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Runx/Cbfβ regulates development of tolerogenic APCs to establish immune tolerance to exogenous antigens

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Multimedia-Room ZQB

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Immune tolerance against commensal microbiota and dietary antigens is established during early life through the induction of RORγt$^+$ Foxp3$^+$ regulatory T (Treg) cells, referred to as periphery induced RORγt$^+$ pTreg cells. Recently, a novel family of RORγt expressing antigen-presenting cells (APCs), including ILC3, eTAC/Janus cells, and Thetis cells (TCs), has been proposed to prime the differentiation of RORγt$^+$ pTreg cells. Among these populations, accumulating evidence suggests that Thetis cell subset IV (TC IV) plays an essential role in establishing intestinal tolerance.
However, the transcription factors governing the differentiation of this subset remain poorly understood. Here we show that Runx/Cbfβ complexes regulate the development of specific TC subsets. Mice lacking Cbfβ2 exhibited a marked reduction of TC II, III and IV, accompanied by a loss of RORγt$^+$ pTreg cells. Transgenic Cbfβ2 expression by *Cd11c-Cre* restored TC IV and RORγt$^+$ pTreg cell differentiation in Cbfβ2-deficient mice.
Furthermore, conditional inactivation of *Runx1* and *Runx3* using *Cd11c-Cre* selectively impaired the development of TC III and IV. Conversely *Cd11c-Cre*-driven transgenic Runx expression enhanced TC IV differentiation, which is accompanied with rescue of antigen uptake capacity of cDCs and TC-IV. As a result, RORγt$^+$ pTreg differentiation was not only restored but further enhanced. Interestingly, we recently observed that the expanded RORγt$^+$ pTreg population co-expresses the transcription factor HELIOS.
We are currently investigating the mechanisms responsible for the induction of this HELIOS$^+$ RORγt$^+$ pTreg subset. Collectively, these findings establish a critical role for the Runx/Cbfβ pathway in TC IV differentiation and provide new insights into therapeutic interventions aimed at promoting RORγt$^+$ pTreg cell induction for the treatment of autoimmune and inflammatory diseases.

Host: Prof. Stefan Britsch, Institute of Molecular and Cellular Anatomy (Phone: 50-23101 stefan.britsch@uni-ulm.de) - Everybody welcome!