II-2

Control of immune responses by regulatory T cells

Shimon Sakaguchi
Immunology Frontier Research Center, Osaka University, Japan

Regulatory T (Treg) cells, which specifically express the transcription factor Foxp3, are actively engaged in the maintenance of immunological self-tolerance and homeostasis. The majority of them develop in the thymus as a functionally distinct and mature T-cell subpopulation, with their stable Foxp3 expression chiefly maintained by Treg-specific DNA demethylation. It is poorly understood, however, how Treg-specific transcriptional and epigenetic changes are initiated and coordinated to determine the Treg cell lineage in the thymus. Here, with recently demonstrated associations of super-enhancers with cell type-specific gene regulation and lineage determination in various cell types, we first identified Treg cell-specific super-enhancers (Treg-SEs), many of which were associated with the Treg signature genes, such as *Foxp3*, *Ctla4* and *Il2ra*. The establishment of Treg-SEs developmentally began in Treg progenitor cells before *Foxp3* transcription and Treg-specific DNA demethylation, facilitating early induction of the associated genes. It required the genome organizer Satb1, which bound to Treg-SEs before their activation and extended its binding sites within the SEs along Treg cell differentiation. T cell-specific deletion of *Satb1* impaired Treg-SE formation in Treg precursor cells, hindering both Treg-specific DNA demethylation and the transcription of Treg-SE-associated genes including *Foxp3*. The consequent arrest of Treg cell differentiation at the precursor stage resulted in spontaneous development of severe autoimmunity and IgE hyperproduction. Our results thus demonstrate how Satb1-dependent Treg-SE establishment and subsequent transcriptional and epigenetic changes control Treg cell linage specification in the thymus, and how molecular anomaly in this process causes autoimmune and other immunological diseases via affecting Treg cell development.