The Forgotten Lymphocyte
Immunity and Stroke

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Inflammation is recognized as a key player in the development of atherosclerosis and is increasingly believed to contribute to reperfusion injury and delayed ischemia in the brain after stroke. The immune system is overwhelmingly complex; clinical interest in stroke and vascular disease has focused particularly on the roles played by specific immune cells and cytokines. Monocyte-macrophages and lymphocytes are the major immune cells within atherosclerotic lesions. Neutrophils and monocyte-macrophages are believed to exacerbate stroke-related ischemia-reperfusion injury. However, lymphocytes are key and versatile regulators of the immune system; their role during ischemic stroke may have been underappreciated. Evidence is now beginning to emerge that lymphocytes may have a greater and earlier involvement during stroke, opening the door for novel and highly specific targets for diagnostic, management, treatment, and prevention strategies for both stroke and vascular disease.

Lymphocytes (eg, CD4⁺ Th1 cells) contribute to and may accelerate atherosclerotic plaque formation. CD4⁺CD28⁻ cells are a rare subset of CD4⁺ T cells that are long-lived, secrete high levels of γ-IFN, and are directly cytotoxic. These cells preferentially infiltrate unstable plaque and contribute to increased endothelial cell lysis in patients with acute coronary syndromes. In stroke-prone rats, induction of mucosal tolerance to E-selectin, a leukocyte adhesion molecule expressed on activated endothelial tissue, may divert the immune response away from a Th1 (proinflammatory) response and prevent ischemic and hemorrhagic strokes. Naturally arising regulatory T cells (CD4⁺CD25⁺) have recently been shown to be potent inhibitors of the development of atherosclerosis in several mice models; immune modulation using naturally arising regulatory T cells may also be a promising approach for vascular disease prevention.

Early on in acute ischemic stroke, the lymphocyte has been thought to play little role, although there has been indirect evidence for some years that this may not be the case. Therapeutic strategies for acute ischemic stroke have focused on preventing the recruitment and trafficking of neutrophils into ischemic lesions through inhibition of cellular adhesion molecules, however so far without success. In this issue of Circulation, in a murine model of transient focal cerebral ischemia (in which specific lymphocyte populations were depleted), Yilmaz et al provide evidence for a role of CD4⁺ and CD8⁺ T lymphocytes and γ-IFN in the exacerbation of ischemic reperfusion injury as early as 5 hours after stroke. CD4⁺ and CD8⁺ T cells and γ-IFN appeared to mediate microvascular dysfunction by causing the cerebral microvasculature to assume a proinflammatory and prothrombotic phenotype. Given that changes in adaptive immunity are believed to take some days, questions arise as to what these results mean and by what mechanisms the lymphocytes act. As suggested by the authors, lymphocytes may be acting indirectly by activating other circulating blood cells and/or extravascular cells such as resident macrophages in the brain. Alternatively, lymphocytes may be acting directly on brain tissue, but this cannot be determined from the results of this study. Clearly, further studies are needed, and the work of Yilmaz et al does have some limitations. Because infarct size was measured only for up to 72 hours after reperfusion, there is the possibility that delayed injury was not detected in this stroke model. The reasons for the similar degrees of neuroprotection seen with either CD4⁺ or CD8⁺ T-cell depletion and that conferred by depletion of the total lymphocyte population also are not clear.

Given the known key regulatory functions of lymphocytes, perhaps the results of this work should not be that surprising. What may be more surprising is that evidence of the potential...

Disclosures

None.

References

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Circulation. 2006;113:2035-2036
doi: 10.1161/CIRCULATIONAHA.105.620732

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