Regulatory T Cells Differ From Conventional T Cells In Resisting The CTLA-4 Reversal Of TCR Stop-Signal

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CTL-4 is a receptor on the surface of T-cells that is crucial in limiting the development of autoimmunity in the immune system. Loss of CTLA-4 in mice leads to massive lympho-proliferation and fatal multi-organ tissue destruction while genetic screening studies have identified a link to multiple human autoimmune disorders. Despite this, the basis of the CTLA-4 effects is not clear. The previously showed that CTLA-4 can induce T-cell motility and in the process limit contact times between T-cells and cells that present antigens from pathogens in a model they call the ‘reverse stop signal model’. However, it has been unclear whether this property of CTLA-4 affects all T-cells in the immune system. In this context, the immune system is made of subsets of different cells, including conventional T-cells (Tconvs) and regulatory T-cells (Tregs). Tconvs proliferate in response to foreign pathogens leading to inflammation, while Tregs suppress and limit T-cell responses and the development of autoimmunity linked to excess inflammation. The fundamental difference between the two subsets where Tregs are relatively resistant to ‘reverse-stop signal’ effects. This would allow Tregs to bind avidly to antigen-presenting cells under conditions where Tconvs are directed away from the presenting cells due to increased motility. In our model, this would limit the proliferative response of Tconvs, while allowing Tregs to interact and suppress responses mediated by antigen-presenting cells. The results suggest that anti-CTLA-4 elicits effects by two mechanisms, inducing motility of conventional T-cells, while blocking the ability of CTLA-4 on Tregs to bind and interfere with the function of CTLA-4 on suppressor regulatory T-cells.

Selected Publications

Lu Y, Schneider H, Rudd CE. (2012) Murine regulatory T cells differ from conventional T cells in resisting the CTLA-4 reversal of TCR stop-signal. Blood 120(23):4560-70

Lu Y, Schneider H, Rudd CE. Regulatory T-cells (Tregs) possess a hyper-stop-signal for motility arrest and binding to dendritic cells. J Exp Med (submitted)


