Adaptability of Regulatory T-cells enables them to travel to the sites of antibody production

Professor Shimon Sakaguchi of Osaka University IFReC has discovered that a specialized set of regulatory T-cells, T-follicular regulatory cells are able to display an unprecedented level of adaptability by compromising core parts of their regulatory T-cell identity in exchange for the ability to travel to a site of antibody production while still maintaining their core function as regulatory cells. This finding is important, as the discovery of these cells will allow their further study and understanding of their importance in disease pathology.

Introduction

During infection and vaccination, the immune system must produce antibodies that attack bacteria and viruses and protect the host. However antibodies may also cause autoimmunity such as rheumatoid arthritis (RA) and systemic lupus erythematous (SLE). The main sites of B-cell antibody production, the germinal centers (GCs) are critical to proper antibody production. These responses are controlled by T-follicular regulatory cells (Tfr), a subset of regulatory T-cells (Tregs), which must also travel to GCs and prevent their over activation. However currently it is unclear how Tfr, which combine aspects of both T-follicular helper cells (Tfh) and Tregs are able to balance some mutual incompatibility since Tfh are known to be inhibited by the cytokine IL-2 while Tregs depend on it.

The key points are:

- Mature Tfr cells in the germinal centers downregulate the IL-2 receptor, CD25, and gain a transcriptional signature mixed between Tfh and Treg cells while retaining their regulatory function.
- These cells represent an IL-2 independent branch of effector Tregs losing CD25 expression but gaining increased expression of Tfh related markers such as BCL6, PD1 and CXCR5 in both mice and humans.
- This demonstrates a previously unknown level of flexibility in Tregs cells since $CD25^{-}$Tfr cells are able to adopt large portions of the Tfh gene signature while retaining their fundamental identity as Treg cells.

  These results are important as they both increase our understanding of the adaptability and function of Treg and Tfr cells while also revealing the fundamental split in Treg identity between IL-2 dependent Tregs and IL-2 independent Tfr.

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James Badger Wing, Yohko Kitagawa, Michela Locci, Hannah Hume, Christopher Tay, Takayoshi Morita, Yujiro Kidani, Kyoko Matsuda, Takeshi Inoue, Tomohiro Kurosaki, Shane Crotty, Cevayir Coban, Naganari Ohkura, Shimon Sakaguchi. **A distinct subpopulation of CD25 negative T-follicular regulatory cells localizes in the germinal centers.** *PNAS*, 2017.

Key words:

Regulatory T-cells (Tregs), T-follicular regulatory cells (Tfr), T-follicular helper cells (Tfh), germinal centers (GCs).

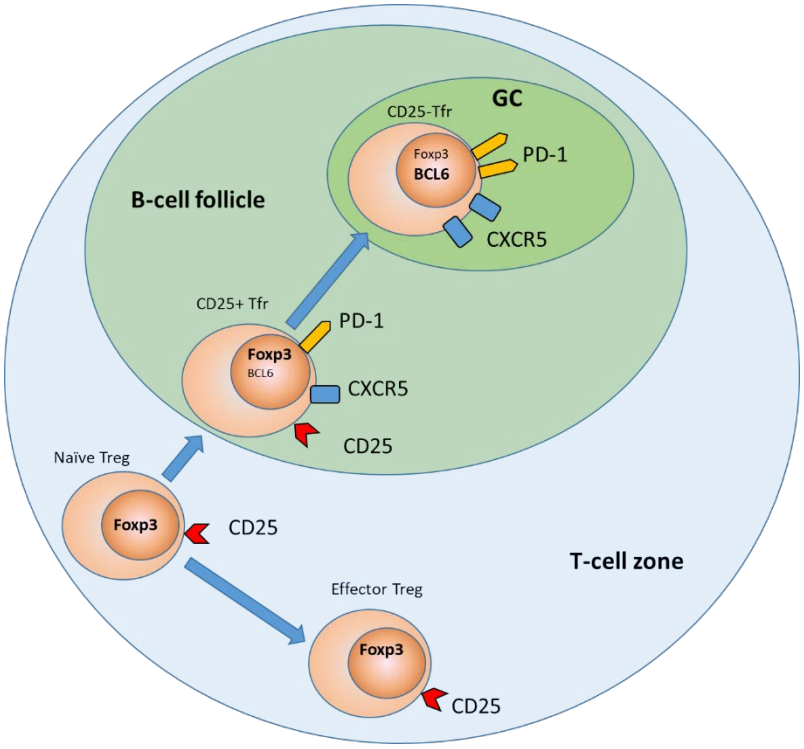

Figure 1: Upon stimulation naïve Tregs may differentiate into IL-2 dependent effector Treg pathway or the IL-2 independent Tfr pathway culminating in $CD25^{-}$ Tfr localized in the germinal centers.