T cell, also known as T lymphocyte, is an important player for immune responses and, thus, can be a therapeutic target for stroke. Three recent translational studies reported how T cells are involved in stroke pathology.

Lee et al (A crucial role of CXCL14 for promoting regulatory T cells in stroke. *Theranostics*. 2017;7:855–875. doi: 10.7150/thno.17558) examined the cellular and molecular mechanisms as to how regulatory T cells (Tregs) are accumulated in stroke brain. Tregs are a subpopulation of T cells and play important roles in suppressing excessive immune responses. This study focused on the roles of CXCL14 (chemokine C-X-C motif ligand 14), which is a CXC chemokine ligand expressed in immune cells and throughout the central nervous system; however, its physiological function was mostly unknown. In a rat stroke model (90-minute middle cerebral artery occlusion by filament insertion), CXCL14 expression was rapidly increased in peri-infarction area for at least 7 days after stroke. This overexpression of CXCL14 maybe contributes to the accumulation of Tregs after stroke because CXCL14 knockout mice showed less accumulation of Tregs. Immature dendritic cells may participate in this CXCL14-induced Treg accumulation. Loss of CXCL14 reduced the accumulation of immature dendritic cell as well, and in cell culture conditions, immature dendritic cells promoted the proliferation of Tregs. In contrast, direct administration of CXCL14 into stroke brain accelerated the Treg accumulation in rats. Because this study showed that deficiency or supplementation of CXCL14 might result in the changes of infarction volume in the rodent stroke models, the CXCL14-Treg cascade would be an attractive approach to reduce inflammatory responses in stroke.

Treg itself can be used as a therapeutic tool. Mao et al (Regulatory T cells ameliorate tissue plasminogen activator-induced brain haemorrhage after stroke. *Brain*. 2017;140:1914–1931. doi: 10.1093/brain/awx111) provided a proof-of-concept study that Treg adoptive transfer would be useful as a cell-based therapy for stroke. Thus far, recombinant tPA (tissue-type plasminogen activator) is the only Food and Drug Administration-approved thrombolytic treatment for acute ischemic stroke. However, delayed tPA treatment may exacerbate blood–brain barrier damage and lead to lethal hemorrhagic transformation in stroke patients. In a mouse stroke model (2-hour middle cerebral artery occlusion by filament insertion), flow cytometry analyses showed the decrease of Tregs in blood 1 day after stroke. The delayed tPA administration (2 hours after the onset of filament occlusion) indeed induced hemorrhagic transformation along with the breakdown of blood–brain barrier in the ischemic territory and also further reduced the number of Tregs in blood. However, these side effects of tPA administration were dramatically suppressed with coinfusion of Tregs. Treg therapy did not only decrease the infarction volume but also ameliorated the neurological function in stroke animals with delayed tPA administration. Therefore, a cell-based therapy of Treg may have a potential for the purpose of combination therapy with tPA.

Although many types of T cells invade into brain parenchyma under stroke conditions, their route into brain is not well documented. Previous research has focused on the vascular route (ie, through damaged blood–brain barrier) for T-cell invasion after stroke, but Llovera et al (The choroid plexus is a key cerebral invasion route for T cells after stroke [published online ahead of print July 31, 2017]. *Acta Neurologica*. doi: 10.1007/s00401-017-1758-y) proposed the new concept that the choroid plexus can be an alternative cerebral T-cell invasion route under stroke conditions. The choroid plexus is present in the ventricles of the brain and is responsible for producing the cerebrospinal fluid. In a mouse stroke model (permanent occlusion of distal middle cerebral artery), T cells were predominantly clustered in the peri-infarct cortex between the lateral ventricle and the lesion site at 5 days after stroke. The authors used the transgenic UBC-PA-GFP (ubiquitin C-photoactivatable green fluorescent protein) mice that express photoactivatable GFP in T cells to show that the choroid plexus is an important route of cerebral T-cell invasion after stroke. Four days after permanent middle cerebral artery occlusion, a thin laser fiber was introduced into the ipsilateral ventricle and illuminated to photoactivate T cells in the ventricle. Photoactivated T cells (GFP-positive T cells) were detected in the peri-infarct cortex as early as 1 hour after illumination, and 4 hours after the illumination, the number of GFP-positive T cells (eg, T cells from the choroid plexus route) became larger than the one of GFP-negative T cells in the peri-infarct region. In addition, when photolithemic lesion was induced in the ipsilateral choroid plexus, cortical T-cell invasion was reduced under stroke conditions. Taken together, these data demonstrated that the choroid plexus is a key route for T-cell invasion into brain parenchyma after ischemic stress.

These 3 articles describe novel aspects of T-cell involvement in stroke pathology. All these studies may have translational relevance because they also used human
samples to show that stroke patients exhibited larger number of CXCL14-positive cells in the penumbra region (by Lee et al), thrombolytic treatment by tPA inhibited the repopulation of circulating Tregs in stroke patients (by Mao et al), and increased choroidal T-cell counts were observed in stroke patients compared with nonstroke patients (by Llovera et al). Further investigations are warranted to determine how T cells may be targeted to ease brain damage in stroke patients.
Stroke Literature Synopses: Basic Science

Ken Arai

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