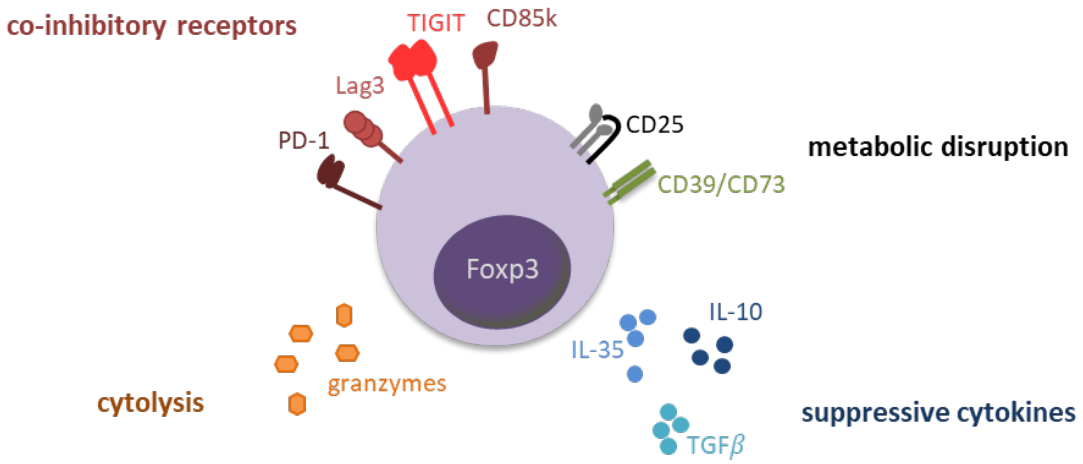
Balancing the immune system – the weapons of Tregs



Regulatory T cells (Tregs) play a crucial role in maintaining peripheral tolerance by modulating the actions of other immune cells, including effector T cells or dendritic cells. Tregs prevent autoimmune diseases and inflammation-caused tissue damage by suppressing immune responses against self- or environmental antigens or during infections. On the other hand, excessive Treg function contributes to chronic infections and tumor immune escape by preventing protective immune responses. Because of their beneficial or deleterious effects, these cells and their regulatory activities are of great interest for targeting as treatment options in different disease scenarios, e.g. autoimmune disorders, chronic infections, as well as antitumor immunity.

Regulatory T cells exert their suppressive capacity through different mechanisms including cell contact-dependent and -independent ways.

Inhibitory cytokines

Key mediators of Treg cell suppressive function include the cytokines interleukin-10 (IL-10), IL-35 as well as transforming growth factor β (TGFβ). Upon receptor binding on counterpart cells, signaling cascades are activated and result in the inhibition of pro-inflammatory effector functions.

Cytolysis

Activated Tregs express effector molecules including granzymes that induce apoptosis in target cells in a cell-contact dependent manner. Granzymes belong to the family of serine proteases and exert their cytolytic function via activation of caspase-dependent cell death pathways.

Metabolic disruption

Through the expression of the high affinity IL-2 receptor alpha chain (CD25), Treg consumption of IL-2 leads to starvation and cytokine-deprivation-mediated apoptosis of effector T cells.

Another mechanism by which Tregs alter the metabolism of other cells is the induction of an anti-inflammatory environment. The ectoenzymes CD39 and CD73 convert the proinflammatory ATP into the anti-inflammatory adenosine which leads to a change of the immune response.

Inhibitory receptors

Regulatory T cells express various membrane-bound receptors both in the steady-state and upon activation. These co-inhibitory receptors act through different and largely unknown mechanisms mainly on effector T cells and dendritic cells. For example Lag3 (lymphocyte-activation gene 3), a CD4 analog, binds MHC class II with high affinity and inhibits activation and maturation of dendritic cells. By interfering with co-stimulatory signaling of T cells, PD-1 (programmed death-1) acts as a negative regulator of immune cell activation and is already used as an immune checkpoint inhibitor in cancer treatments. For other receptors like CD85k, the mechanisms of action still remain largely unknown.

Gaining further insight into Treg-mediated suppressive mechanisms could provide a new perspective for the development of immune therapies to treat autoimmune diseases, chronic infections or cancer patients.