Response to Letter Regarding Article, “Amplification of Regulatory T Cells Using a CD28 Superagonist Reduces Brain Damage After Ischemic Stroke in Mice”

In their insightful and stimulating comment on our article and on the persistent controversy over the pathophysiological role of regulatory T cells in general, Gauberti and Vivien address perspectives and potential pitfalls of experimental stroke research in the field of neuroinflammation. Obviously, we share their overall view that there is potential for immunomodulatory therapies, including amplification of regulatory T cells, that limit early inflammatory cytotoxicity after stroke.

Specifically, Gauberti and Vivien make the convincing argument that the most widely used stroke model, transient mechanical vascular occlusion of the middle cerebral artery (TMVO), may induce pathophysiological processes, including thromboinflammation, that are unlikely to play a role in other models and in the majority of strokes in patients. General scepticism toward the translational validity of the TMVO model has also been expressed by Hossmann. Even within the TMVO model, some questions on the role of thromboinflammation deserve further attention. It is an unresolved paradox that thromboinflammation seems to be stronger in the TMVO model although it induces less leukocyte brain infiltration compared with other stroke models causing smaller infarcts.

Should we therefore ban the popular TMVO model from preclinical stroke research in general or at least in the area of neuroinflammation? Unfortunately, there is no model to date with a track record of successful translation in stroke. In fact, it is unrealistic that any model can ever adequately reflect the heterogeneous pathophysiology of human strokes and the heterogeneity of patients with stroke. Alternatively, testing potential therapies in different ischemia models may better approximate the clinical heterogeneity of stroke.

To better choose adequate animal models for research into neuroinflammation, we also need to understand much more about the neuroinflammatory response in patients with stroke. For example, a combination of experimental and postmortem pathological techniques has recently challenged long-held views about the postischemic brain immigration by neutrophils. Beyond revisiting the pathology laboratory, neuroimaging using molecular cell labeling techniques can provide essential in vivo information on neuroinflammation in patients with stroke.

Another important challenge for research into the inflammatory response after stroke is to avoid studying the brain in isolation. Extensive brain lesions cause perturbations of the systemic immune system. Initial immune system activation after stroke is followed by profound immunosuppression. Mounting evidence suggests that the immunosuppressive response predisposes patients with stroke to infections and thereby increases morbidity and mortality. Using a variety of stroke models, various aspects of the spectrum of systemic immune changes in patients can be modeled with reasonable adequacy. In murine and human stroke, infarct size is the major determinator of the systemic immune response, and this may be driven by autonomic nervous system dysregulation or release of alarmins from the injured brain. These systemic immunologic changes have implications for the development of neuroprotective immunomodulatory therapies. Exploring systemic effects of immunotherapeutic drugs in a variety of stroke models, including TMVO, may not only provide relevant information on their efficacy but also on their safety for translation into patients.

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