2-PL Plenary Lecture

Pharmacological control of regulatory T cells in immunological diseases

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Regulatory T (Treg) cells, which are expressing the transcription factor Foxp3, are actively engaged in the maintenance of immunological self-tolerance and homeostasis. Depletion or functional impairment of Treg cells is able to enhance cancer and microbial immunity, while their numerical expansion or functional augmentation is instrumental in treating autoimmune disease and establishing graft tolerance. How to achieve these aims by targeting Treg cells with biologicals (such as monoclonal antibodies) or chemicals has been an issue of intense investigation. We have recently shown that certain tyrosine kinase inhibitors that blocked T-cell receptor-proximal signaling in T cells were able to specifically deplete mature Treg cells, thereby enhancing tumor immunity in humans. On the other hand, inhibitors of a serine threonine kinase involved in a T-cell signaling pathway evoked Foxp3 expression in conventional T cells and converted them to functionally competent Treg-like cells, which effectively suppressed autoimmune disease and allergy in animal models. It will be discussed how Treg cells be pharmacologically targeted to control a variety of physiological and pathological immune responses.

正常個体中に存在する制御性T細胞 (Regulatory T cells, Treg)は、免疫自己寛容の維持、様々な免疫応答の抑制的制御に枢要である。内在性Tregの大部分は胸腺で、機能的に成熟した形で産生される。転写因子Foxp3は、Tregに特異的に発現し、Tregの発生、機能発現を制御するマスター制御遺伝子である。Foxp3+Tregの量的・質的異常は、様々な自己免疫／炎症性疾患の直接的原因となる。逆に、正常T細胞にFoxp3を発現させると、機能、表現型の点で内在性Tregと同等のTreg様T細胞に転換できる。一方、抗体、小分子を用いてTregの量的減少、抑制活性の減弱を図れば、がん免疫、微生物免疫を亢進できる。本講演では、Tregによる免疫抑制の分子機構、およびその機能、細胞系譜の維持機構について述べる。さらに、如何にTregを増やし、あるいは通常T細胞をTregに転換できるか、またTregを用いた細胞療法による自己免疫病、炎症性腸炎などの予防・治療が可能か、について議論する。