

Regulatory T lymphocytes and Transplantation



Control of central nervous system inflammation by regulatory T cells depends on TNF/TNFR2

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Anti-TNF drugs have significantly improved the treatment of rheumatoid arthritis and several other auto-immune diseases. Unfortunately, these therapies cannot be proposed in patients with multiple sclerosis because they induced disease exacerbation for poorly known reasons. In the same line, mice deficient for TNF receptor type 2 (TNFR2) developed an exacerbated experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis. These findings suggest that TNF α has an immuno-regulatory facet, besides the well-established pro-inflammatory properties of the cytokine. Our recent findings may bring a mechanistic explanation for the immuno-regulatory role of TNF α . We found that TNF α could efficiently boost expansion and suppressive function of Foxp3 expressing regulatory T cells (Tregs) in the pancreas and pancreatic lymph nodes during type 1 diabetes in mice*. More recently, we observed high levels of Treg expansion in the infiltrated central nervous system (CNS) during EAE. Importantly, this expansion was dramatically reduced in mice deficient for TNFR2, and that was associated with an exacerbated EAE and absence of disease remission. In further support for an immuno-regulatory role of TNF α in EAE, we showed that TNF blockade in wild type mice induced disease exacerbation and reduced Treg expansion in the CNS. Disease worsening was associated with increased GM-CSF, but not IFN γ or IL-17, produced by T cells infiltrating the CNS. By using mixed bone marrow chimeras, we determined that intrinsic expression of TNFR2 in Tregs was needed for their optimal expansion in the CNS during EAE, as well as their optimal Foxp3 and CD25 expression. Finally, we showed that mice with conditional knock-out of TNFR2 in Tregs had a very severe disease compared to controls, demonstrating that spontaneous disease remission was due to TNFR2 expression by Tregs. From these observations, we propose that TNFR2 expressed by Tregs is critical for their expansion and progressive accumulation in the CNS during EAE, reducing disease severity.