

Following an immune cell's career path

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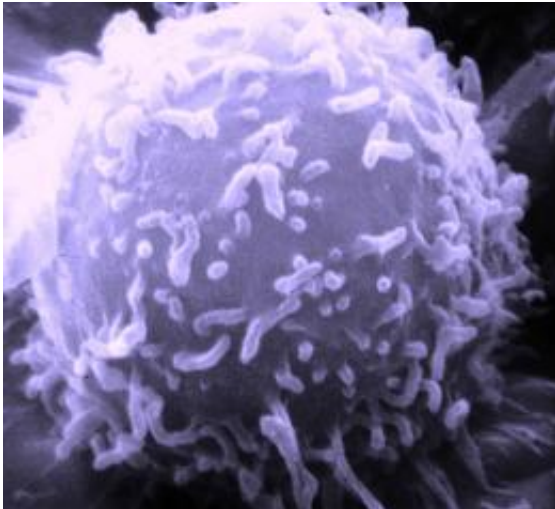


Figure 1: The various classes of T cells are capable of responding to pathogenic threats and restraining the resulting immune response to avoid inflicting damage on host tissues. Credit: Dr Triche, National Cancer Institute, USA

The immune system produces diverse varieties of T cells (Fig. 1), such as pathogen-destroying cytotoxic T cells and immune response-boosting helper T cells. Regulatory T (T_{reg}) cells restrain these other cells and prevent the body from overreacting to threats or generating a dangerous autoimmune response.

T_{reg} [cells](#) are usually identified by expression of the transcriptional regulator protein Foxp3, but new work from a team led by Shohei Hori of the RIKEN Research Center for Allergy and Immunology in Yokohama has demonstrated that this is not a reliable signature.

Several groups have obtained data suggesting that T_{reg} cells can essentially 'change careers', losing their Foxp3 expression and transforming into other T cell types. However, findings from Hori and colleagues led them to propose an alternative 'heterogeneity model'. "Our observations suggested that these phenomena can be fully explained by a minor 'uncommitted' population of Foxp3+ T cells without assuming reprogramming," he says. His group has now provided compelling evidence for this hypothesis by using a labeling technique that allowed them to distinguish cells currently expressing Foxp3 from those that are not, but which have expressed this protein in the past.

The researchers identified two groups of Foxp3-expressing cells that responded differently to an immune stimulus. Most expressed this protein stably and at high levels, and exhibited the functional characteristics of T_{reg} cells. A minority fraction displayed transient bursts of Foxp3 expression, but ultimately developed into other T cell types. These 'exFoxp3' cells did not appear to represent reprogrammed T_{reg} cells, but rather a separate pool of T cells that only produce this protein sporadically.

Interestingly, his team also learned that some T_{reg} cells do enter a state where they stop expressing Foxp3, although they retain 'memory' of their identity as T_{reg} cells. This is achieved via chemical modifications to the DNA within the gene encoding Foxp3, and immune stimulation promptly leads to robust re-expression of this [protein](#). "This should force people to reconsider the popular but oversimplified view of Foxp3 as the master regulator of T_{reg} cells," says Hori.

The events that determine this expression profile are therefore likely to prove more important in establishing cellular identity than the presence or absence of Foxp3. "It has been speculated that the T_{reg} lineage is determined by a higher-order regulatory pathway upstream of Foxp3, but the nature of this system is unknown," says Hori. In future work, he

plans to partner with colleagues at other RIKEN laboratories to investigate this question more closely.

More information: Miyao, T., et al. Plasticity of Foxp3+ T cells reflects promiscuous Foxp3 expression in conventional T cells but not reprogramming of regulatory T cells. [Immunity](#) 36, 262 - 275 (2012).

Komatsu, N., et al. Heterogeneity of natural Foxp3+ T cells: a committed regulatory T-cell lineage and an uncommitted minor population retaining plasticity. [Proceedings of the National Academy of Sciences](#) 106, 1903 - 1908 (2009).

Provided by RIKEN

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