrinsic factors. For instance, the use of different experimental models of stroke may differentially influence the dynamics of leukocytes recruitment to the brain by modifying the point of entry of leukocytes subsets into the brain. In fact, leukocyte adhesion during focal ischemia is mediated by the post capillary venule endothelium (Muldoon et al., 2013), but a critical role for meninges covering the ischemic areas has also been described in the early stages of ischemia (Moller et al., 2014). Therefore, the integrity of meninges in stroke models using craniotomy is compromised and may promote an early recruitment of leukocytes to the brain parenchyma (Cuartero et al., 2013; Moller et al., 2014) if compared to those cerebral ischemia models where meningeal damage is secondary (Gelderblom et al., 2009). The presence of comorbidities such as hypertension, aging, obesity or bacterial infection (Dénes et al., 2014; Manwani et al., 2013; Moller et al., 2014; Murray et al., 2013; Pradillo et al., 2012) can modify stroke outcome by influencing immune activation, but even intrinsic factors such as biological sex or the selected mouse strain (Kim et al., 2014; Manwani et al., 2013) could be critical determinants of stroke-induced inflammation.

Although a large number of reports implicate blood-borne derived leukocytes and microglia in brain injury after ischemic stroke, there are also several studies that do not support this conception. In fact, these cell subsets may play distinct functional roles associated either to damage or neuroprotection. This is logically associated to the heterogeneity of the different myeloid cell populations that participate on stroke-induced inflammation. In this sense, the cellular origin and the plasticity of the myeloid cell lineage are believed to be determinant for the specific role of these cells on stroke outcome. However, the mechanisms that regulate their recruitment, activation state or transformation in situ in response to brain inflammation are not well established yet.