nature REVIEWS
IMMUNOLOGY

Regulatory T cells

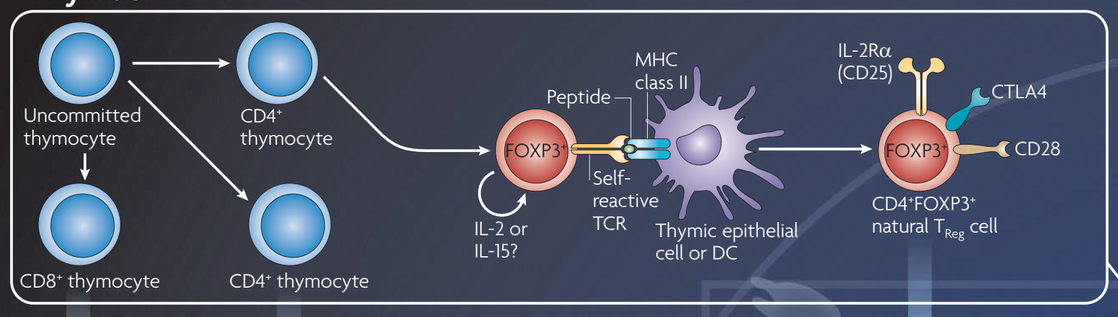
Ethan Shevach and Todd Davidson

To avoid immune-mediated pathology and unrestricted clonal expansion of responder T cells, the immune system has subsets of T cells, known as regulatory T (T_{Reg}) cells, that are dedicated to mediating immune suppression. The most important subset of T_{Reg} cells expresses the transcription factor forkhead box P3 (FOXP3). Both mice and humans with genetic deficiencies of FOXP3 develop severe abnormalities of immune homeostasis. T_{Reg} cells modulate the immune response in numerous settings, including autoimmune disease, allergy, microbial infection, tumour immunity, organ transplantation, foetal–maternal tolerance and even obesity. Defects in T_{Reg} cell function may be an important factor in the development of autoimmunity or in the failure to control immunopathology, whereas overactive T_{Reg} cell function may contribute to the suppression of tumour immunity. Enhancement of T_{Reg} cell function either pharmacologically or by cell-based therapy may prove to be an adjunct to the treatment of autoimmunity, whereas deletion or inactivation of T_{Reg} cell function may facilitate the generation of tumour immunity or enhance responses to weak vaccines.

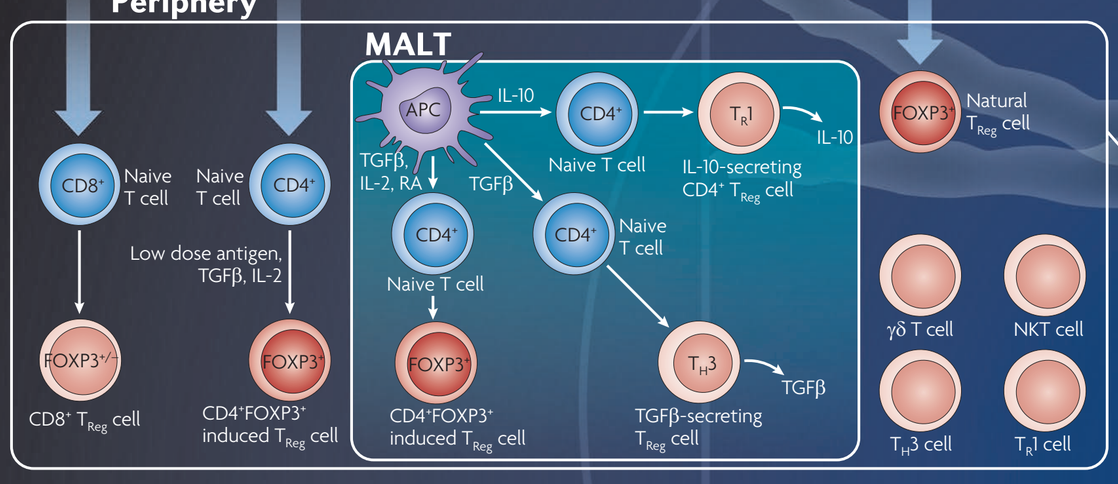
Development and phenotype of regulatory T cells

Many T cell types have immune regulatory function, but the two most important T_{Reg} cell subsets express the transcription factor FOXP3 and develop in the thymus or can be induced in peripheral sites including the mucosa-associated lymphoid tissue (MALT). Although expression of FOXP3 is considered a useful marker for these cell subpopulations in mice, FOXP3 expression may also be induced in human T cells that lack T_{Reg} cell function. However, functional activated human $FOXP3^+$ T_{Reg} cells express a unique pattern of cell surface markers that can facilitate their isolation. A third important type of T_{Reg} cell secretes the immunosuppressive cytokine interleukin-10 (IL-10) and may develop from conventional $CD4^+$ T cells by activation in the presence of IL-10 or may develop from T helper 1 (T_H1) or T_H2 cell subsets. Other T cell subpopulations including natural killer T (NKT) cells, γδ T cells and $CD8^+$ T cells can also exert potent suppressor functions in certain settings. Although both human and mouse $CD8^+$ T cells can be induced to express FOXP3, a suppressive function for these cells *in vivo* has yet to be clarified.

Thymus

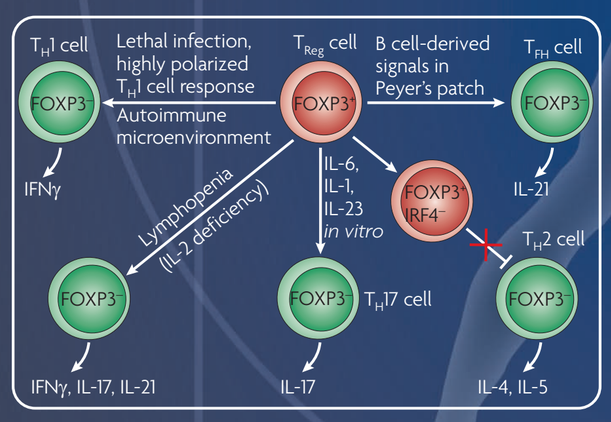


Periphery



Plasticity in the periphery

Under certain conditions, $FOXP3^+$ T_{Reg} cells can downregulate their expression of FOXP3, lose suppressor functions and manifest some of the functions of conventional effector T_H1, T_H2, T_H17 and T_{FH} cell subsets. The key causes of this loss of FOXP3 expression include inflammatory environments with high levels of cytokines that are normally involved in the induction of effector T cells, such as IL-6 and interferon-γ (IFNγ). In addition, T_{Reg} cell-specific deletion of certain transcription factors that are shared between T_{Reg} cells and effector cell subsets (for example, the T_H2 cell-specific factor IRF4) results in impaired suppression of T_H2 cell responses by the T_{Reg} cells.



Phenotypic markers of FOXP3⁺ regulatory T cells

Markers shared by $FOXP3^+$ T_{Reg} cells and conventional activated $CD4^+$ T cells (mice and humans)
- CD25
- $CD127^{low}$
- GITR
- CTLA4
- $CD45RB^{low}$ (mice only)
- CD45RO (humans only)
- Folate receptor 4 (mice only)

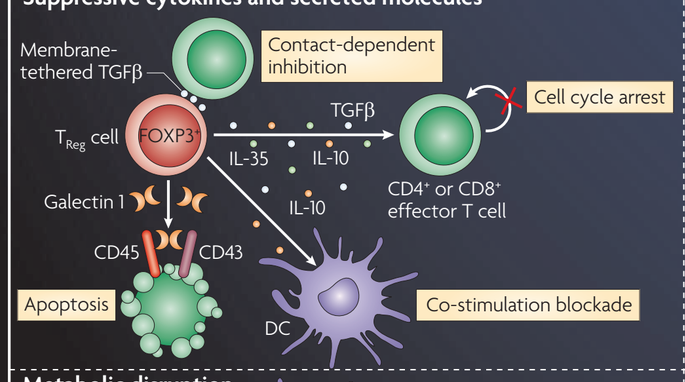
Markers preferentially expressed by activated mouse $FOXP3^+$ T_{Reg} cells
- FOXP3
- Latent TGFβ
- CD103

Subpopulations of human $FOXP3^+$ T_{Reg} cells
- $CD45RA^+FOXP3^{low}$ (naive)
- $CD45RA^-FOXP3^{hi}$ (activated)
- $CD45RA^-FOXP3^{low}$ (cytokine-secreting)

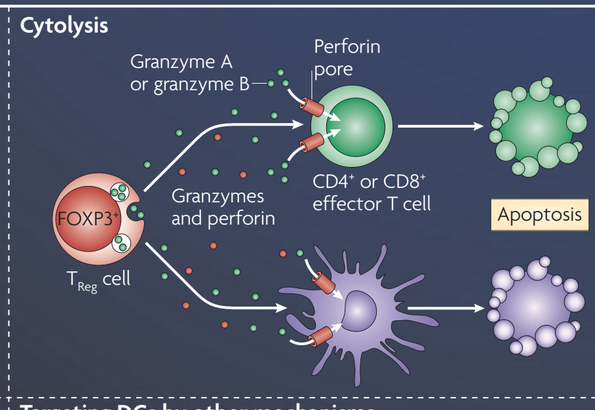
Markers specifically expressed by activated human $FOXP3^+$ T_{Reg} cells
- $FOXP3^{hi}$
- Latent TGFβ
- GARP
- CD121a (IL-1R1)
- CD121b (IL-1R2)

Mechanisms of action of FOXP3⁺ regulatory T cells

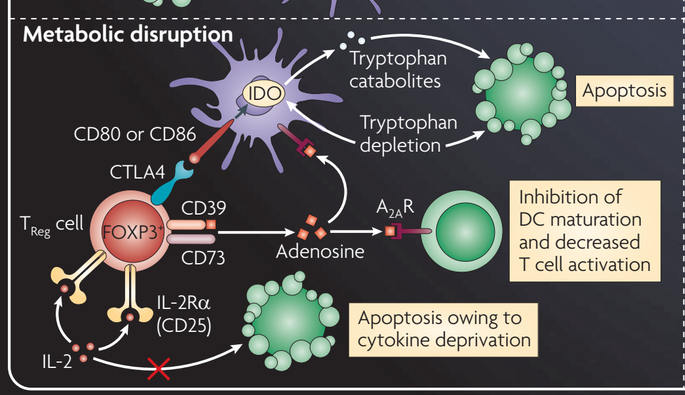
Suppressive cytokines and secreted molecules



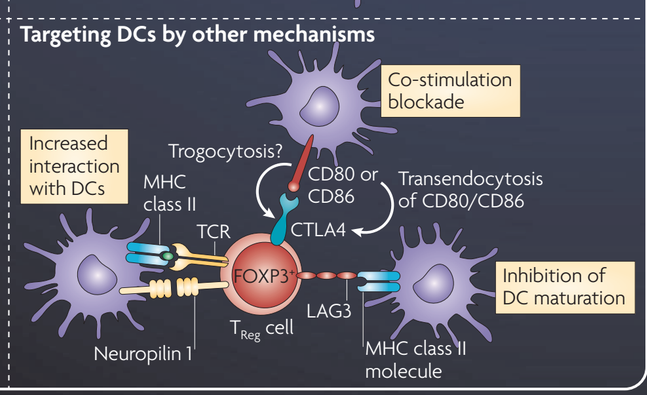
Cytolysis



Metabolic disruption



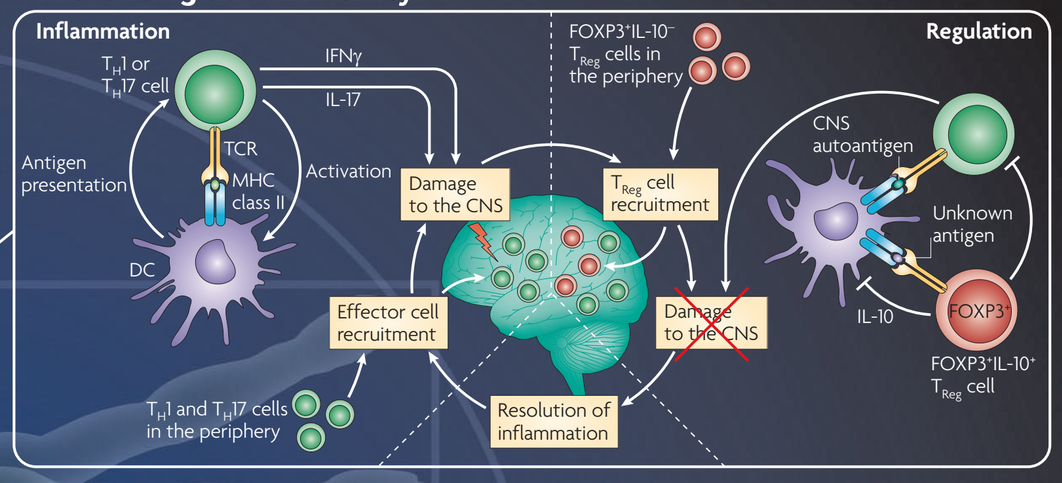
Targeting DCs by other mechanisms



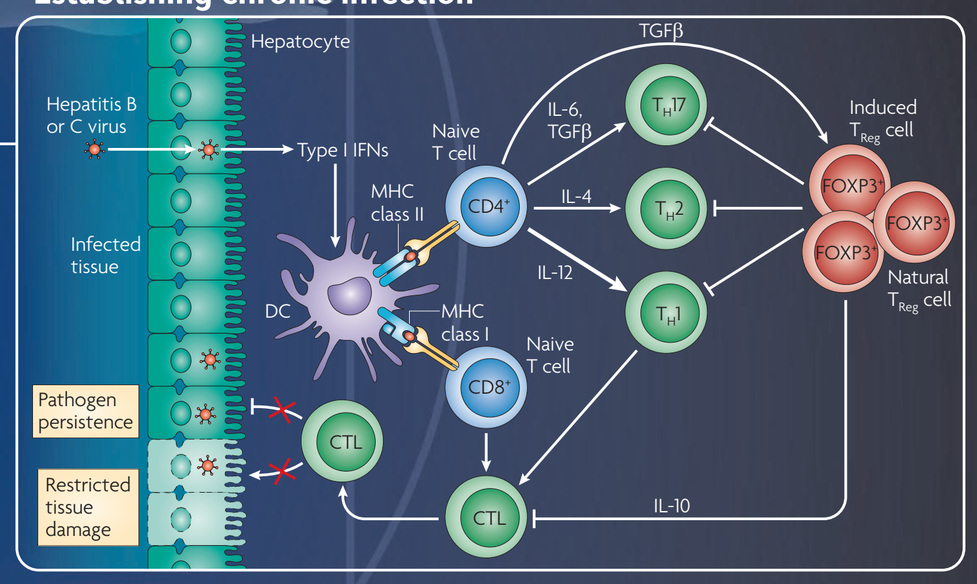
Function of FOXP3⁺ regulatory T cells

$FOXP3^+$ T_{Reg} cells have been shown to influence the outcome of immune responses in several tissues. For example, in the intestine T_{Reg} cells have a key role in maintaining tissue homeostasis by inhibiting the overactivation of dendritic cells (DCs) and effector T cells. In the case of autoimmunity, such as that depicted in the central nervous system (CNS), T_{Reg} cells can have a beneficial effect by short circuiting the inflammatory loop of T cells and antigen-presenting cells (APCs). This same general mechanism can have negative consequences in the setting of a tumour, in which T_{Reg} cells can inhibit the antitumour immune response, thereby preventing tumour clearance. During infection T_{Reg} cells carry out a delicate balancing act; preventing immunity would lead to the inability to clear the pathogen, whereas unrestrained immunity would lead to unwanted immune-mediated tissue destruction. In each of the examples shown, we focus on the role of $FOXP3^+$ T_{Reg} cells, although interactions between multiple immune cell types and indeed different types of regulatory T cell are also likely to be important in the regulation of immune responses.

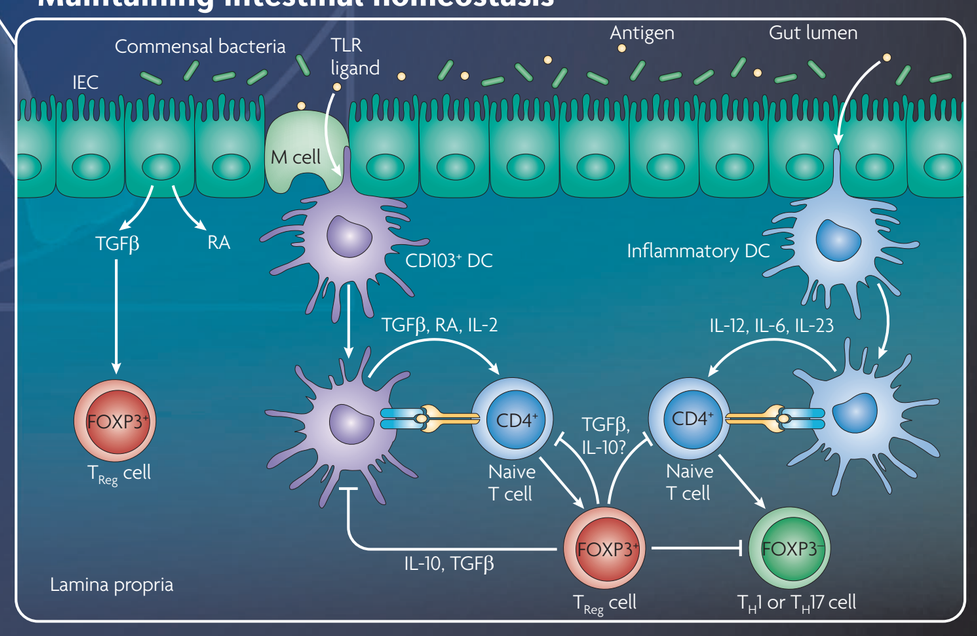
Preventing autoimmunity



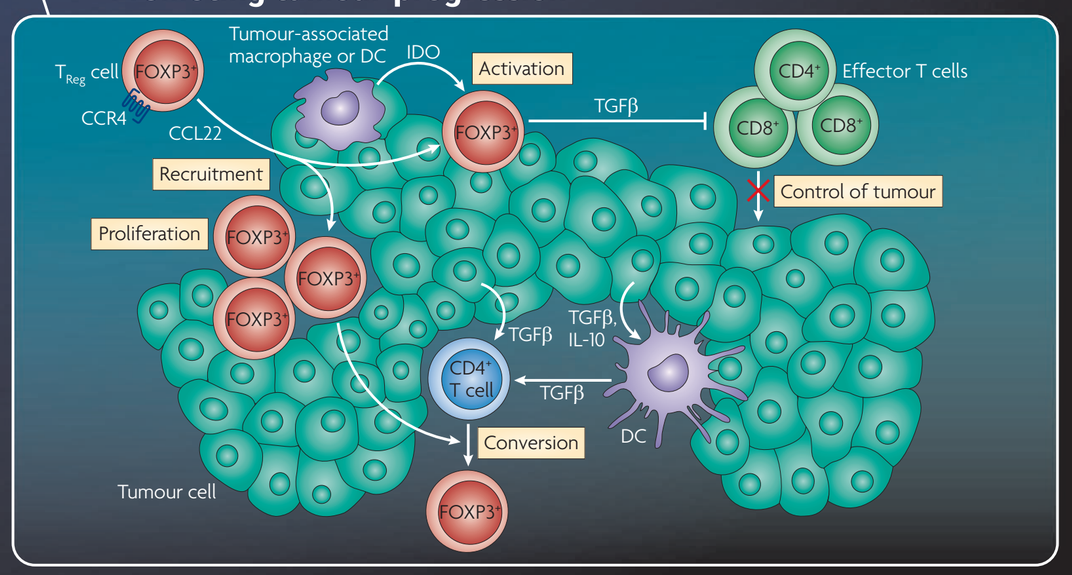
Establishing chronic infection



Maintaining intestinal homeostasis



Promoting tumour progression



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The authors declare no competing financial interests.

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