Molecular targeting of regulatory T cells for control of immune responses

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Regulatory T (Treg) cells, which specifically express the transcription factor Foxp3, are actively engaged in the maintenance of immunological self-tolerance and homeostasis, for example, preventing autoimmune disease and allergy. They can also be exploited to induce transplantation tolerance by expanding them in an antigen-specific fashion or to evoke effective tumor immunity by reducing them or attenuating their suppressive activity. Treg cells can therefore be a key target for clinical immune suppression or enhancement.

The majority of Foxp3⁺ Treg cells develop in the thymus as a functionally distinct and mature T-cell subpopulation, while some conventional T cells in the periphery can differentiate into Foxp3⁺ Treg cells under certain conditions, for example, by in vitro antigenic stimulation in the presence of TGF-beta. Ectopic expression of Foxp3 is also able to confer suppressive activity on conventional T cells. We have recently made attempts to pharmacologically control Treg-specific transcriptional and epigenetic changes and thereby control Treg cell development and function. We found that certain tyrosine kinase inhibitors that blocked T-cell receptor-proximal signaling in T cells were able to specifically deplete mature Treg cells, thereby enhancing tumor immunity in humans. On the other hand, inhibitors of a serine threonine kinase involved in a T-cell signaling pathway evoked Foxp3 expression in conventional T cells and converted them to functionally competent Treg-like cells, which effectively suppressed autoimmune disease and allergy in animal models.

This lecture discusses how the development and function of Treg cells can be controlled by transcriptional and epigenetic interventions and how Treg cells be pharmacologically targeted to control a variety of physiological and pathological immune responses.