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EDITORIAL

Stroke, Inflammation and the Immune Response: Dawn of a New Era

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This issue of *Neurotherapeutics* focuses on immunologic changes after stroke, a promising target for stroke therapies. Stroke is a deadly and disabling disease; globally, it kills 12 % of all people and is a leading cause of disability [1]. In the last few decades, great strides have been made in stroke prevention and also in acute therapies to restore blood flow to the brain before cells die. The next therapeutic frontier is to help people who have already suffered a brain infarction, and one of the most promising interventions is modulation of the immune system. This issue focuses on what is known about immunologic changes set into motion by stroke and targets for immunologically based therapies.

There are numerous potential targets for immune therapies after stroke. Stroke leads to a cascade of immunologic changes that affect the entire body in ways that are just beginning to be appreciated. Until recently, research focused primarily on the inflammatory response within the peri-infarct region after stroke, but it is now clear that stroke also leads to a profound systemic inflammatory response. Following stroke, there is an increase in inflammatory biomarkers in the bloodstream [2, 3], but at the same time activation of the sympathetic nervous system mediates a systemic immunodepression that includes a defect in the T helper 1 response [4, 5]. This sympathetically mediated immunodepression likely contributes to an increase in the risk of poststroke infection [6]. Poststroke infection, primarily pneumonia, is independently associated with increased morbidity and mortality [7, 8].

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In addition to neurological deficits caused by focal brain infarcts, it is now appreciated that stroke affects a broader range of outcomes. For instance, both depression and fatigue are common after stroke, and these "silent sequelae of stroke" may be related to poststroke inflammation [9, 10]. There are also convincing data suggesting that cognitive decline after stroke may be related to immune responses put into play by the stroke [11, 12]. New immunomodulatory therapies will thus target symptoms that affect quality of life but have not received adequate recognition in stroke trials to date.

An exciting new chapter in biology is the appreciation of the gut microbiome in health and disease. Accumulating data show that stroke induces a change in the gut microbiome, and further, that outcome can be changed by altering the gut microbiome [13, 14]. Future studies will thus need to assess the effects of antibiotic treatments for poststroke infection on the microbiome and the contribution of these changes to morbidity and mortality after stroke.

Even within the brain itself, the complexity of the immune response is becoming apparent. Stroke affects more than just neurons. There are robust microglial and astroglial responses to cerebral ischemia, and brain glia play a major role in not just carrying out, but also targeting and modulating the immune response. This immune response serves the necessary function of removing dead cells to make way for adaptive regenerative responses. New approaches will focus on preserving these effects while limiting harmful ones such as tissue edema that causes brain herniation, bystander death of neurons, and prolonged inflammatory responses.

The immune response is an attractive target for stroke therapeutics because of the broad changes induced in the response by stroke, the diverse effects on stroke outcomes, as well as the fact that it is tremendously amenable to modulation. Immune cells circulate in the bloodstream and home to tissues of interest, which means that the cells are exposed to biological modulators

that are systemically administered and also serve as potential biomarkers of the therapeutic response. Further, a number of successful immune modulatory therapies already exist, and the number of these therapies is growing exponentially.

Early clinical trials of immunomodulation used acute administration of drugs that inhibit leukocyte trafficking into the infarct core and focused on near-term stroke outcomes [15]. Newer trials use approaches that globally affect the immune response, such as preconditioning and the administration of stem cells. The goal of these therapies is to improve stroke outcomes, as assessed by neurological impairment, as well as to enhance functional recovery in the months to years after stroke. With a better understanding of the immunological underpinnings of ischemic brain damage and stroke recovery, future trials will be armed with better biomarkers to monitor the effects of intervention and will be able to better refine and focus the approaches to target inflammation.

In this issue of *Neurotherapeutics* we invited those researchers that have provided insight into the immune/inflammatory issues surrounding stroke to provide an update in this important field of research. The shift in the conceptual framework of stroke as a brain disease to stroke as a systemic disease has been most clearly demonstrated by understanding how stroke affects the immune response. There is still much to learn, but this conceptual shift will undoubtedly lead to new strategies to modulate the immune response, new targets for this immunomodulation, and better-designed trials with additional outcomes that address the patient experience.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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