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 with other stroke models causing smaller infarcts may not only provide relevant information on their efficacy but also on their safety for translation into patients.

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