Modulation of the Postischemic Immune Response to Improve Stroke Outcome

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Abstract—Recent advances in understanding how the poststroke immune response may contribute to ischemic brain injury are discussed in this article. In particular, the potential of modulating the postischemic immune response to improve stroke outcome is explored. (Stroke. 2010;41[suppl 1]:S75-S78.)

Key Words: immunology ■ inflammation ■ neuroprotection

There are profound alterations in the systemic immune response following stroke. The stroke induced changes include a dramatic increase in the systemic inflammation, as measured by plasma concentrations of C-reactive protein and interleukin (IL)-6. More recent data also demonstrate that stroke leads to a sympathetically mediated dysfunction of the systemic immune response that predisposes to infection; the degree of these immunologic alterations depends on stroke severity. Infection is common following stroke, and data demonstrate that infection in the poststroke period, especially pneumonia, is an independent risk factor for poor outcome.

Why infection predisposes to worse outcome is unclear, but our laboratory has focused on the possibility that an infection in this vulnerable time period may lead to changes in the microenvironment of the lymphoid organs and brain that allow for the development of a detrimental immune response toward brain antigens.

The immune response is generally thought of as having an innate, or antigen nonspecific, arm and an adaptive, or antigen specific, arm. The innate immune response is also referred to as the inflammatory response and is the first line of defense against invading pathogens and the primary response to tissue injury. It is thus not surprising that there is evidence of systemic inflammation following stroke and that the degree of inflammation correlates with stroke severity and ultimately to the amount of tissue infarcted. The amount of tissue infarcted is also reflected by the concentration of C-reactive protein and interleukin (IL)-6. More recent data also demonstrate that stroke leads to a sympathetically mediated dysfunction of the systemic immune response that predisposes to infection; the degree of these immunologic alterations depends on stroke severity. Infection is common following stroke, and data demonstrate that infection in the poststroke period, especially pneumonia, is an independent risk factor for poor outcome.

Th1 cells are associated with cellular immunity and are characterized by the secretion of interferon-γ and lymphotoxin α, whereas Th2 cells are associated with humoral immunity and the secretion of IL-4, IL-5, and IL-13. Furthermore, although Th17 cells play a role in host defense, they also appear to be important in the genesis of autoimmunity; Th17 cells are characterized by the secretion of IL-17. Inducible Tregs, on the other hand, are characterized by the secretion of TGF-β and IL-10 and, as the name implies, regulate immune responses.

To date, there has been little interest in exploring the possibility that autoimmune responses to brain might affect outcome from stroke. There are, however, studies that document the fact immune responses to brain antigens do occur following stroke. For instance, lymphocytes from stroke survivors show more activity against MBP than the lymphocytes from patients with multiple sclerosis. In addition, myelin-reactive T cells are found in higher numbers among stroke survivors, allowing for the possibility of novel antigen encounter within the CNS itself.

For a lymphocyte to become activated to an antigen, it must generally be presented that antigen by a professional antigen-presenting cell (APC) in the context of the major histocompatibility II molecule and receive an additional costimulatory signal. The nature of the immune response is further shaped by the cytokine milieu of the environment at the site of antigen encounter (Figure). For instance, if a naïve lymphocyte recognizes its cognate antigen in the presence of interferon-γ, a Th1-type response usually develops; if the recognition occurs in the presence of IL-4, a Th2-type response develops. Furthermore, if antigen recognition occurs in the presence of transforming growth factor (TGF)-β1 and IL-6, a Th17 response occurs; in the absence of IL-6, a regulatory T-cell response (Treg) develops. A Treg response can also be induced in the presence of IL-10. As would be expected, the type of the effector cell/response generated after antigen encounter is associated with very different immunologic outcomes. For instance, Th1 cells are associated with cellular immunity and are characterized by the secretion of interferon-γ and lymphotoxin α, whereas Th2 cells are associated with humoral immunity and the secretion of IL-4, IL-5, and IL-13. Furthermore, although Th17 cells play a role in host defense, they also appear to be important in the genesis of autoimmunity; Th17 cells are characterized by the secretion of IL-17. Inducible Tregs, on the other hand, are characterized by the secretion of TGF-β and IL-10 and, as the name implies, regulate immune responses.

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patients with cerebrovascular disease. These data thus provide evidence that a cellular immune response to brain antigens occurs following stroke. Furthermore, there are increased titers of antibodies to brain antigens, including neurofilaments and portions of N-methyl-D-aspartate receptor, following stroke, indicating that there is also the development of a humoral response to these antigens. The immune response to CNS antigens after stroke is likely just an epiphenomena of stroke given that cerebral ischemic injury to the blood–brain barrier allows for the systemic immune system to come into contact with the antigens that are normally sequestered from it. Nonetheless, it is possible that this response leads to “collateral damage”; whether these immune responses affect outcome from stroke is largely an unanswered question.

In an animal model of stroke, we have demonstrated that the predominant immune response to brain antigens following stroke is that of a Treg response characterized by secretion of TGF-β1. Using the paradigm of mucosal tolerance, we also found it possible to induce Treg responses before stroke; animals that exhibit a Treg response experience both better short-term (days) and long-term (1 month) outcome from stroke. It is thus not surprising that a recent study found that the absence of Treg cells is associated with worse outcome from stroke. Induction of Treg cells characterized by the secretion of IL-10 before stroke also improves short-term outcome and decreases infarct size. These data suggest that modulation of the postischemic immune response by inducing a more robust Treg response might be a viable strategy for neuroprotection.

In our animal model, we also found that exposure to an inflammatory stimulus at the time of stroke leads to a deviation of the immune response to that of a Th1 response, and the Th1 response to brain antigens is associated with worse outcome. This deviation from an endogenous Treg response to that of Th1 response induced by an inflammatory stimulus at the time of stroke appears to be related to a change in the milieu of microenvironment at the site of antigen presentation. This observation may help to explain why persons who develop an infection in the poststroke period have increased morbidity and mortality. It also suggests that attempts to avoid infection in the poststroke period may be of therapeutic value. To date, however, there have only been a few trials of antibiotic prophylaxis following stroke, and these relatively small trials have conflicting results, suggesting that prophylactic antibiotic therapy may improve, worsen, or have no effect on stroke outcome.

Figure. Following stroke, there is ample opportunity for the immune system to come into contact with CNS antigens, either in the brain or in the periphery. The type of immune response/effector cell that results from lymphocyte engagement with the antigen (red dot) depends on the microenvironment/cytokine milieu at the site of antigen encounter. Treg responses are associated with better outcome from stroke, whereas Th1 responses are associated with worse outcome. Nothing is known about the Th17 response after stroke; based on what is known about the role of Th17 cells in autoimmunity, however, it is likely that Th17 responses would be similarly detrimental. Neuroprotective strategies could either serve to enhance the Treg response after stroke or prevent the Th1 (and Th17?) response. APC indicates antigen-presenting cell; IFN, interferon; lymph, indicates lymphocyte; LTA, lymphotoxin α; MHC II, major histocompatibility complex II; TCR, T-cell receptor; TGF, transforming growth factor.
IL-17 was recently shown to contribute to ischemic brain injury up to 7 days after stroke onset. In this study, the IL-17 was being produced by γδ T cells, which are important mediators in the antigen-nonspecific inflammatory response, and not by Th17 cells. Given the fact that there is robust upregulation of IL-6 following stroke and increased expression of TGFB-β in brain, however, the postischemic cytokine milieu could favor the development of Th17 cells. Whether or not CNS-specific Th17 cells contribute to injury in cerebral ischemia has yet to be explored, but their importance in autoimmune diseases, including experimental allergic encephalomyelitis (EAE), is clear. Recent data highlight the fact that the ratio of antigen-specific Th17 cells to antigen-specific Th1 cells, as well as the cell type used to induce EAE (Th17 versus Th1), influence both EAE phenotype and pathology. These data further suggest that the nature of the immune response to brain after stroke has the potential to differentially affect outcome.

The potential of modulating the posts ischemic immune response to improve outcome following stroke is an intriguing neuroprotective approach because it is among the rare interventions that could be initiated in a delayed fashion and still be expected to have an effect. There are, however, potential dangers of manipulating a response that is so complex and incompletely understood. As an example, we found that induction of MBP-specific Treg cells before experimental stroke using the paradigm of mucosal tolerance was associated with better outcome up to 1 month after the ischemic injury; this benefit was not sustained to 3 months, however, and there was a tendency for the animals “tolerized” to MBP exhibit a Th1 response to the antigen. Studies suggest that the phenotype of inducible Treg cells is unstable, so understanding how to prevent this “immunologic drift” would be important before use in therapeutic trials. Furthermore, although immunosuppressive strategies might decrease the risk of developing a Th1 (and possibly Th17) response after stroke, such interventions might increase the risk infection, a risk that is already high in the poststroke period. On the other hand, strategies to enhance the immune response to prevent infection in the poststroke period might increase the risk of developing a detrimental Th1 (and possibly Th17) immune response to brain, and, as already discussed, these responses might predispose to worse functional outcome from stroke. It is also in the realm of possibility that the development of immune responses to brain antigens, be they cellular or humoral, may have longer-lasting effects. For instance, it is appreciated that stroke is a potent risk factor for dementia, and it could be that autoimmune responses to brain contribute to cognitive decline and even the progression of white matter disease. Future clinical studies will need to address the contribution of the posts ischemic immune response to these long-term outcomes.

In summary, the nature of the posts ischemic immune response affects outcome from stroke (Figure). Modulation of this response may be a viable approach to improving outcome in stroke, but there are potential dangers associated with immunomodulation. A more complete understanding of the endogenous immune response following stroke is needed to safely manipulate this response in the poststroke period.

Sources of Funding
This work was supported by the NINDS (RO1NS049197 and RO1NS056457). Disclosures None.

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Stroke. 2010;41:S75-S78
doi: 10.1161/STROKEAHA.110.592881

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