Autoimmune range of TCR signaling

Short summary: How an anomaly in a TCR signaling molecule leads to spontaneous autoimmunity over immunodeficiency is unclear. Qualitative/quantitative reduction of ZAP-70 to a critical range produces autoimmune T cells and impairs Treg function, together eliciting autoimmune arthritis and colitis in mice.

Thymic selection and peripheral activation of conventional T (Tconv) and regulatory T (Treg) cells depend on TCR signaling, whose anomalies are causative of autoimmunity. Here, we expressed in normal mice mutated ZAP-70 molecules with different affinities for the CD3 chains, or wild-type ZAP-70 at graded expression levels under tetracycline-inducible control. Both manipulations reduced TCR signaling intensity to various extents and thereby rendered those normally deleted self-reactive thymocytes to become positively selected and form a highly autoimmune TCR repertoire. The signal reduction more profoundly affected Treg development and function because their TCR signaling was further attenuated by Foxp3 that physiologically repressed the expression of TCR-proximal signaling molecules, including ZAP-70, upon TCR stimulation. Consequently, the TCR signaling intensity reduced to a critical range generated pathogenic autoimmune Tconv cells and concurrently impaired Treg development/function, leading to spontaneous occurrence of autoimmune/inflammatory diseases, such as autoimmune arthritis and inflammatory bowel disease. These results provide a general model of how altered TCR signaling evokes autoimmune disease.

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Title: Construction of a T-cell receptor signaling range for spontaneous development of autoimmune disease.

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Graphical Abstract