Regulation of Treg cell functional stability by the Foxp3-Ikzf1 complex

Laboratory of Experimental Immunology, Immunology Frontier Research Center

Specially Appointed Associate Professor Kenji Ichiyama

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Abstract

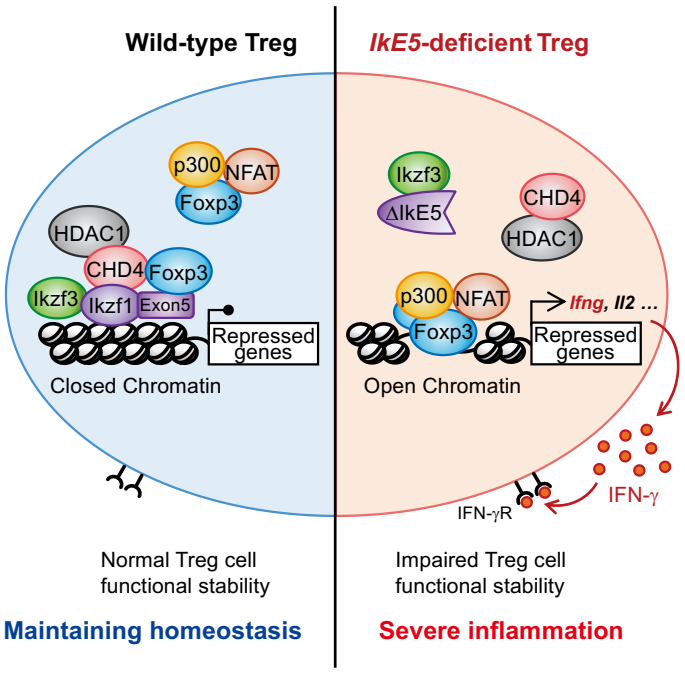
We have discovered that the transcription factor Ikzf1 binds to Foxp3 via its own Exon 5 (Ikzf1 Exon 5: IkE5) region in regulatory T cells (Tregs). Furthermore, Treg-specific deletion of *IkE5* in mice induced Treg functional instability via excessive IFN-γ production, leading to the development of severe inflammatory disease. This demonstrates that the interaction between Foxp3 and Ikzf1 is crucial for maintaining Treg functional stability. Moreover, we have discovered that reducing IKZF1 expression in human Tregs can also induce Treg functional instability, suggesting its potential as a therapeutic target.

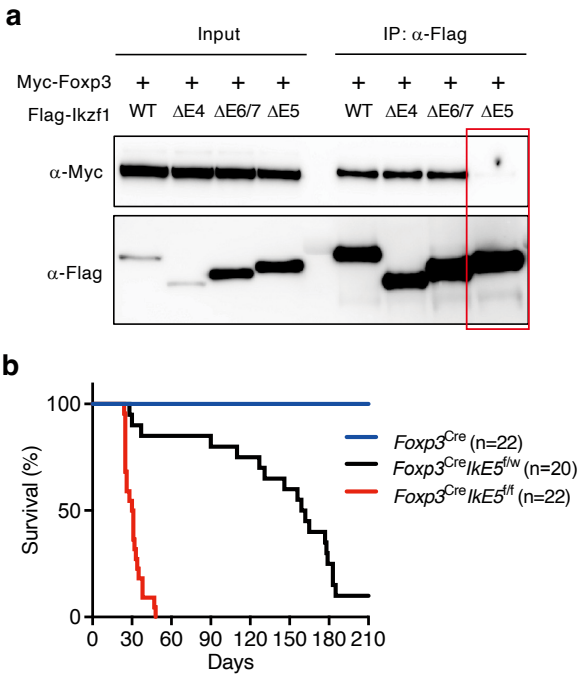
Background & Results

Tregs play a central role in establishing immune self-tolerance and are thought to be involved in the suppressive control of all immune responses, including autoimmunity and anti-tumor immunity. Foxp3, the master transcription factor of Tregs, is known to interact with numerous factors to form protein complexes, thereby regulating Treg differentiation and function by promoting or suppressing the expression of target genes. However, the detailed molecular mechanism by which the Foxp3 complex acts on target genes to control their expression remains unclear. Although the transcription factor Ikzf1 has previously been reported as a Foxp3-interacting factor, its physiological significance remains poorly understood. Using various Ikzf1 deletion variants, we performed co-immunoprecipitation with Foxp3 and identified Exon 5 of Ikzf1 (IkE5) as an essential region for its interaction with Foxp3. Furthermore, by generating and analyzing mice with Treg-specific IkE5 deficiency, we revealed that inhibition of the Foxp3-Ikzf1 interaction disrupts Treg functional stability, leading to lethal systemic autoimmune responses. Subsequently, attempts to elucidate the detailed molecular mechanism underlying the impaired Treg functional stability revealed that the loss of Foxp3-Ikzf1 interaction inhibits the formation of the repressive Foxp3 complex, including the NuRD complex. This, in turn, activates the transcription of gene clusters normally suppressed through chromatin structural changes. Specifically, it was suggested that excessive production of the inflammatory cytokine IFN-γ may be one of the primary causes of impaired functional stability in *IkE5*-deficient Tregs. Moreover, analyses using human peripheral blood mononuclear cells demonstrated that FOXP3 and IKZF1 interact in human Tregs and that knockdown of IKZF1 induces destabilization of human Tregs, leading to IFN-γ overproduction and reduced FOXP3 expression. This suggests that the interaction between FOXP3 and IKZF1 also contributes to the control of Treg functional stability in humans.

Significance of the research and Future perspective

In recent years, since it became apparent that Tregs may play a crucial role in various human immune-related diseases, the development of therapies manipulating or targeting Tregs for the control of human immune disorders has garnered worldwide attention. Based on these research findings, establishing a method to artificially control the functional stability of Tregs by targeting the interaction between Foxp3 and Ikzf1 could lead to the development of groundbreaking treatments for various immune-related diseases, including autoimmune disorders and cancer.





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