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.

When the immune system becomes activated, a delicate balance between inflammatory and anti-inflammatory states is maintained by the innate (nonspecific) and adaptive immune systems. The adaptive immune system is characterized by its ability to alter receptor expression and cellular functions when encountering new antigens, whether self or foreign; functions include cell-mediated immunity, humoral immunity, immune response regulation, memory, and immunological tolerance. Cells of the adaptive immune system include T-cell lymphocytes (helper T cells [generally CD4+] and cytotoxic T cells [generally CD8+]), natural killer cells, and B-cell lymphocytes. After antigenic activation, CD4+ T cells can be differentiated into at least 3 subsets: Th1 (which are involved in cell-mediated immunity and secrete proinflammatory cytokines such as gamma-interferon [γ-IFN], interleukin [IL]-2, and lymphotoxin), Th2 (which promote humoral immunity and secrete anti-inflammatory cytokines such as IL-4 and IL-10), and regulatory T cells (CD4+CD25+, which secrete transforming growth factor-β [TGF-β] and IL-10).

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...
roles of lymphocytes during acute stroke may have been underappreciated. In the clinical setting, there is evidence of T-cell activation in the first 24 hours of stroke; increases in circulating CD4^+CD25^+ T cells have been shown, although the functional consequences, which could potentially include suppression of other antigen-activated T cells, are not clear. Apart from early T-cell activation, it also is quite possible, and even likely, that different functional classes of lymphocytes present before or at the time of stroke could affect the evolution of ischemic lesions and outcomes. As an example, elevated CD4^+CD28^− T-cell counts recently have been associated with worse outcomes after ischemic stroke. Nadareishvili et al found that patients with CD4^+CD28^− levels >8% (normally present in <1% of CD4^+ cells) during the first 48 hours of stroke had a 6-fold increase in dying or developing a recurrent stroke during the following year. A notable finding was that patients with prior stroke had higher levels of these cells, raising the possibility that this population of T cells, already sensitized to brain antigens, contributed to a greater proinflammatory reaction to the new stroke. (The potential for exposure to local and leaking brain antigens in ischemic brain to sensitize peripheral lymphocytes has been recognized in prior studies.) As described above, elevated levels of this proinflammatory T-cell subset also have been associated with the development of unstable atherosclerotic plaques. One can start to envisage multiple feedback loops between the brain, the immune system, and the vascular system that could affect the extent and severity of vascular disease, as well as stroke outcome and recurrence. Furthermore, depressed immunity and altered immune responses during the acute phase of stroke may predispose patients to infections. Apart from probable negative effects, a positive role for the immune system may be in tissue remodeling and repair days to weeks after stroke. It also has been suggested that ischemic preconditioning, for which there is evidence in clinical stroke, may be immunologically mediated.

This increasingly complex interplay between the immune system, the brain, and the vasculature in stroke highlights the rationale for using newer technologies for cellular and molecular profiling of blood and tissue in clinical and translational research studies. This is now possible using multiple combinations of antibodies in flow cytometry studies and with microarray analyses. These studies may permit identification of functional classes of lymphocytes that affect disease severity and outcome (cf, CD4^+CD28^−CD161^+ T cells contributing to coronary artery plaque destabilization in acute coronary syndromes) and may permit reclassification of disease (cf, novel subgroups of B-cell lymphoma in gene expression studies). Targeting lymphocyte populations may permit more focused approaches to the diagnosis, treatment, management, and prevention of stroke and vascular disease.

Many aspects of the role of inflammatory cells in ischemic stroke are still controversial. However, work such as that by Yilmaz et al could highlight a possible early role of T cells and γ-IFN in stroke-related ischemic reperfusion injury. If the results are transferable to humans, this work could suggest new and different therapeutic targets for acute ischemic stroke, in addition to novel approaches that are ongoing for the prevention of cardiovascular disease. It is good to see that the lymphocyte is no longer forgotten.

**Disclosures**

None.

**References**


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