論　文　内　容　の　要　旨
Synopsis of Thesis

氏　　名 Name	北川　瑶子
論文題名 Title	Guidance of regulatory T cell development by Satb1-dependent super-enhancer establishment (Satb1依存的スーパーエンハンサー構築による制御性T細胞の分化誘導)

論文内容の要旨

〔目　的(Purpose)〕

The majority of naturally occurring regulatory T (Treg) cells are produced in the thymus as a functionally distinct and mature T-cell subpopulation, actively engaging in the maintenance of immunological self-tolerance and homeostasis. They specifically express the transcription factor Foxp3, which plays crucial roles for Treg cell development and function. In addition, Treg cells acquire specific DNA hypomethylation patterns enriched at Treg cell signature genes including *Foxp3*, *Il2ra*, *Ctla4* and *Ikzf2*. The acquisition of this epigenetic feature is a Foxp3-independent process and associated with stable Treg cell-type gene expression required for Treg cell lineage commitment and maintenance. It is obscure, however, how the Treg cell-specific gene transcription and epigenetic changes are coordinately controlled in developing Treg cells in the thymus.

〔方法ならびに成績(Methods/Results)〕

To address how Treg cell-lineage specification occurs before the expression of Foxp3 and other Treg cell signature genes, we conducted global analyses of various epigenetic marks and transcription factor binding. Among these changes, we focused on super-enhancers, given the previous findings that enhancer activation precedes promoter activation and associated gene expression, and that super-enhancers, defined as clusters of highly active enhancers, are associated with lineage specifying genes. We observed that Treg cell-specific super-enhancers (Treg-SEs) were associated with Treg cell signature genes including *Foxp3*. Moreover, they were gradually activated from the Treg precursor stage, prior to Foxp3 expression.

We next searched for a molecule involved in Treg-SE activation by differential gene expression analyses of Treg precursor cells and Treg cells. One of the candidate molecules was the genome organizer Satb1, which was able to bind to most Treg-SEs from the early stage of Treg cell development and enhancer activation and transcription factor binding occurred around Satb1-bound sites. T cell-specific deletion of Satb1 revealed that Satb1 is indeed required for Treg-SE activation at the Treg precursor stage and failure to activate Treg-SE was strongly associated with impaired induction of Treg cell signature genes. Consequently, Satb1-deficient mice showed severely reduced Treg cell production from the thymus and developed autoimmune diseases and immunoglobulin E (IgE) hyper-production.

〔総　括(Conclusion)〕

In conclusion, the present study strongly suggests that Satb1-dependent establishment of T_{reg}-SEs critically controls the expression of T_{reg} cell signature molecules, including Foxp3, during tT_{reg} cell development. Impairment of this epigenetic event in developing T_{reg} cells is associated with autoimmunity similar to the one induced by tT_{reg} cell depletion. Further study of how T_{reg}-SEs are primed and activated would help our understanding of the molecular basis of T_{reg} cell differentiation and of autoimmune and other immunological diseases.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本論文は、制御性T(Treg)細胞の分化におけるエピジェネティック制御の重要性を示した。北川瑶子氏らは、分化時の転写・エピジェネティック制御を網羅的に解析し、Treg特異的スーパーエンハンサーの活性化がマスター転写因子Foxp3の発現に先行することを明らかにした。さらに、Treg特異的スーパーエンハンサー活性化に必須因子としてSatb1を同定した。Satb1欠損マウスではTreg特異的スーパーエンハンサーの活性化に異常が認められ、Foxp3を含むTreg関連遺伝子の発現が著しく低下していた。その結果、胸腺でのTreg発生が損なわれ多臓器に自己免疫疾患が発症した。ヒトSATB1遺伝子付近には自己免疫疾患に関連する一塩基多型が報告されており、本論文で示された分化初期のエピジェネティック制御異常と自己免疫疾患の関係性は、ヒト自己免疫疾患の発症機構解明の手がかりになると考えられる。この論文はTregのみならず一般的な細胞分化を理解する上で重要であり学位論文に値する。