PAPER OF THE MONTH 01/2023

TRR 295 ReTune

Expansion of regulatory T cells by CD28 superagonistic antibodies attenuates neurodegeneration in A53T-α-synuclein Parkinson's disease mice.

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J Neuroinflammation. 2022; 19(1): 319. doi: 10.1186/s12974-022-02685-7. PMID: 36587195.

Parkinson's Disease (PD) is characterized molecularly by dopaminergic neurodegeneration, α-Synuclein aggregation, and more recently neuroinflammation. Pro-inflammatory T cells have been shown to infiltrate the substantia nigra (SN) of PD patients and animal models. Through novel transgenic and cell culture techniques, it has become apparent that these pro-inflammatory T cells are responsible for the neurodegeneration occurring in PD. Targeting these immune cells could provide a novel mechanism of halting neurodegeneration and therefore disease progression.

Regulatory T cells (Treg) are a subgroup of anti-inflammatory T cells, which function to supress pro-inflammatory effector T cell subgroups (Teff), like those found in PD brains. Analysis of patient blood samples have demonstrated that the level and suppressive activity of Tregs are altered in PD. These alterations in Tregs may be the mechanism underlying the shift to a proinflammatory environment in PD. The superagonist CD28 antibody (CD28SA) activates Treg and increases their suppressive activity. We hypothesized that treatment with the CD28SA would cause a shift towards an anti-inflammatory environment in PD mice and therefore neuroprotection.

To test this hypothesis, we utilized the AAV1/2 A53T-αSyn PD mouse model which overexpresses the human mutated form of αSyn (A53T) in the SN of mice. Ten weeks following disease initiation, this mouse model demonstrates motor dysfunction, neurodegeneration, and neuroinflammation. Seven days after PD initiation, these mice were treated with a one-time intra-peritoneal injection of the CD28SA. This one-time injection led to an increase in both peripheral and brain-localized Tregs in addition to the anti-inflammatory cytokine, IL-10. Stereological investigation demonstrated a neuroprotective effect in the SN of CD28SA-treated mice, 10 weeks following disease initiation. This neuroprotection was associated with an increase in dopamine and improvement of motor dysfunction.

To further understand the mechanisms underlying the neuroprotective effect of CD28SA, we performed immunohistochemical and flow cytometry analysis of the pro-inflammatory T cells in the PD mice. This analysis revealed a significant reduction in T cell infiltration in the brain as well as Teff levels. These effects appeared to be mediated by Tregs as increasing Treg numbers through adoptive transfer had the same neuroprotective and anti-inflammatory effects. Interestingly, injection of the CD28SA later on in the disease did not alter the disease course, suggesting that early immunomodulation is essential for neuroprotective effects.

Current treatment strategies for PD are focused on symptom management. Our findings point to modulation of the neuroimmune network as being key to altering the course of PD. The CD28SA-treatment strategy utilized here was an important proof-of-concept treatment design, however future treatment strategies will focus on specific regulation of the SN-localized immune cells in order to halt PD progression.

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