ASHBi SEMINAR

Genetic and Environmental factors Driving Human Foxp3+ Regulatory T cells Dysfunction in Autoimmune Diseases

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Date Friday, 5 January 2024

Time ~~18:00 – 19:00 [JST]~~ 19:00 – 20:00 [JST] ◁◁NEW

Venue Conference Room / Zoom
B1F, Faculty of Medicine Bldg. B

*Register via the right QR code

Abstract

Autoimmune diseases, including multiple sclerosis (MS), are mediated by genetic and environmental factors where genetic perturbation of cis-regulatory elements in pathogenic immune cells leads to immune dysregulation and generation of autoreactive T cells and antibodies. While Foxp3+ regulatory T cells (Tregs) play a central role in governing peripheral tolerance and thus preventing autoimmunity, the molecular mechanism underlying their dysfunction in human is not fully explored yet. Here, we performed comprehensive transcriptomic and epigenomic profiling of Tregs in the autoimmune disease MS to identify central genetic programs regulating human autoimmunity. We discovered that upregulation of a primate-specific short PRDM1 isoform (PRDM1-S) induces SGK1 independent from evolutionally conserved long PRDM1 (PRDM1-L), leading to destabilization of Foxp3 protein and Treg dysfunction. This aberrant PRDM1-S/SGK1 axis is linked with Foxo1 deactivation that is shared among other autoimmune diseases, which shares multiple features of high salt mediated Treg dysfunction. Furthermore, integrative analysis of chromatin accessibility and histone modification with CRISPR regulation highlighted an upstream cis-regulatory element of PRDM1-S. Genome wide transcription factor footprint analysis further revealed epigenetic priming of AP-1/IRF factors and decreased binding of Fli1 in MS Tregs. Our study highlights the role of evolutionally emerged PRDM1-S as a part of dysfunctional program of Tregs associated with human autoimmune disease.

Organizer : Graduate School of Medicine
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