Tregs Strike a Delicate Balance in Dealing with Infection in the Brain

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Regulatory T cells (Tregs) serve a variety of functions in a healthy immune system, from the suppression of T cell activation to the modulation of immune cell migration to sites of infection. Their ability to dampen immune responses is fundamental in preventing unwanted responses to self-antigens. However, the ability to mount an effective immune response against infectious agents may also be hindered by Treg activity. Another possibility is that Tregs contribute to limiting immune responses in areas of the body where an overly active response could be detrimental, such as regions with slow cell regeneration like the central nervous system. Researchers in Dr. Jennifer Lund's lab in the Vaccine and Infectious Disease Division used a transgenic mouse model to investigate the role of Tregs on immune responses in the brain following infection with the neurotropic West Nile virus (WNV). Specific Treg ablation is possible in this mouse model via administration of a drug. By comparing Treg-deficient mice with Treg-sufficient mice following infection with WNV, the researchers were able to pinpoint several effects of Tregs on the immune response. Their findings were recently published in *The Journal of Immunology*.

The researchers first detected Tregs in the wild-type mouse brain following infection with WNV, indicating that these cells might play a role in controlling the immune response in this tissue. Following infection of the transgenic mice, Treg-deficient mice had higher numbers of activated $CD4^+$ and $CD8^+$ T cells in the brain when compared to Treg-sufficient mice. Additionally, these activated effector cells in the brains of Treg-deficient mice produced more IFN-γ and TNF-α than Treg-sufficient mice. Thus, the degree of effector T cell activation in the brain appeared to be greater in mice with depleted Tregs.

Long-lived memory T cells are essential for recognizing and mounting responses to subsequent infections. The authors next investigated the effect of Tregs on the development of these memory cells by defining differences between the mice at longer time points following infection. The researchers observed that in contrast to their effect on short-lived effector T cells, the presence of Tregs highly promoted the establishment of memory T cells in the brain. Interestingly, the effects of Tregs on both short-lived effector T cells and long-lived memory T cells in the brain were not

mirrored in the spleen, indicating a distinct effect of Tregs depending on the tissue microenvironment. Finally, the researchers determined that the effect of Tregs on establishing immunological memory to WNV infection in the brain relied on their production of TGF-β. Treg-dependent production of TGF-β results in increased expression of CD103 on $CD8^+$ T cells, allowing for these resident memory T cells to be maintained in the brain after infection.

Dr. Jessica Graham, lead author of the study, summarizes that their work "suggests a mechanism by which Tregs control and maintain the tissue-resident memory population needed to protect against recurrent infections in the central nervous system." The nature of Treg activity in the brain is of special interest, as both infection and overactive immune responses can be especially detrimental to this organ. Dr. Graham highlights that, "the tissue microenvironment plays a large role in providing cues necessary to balance the host immune response to infection." Indeed, the importance of protecting the brain from both infection and the body's own immune response may be reflected in the highly specialized activity of these important immune system cells.

Graham JB, Da Costa A, and Lund JM. 2014. Regulatory T Cells Shape the Resident Memory T Cell Response to Virus Infection in the Tissues. *The Journal of Immunology*. 192:683-90

See also: Lund JM, Hsing L, Pham TT, and Rudensky AY. 2008. Coordination of early protective immunity to viral infection by regulatory T cells. *Science*. 320:1220-4

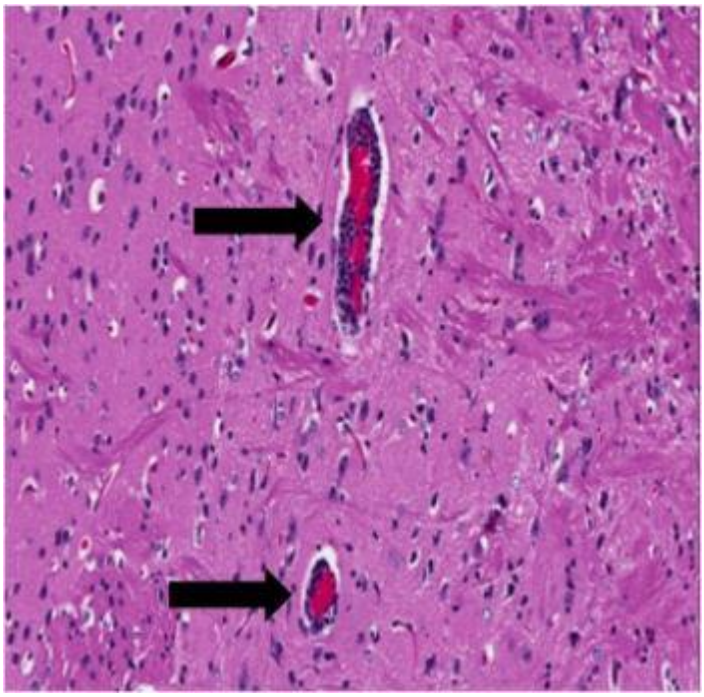

Image provided by Dr. Jessica Graham.

A histology sample of a WNV-infected mouse brain. Encephalitis is characterized by lymphocytic perivascular cuffing (large arrows) and meningitis characterized by focal lymphocytic infiltrates in the meninges.