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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.

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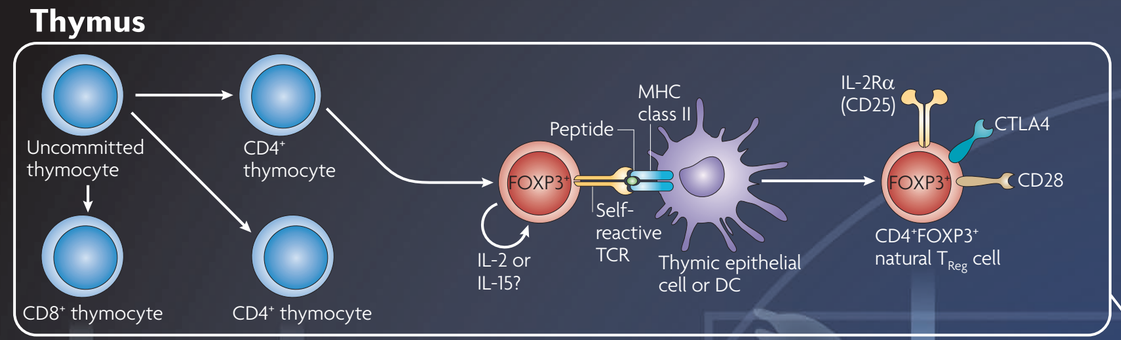
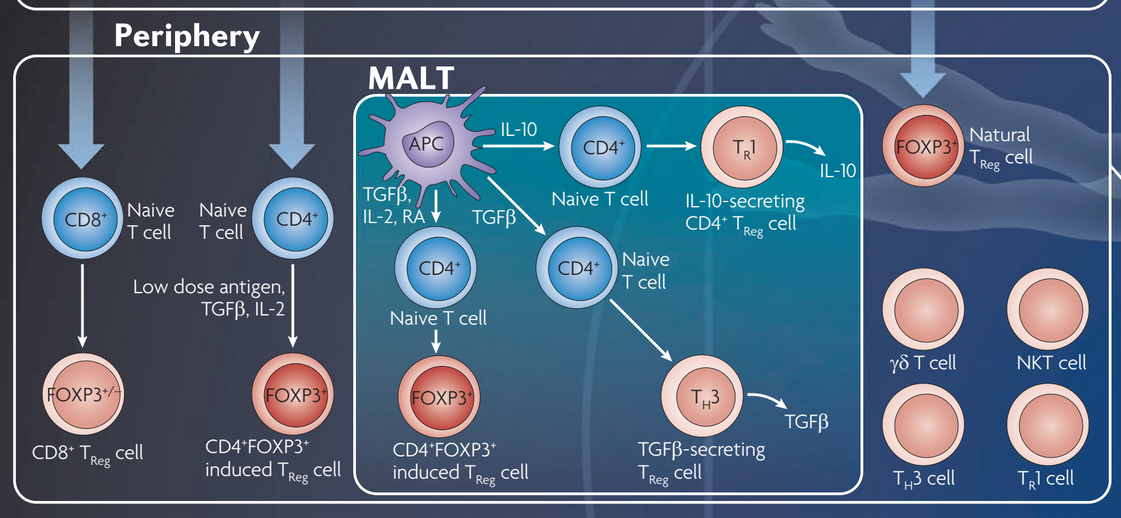
Development and phenotype of regulatory T cells

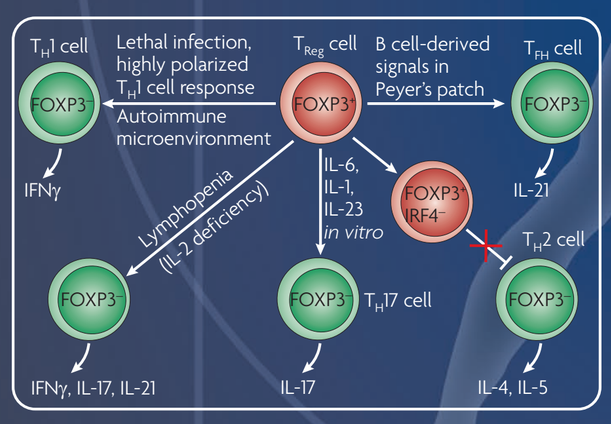
Many T cell types have immune regulatory function, but the two most important T_{Reg} cell subsets express the transcription factor FOXP3 and develop in the thymus or can be induced in peripheral sites including the mucosa-associated lymphoid tissue (MALT). Although expression of FOXP3 is considered 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.

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.







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

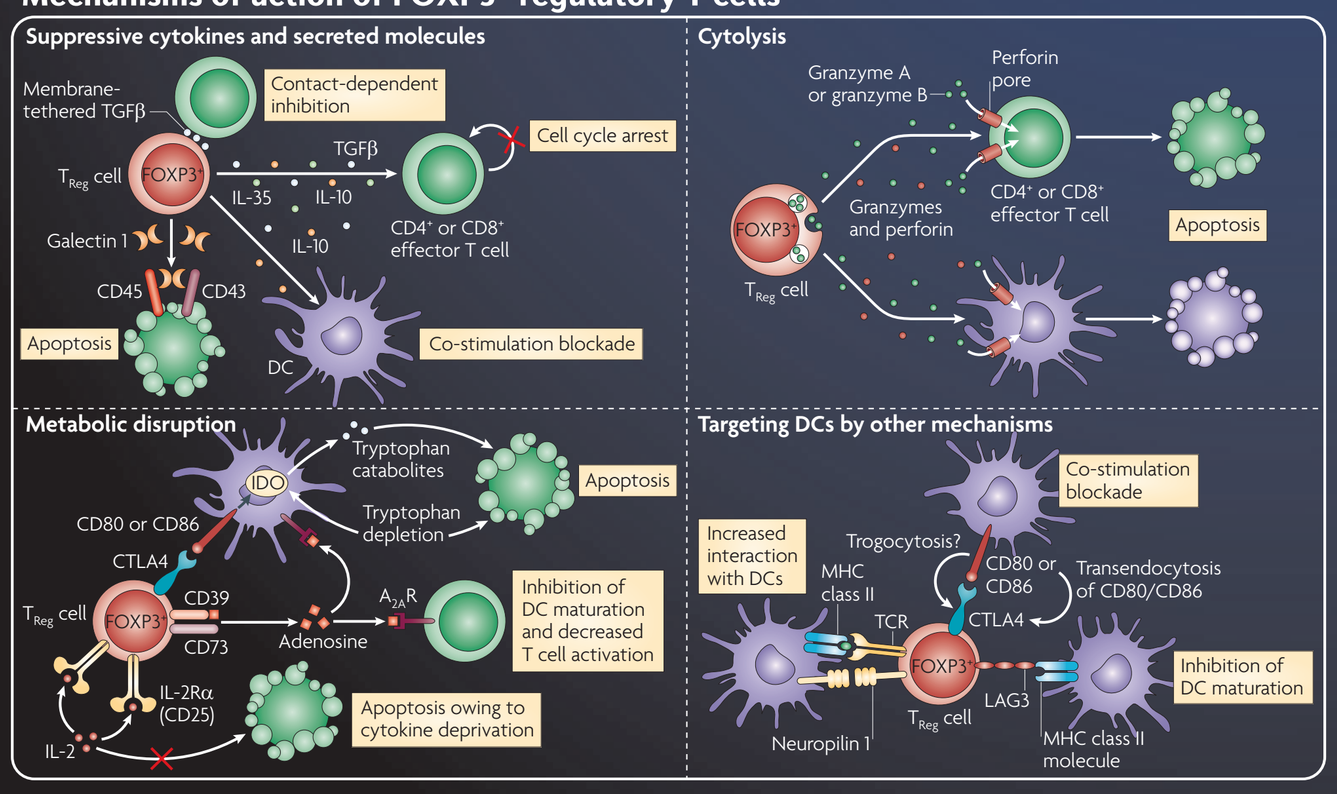
Markers shared by FOXP3$^+$ T_{Reg} cells and conventional activated CD4$^+$ T cells (mice and humans)
CD25
GITR
CD45RB^{low} (mice only)
CD45RO (humans only)
Folate receptor 4 (mice only)
CD127^{low}
CTLA4

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

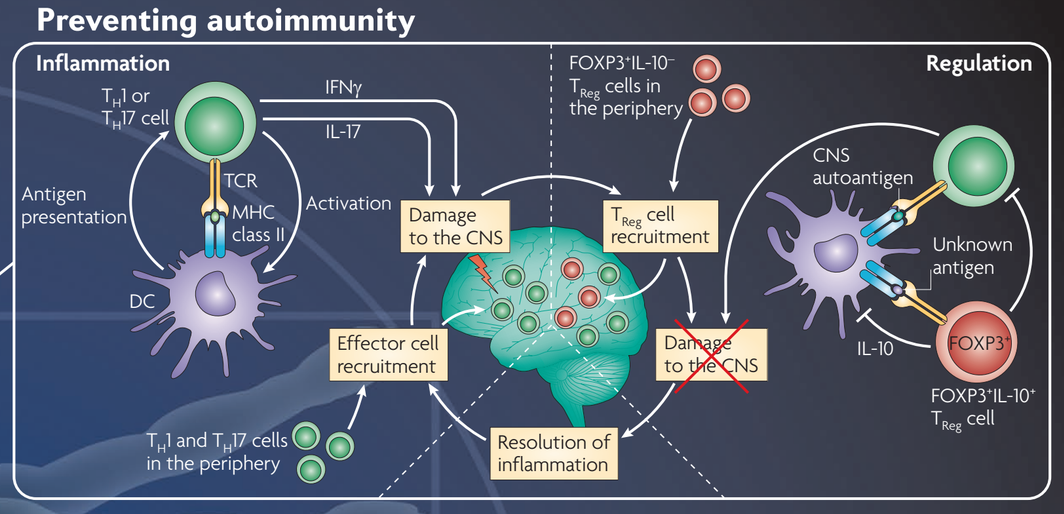
Subpopulations of human FOXP3$^+$ T_{Reg} cells
CD45RA$^+$FOXP3^{low} (naive)
CD45RA$^-$FOXP3^{hi} (activated)
CD45RA$^-$FOXP3^{low} (cytokine-secreting)

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

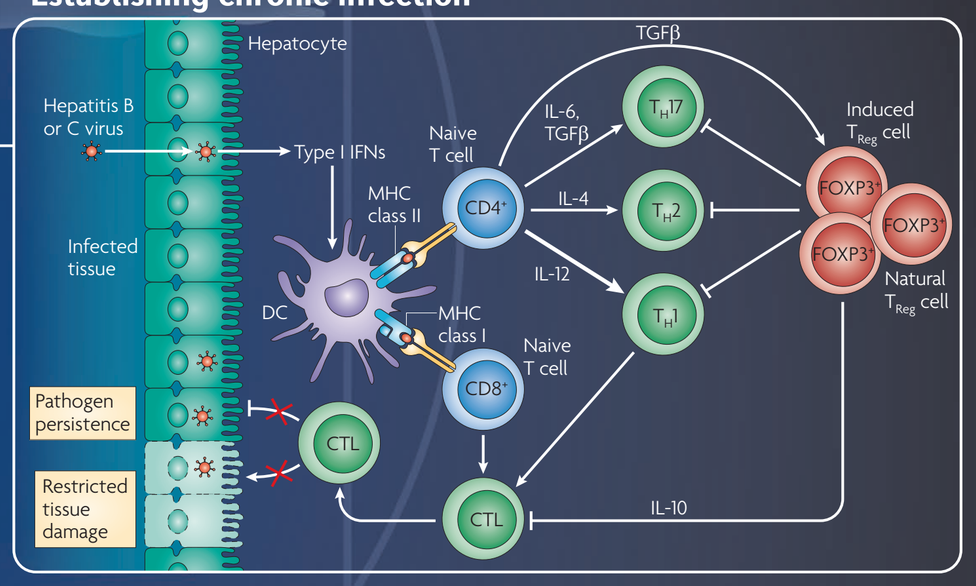
Mechanisms of action of FOXP3$^+$ regulatory T cells



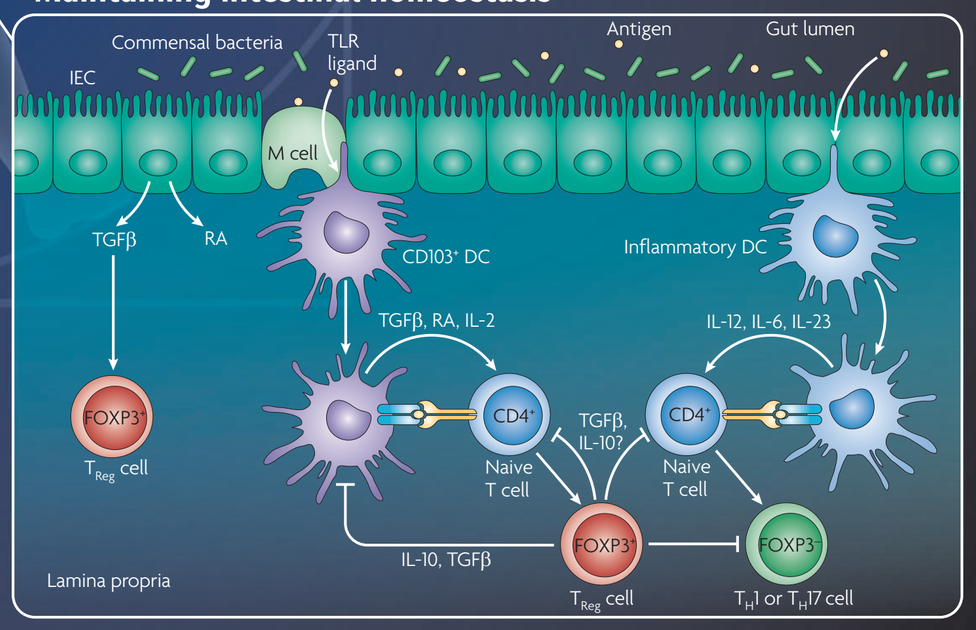
Preventing autoimmunity



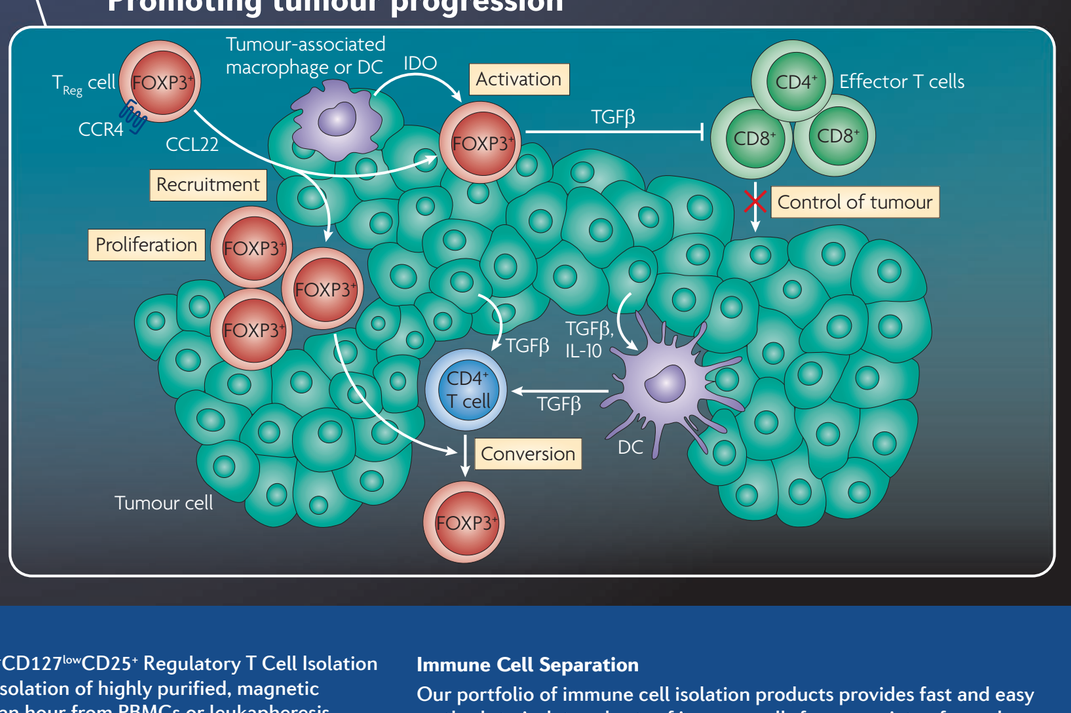
Establishing chronic infection



Maintaining intestinal homeostasis



Promoting tumour progression



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Abbreviations for poster entitled Regulatory T cells by Ethan Shevach and Todd Davidson

$A_{2A}R$, adenosine receptor 2A; CCL, CC-chemokine ligand; CCR, CC-chemokine receptor; CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T lymphocyte antigen 4; GARP, glycoprotein A repetitions predominant (also known as LRRC32); GITR, glucocorticoid-induced TNF-receptor-related protein; IDO, indoleamine 2,3-dioxygenase; IEC, intestinal epithelial cell; IRF4, interferon-regulatory factor 4; LAG3, lymphocyte activation gene 3; M cell, microfold cell; PBMC, peripheral blood mononuclear cell; R, receptor; RA, retinoic acid; TCR; T cell receptor; T_{FH} cell, T follicular helper cell; TGFβ, transforming growth factor-β; TLR, Toll-like receptor; T_R1 cell, inducible regulatory type 1 T cell.