CON: Regulatory T Cells Are Protective in Ischemic Stroke

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For many years ischemic stroke was regarded as a purely thrombotic disease resulting from the occlusion of cerebral arteries and subsequent breakdown of energy supply to neuronal tissues. Back in the late 1970, however, some pioneers in experimental stroke research, above all John Hallenbeck at the National Institute of Neurological Disorders and Stroke recognized the existence of polymorphonuclear leukocytes and macrophages in brain specimen from animals and patients with cerebral ischemia, thereby establishing the conceptual basis for the immunobiology of stroke.1 Since then a plethora of experimental studies stressed the importance of these typically innate immune cells in brain ischemia but clinical trials testing, for example, neutrophil blocking agents, ultimately bombed. Several years later Stoll and Jander2 from Düsseldorf, Germany, were among the first to describe the infiltration of T lymphocytes, which per definition belong to the adaptive immune system, into ischemic brains of rodents. Of note, this happened accidentally while searching for a central nervous system lesion paradigm devoid of inflammation which could be used as control for experimental autoimmune encephalomyelitis.

It is meanwhile well accepted that T cells exert deleterious effects in brain ischemia. However, the functional relevance of the different T cell subsets for stroke progression is less clear, as is their pathological contribution at the different stages of infarction (i.e., acute versus chronic). In particular, a controversial dispute recently arose on the function of regulatory T cells (Tregs) in the ischemic brain.

In a rather simplistic view, many people think about Tregs as the good immune cells which without exception maintain immune tolerance and counteract tissue damage in a variety of (neurological) diseases, such as multiple sclerosis. However, biology usually does not follow a plain black and white dichotomy, and in most situations an exception to the rule exists. In the case of Tregs this exception is ischemic stroke. Using a mouse model of selective Tregs depletion (Depletion of Regulatory T cells [DEREG] mice), we could unambiguously show that Tregs are strong promoters of ischemic neurodegeneration.3 Depletion of Tregs dramatically reduced infarct size and improved neurological function 24 hours after 60 minutes of transient middle cerebral artery occlusion, and this protective phenotype was preserved at later stages of infarct development (until day 7) and in models of mild ischemic stroke. Mechanistically, Tregs induced microvascular dysfunction in vivo by increased interaction with the ischemic brain endothelium and platelets. Accordingly, ablation of Tregs reduced microvascular thrombus formation and improved cerebral reperfusion on stroke, reinforcing the recently established concept of thrombo-inflammation. In contrast, common immunoregulatory characteristics of Tregs, such as cytokine release or modulation of other immune cell populations, had no functional relevance.3

Apart from our study which was the first to report a detrimental Tregs effect in a primary nonimmunologic disease model, there are currently 4 other studies that examined the consequences of Tregs on stroke outcome in rodent models of cerebral ischemia. Two of these described a protective role of Tregs,4,5 whereas the remaining ones were neutral.6-7

What are the particular strengths of our investigation? First, we introduced a genetic mouse model (DEREG) that allows for the ablation of FoxP3+ Tregs with high specificity, while most other groups used an anti-CD25 antibody to deplete CD4+CD25+ T cells.4,5,7 There have been convincing reports that this antibody induces shedding of the binding epitope rather than depletion of the cells and the fact that CD25 is also upregulated on activated T cells, as well as the existence of CD25-negative Tregs subpopulations limits the interpretation of the data. Second, Tregs depletion is reversible in DEREG mice, hence bearing the unique possibility to use intrinsic phenotype rescue as a control. Finally, we validated our results from DEREG mice by adoptive transfer experiments of Tregs in Rag1−/− mice lacking T lymphocytes.

Li et al8 reported that exogenously applied Tregs induce neuroprotection in stroke mainly by modulating the effector functions of neutrophils. Given that the true pathophysiological relevance of neutrophils in stroke has recently been heavily tackled however,9 the findings should be interpreted with caution. Also, the in vivo expansion of Tregs for clinical translation as suggested by the authors already produced unforeseen adverse effects in a phase 1 trial.6 Here, an antibody directed against CD28 (TGN1412) induced a massive cytokine storm in healthy volunteers. However, whether this is also of relevance in the setting of ischemic stroke or when using other approaches to expand Tregs is unknown so far.
Moreover, Tregs might take over different tasks in stroke and their net biological effects probably depend on the stage of the insult and the timing of application.

As it becomes increasingly clear that ischemic stroke is far more than a simple vessel occlusive disease, the novel Basic Science Controversy Section will hopefully help the stroke community to develop new ideas that reach beyond the everlasting extension of time windows and vascular recanalization or dubious neuroprotection strategies.

Disclosures

None.

References


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