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CD4+ T-cell diversity

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CD4+ T helper (T_H) cells are central players in orchestrating innate and adaptive immune responses. T_H cells have been classically considered to belong to one of two subsets — T_H1 cells or T_H2 cells — each of which has unique cytokine products, signalling pathways and lineage-specific transcription factors or master regulators. Recently, T_H cells that secrete IL-17 (T_H17 cells) have emerged as a third lineage of CD4+ T_H cells. Together with regulatory T (T_{Reg}) cells, which preserve peripheral tolerance, these two newly described T-cell subsets have raised fundamental questions about lineage commitment and fate determination of CD4+ T cells. This Poster depicts the various cytokines, transcription factors and signalling pathways that are associated with the differentiation, survival and function of CD4+ effector T cells. The differentiation of CD4+ T cells is typically depicted as a one-way route, implying that there is terminal differentiation with little plasticity in cytokine responses. However, recent data argue for more complexity and flexibility than was previously assumed. As with any model, this is a work in progress and subject to enhancement in the coming years.

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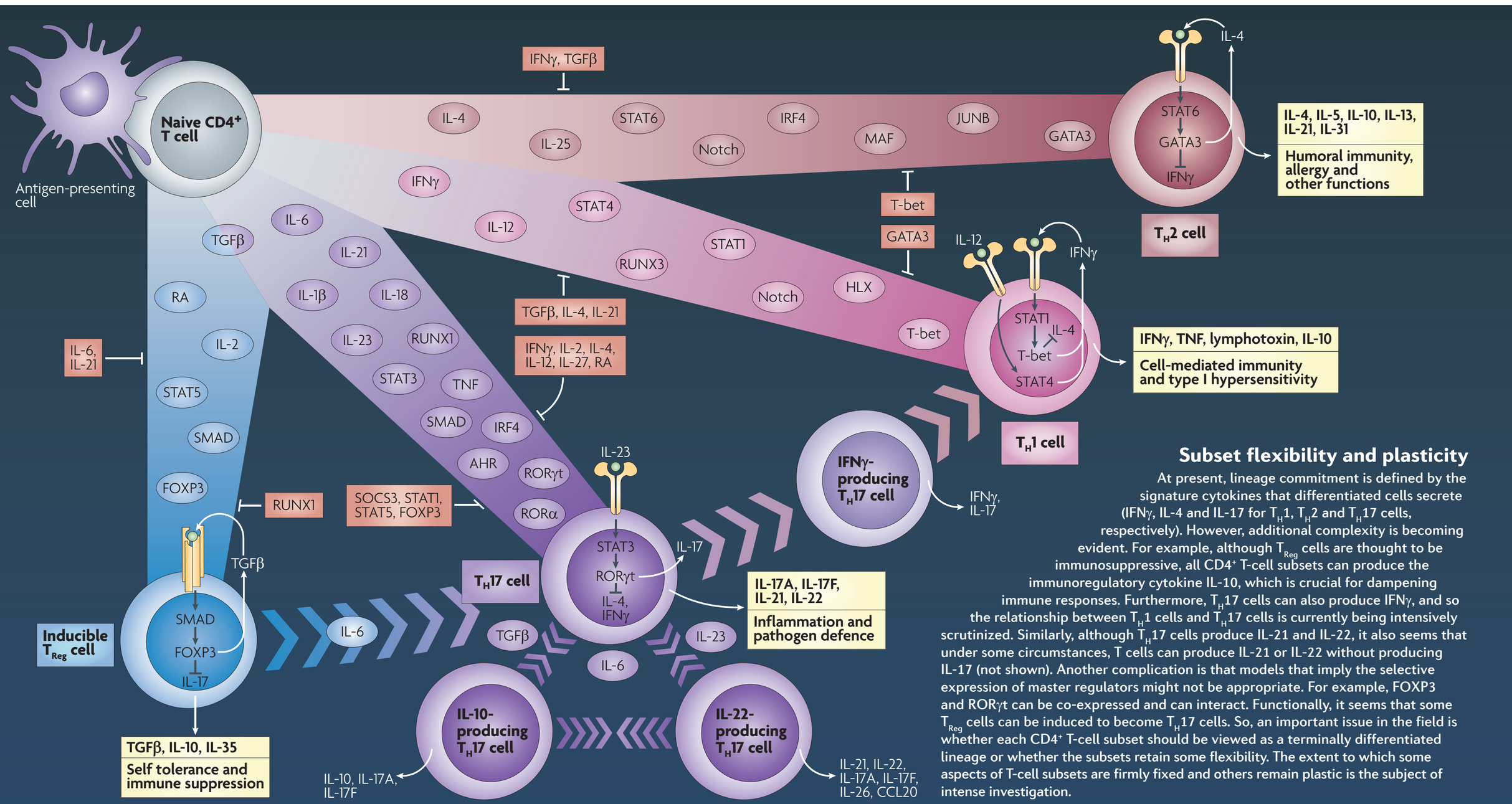
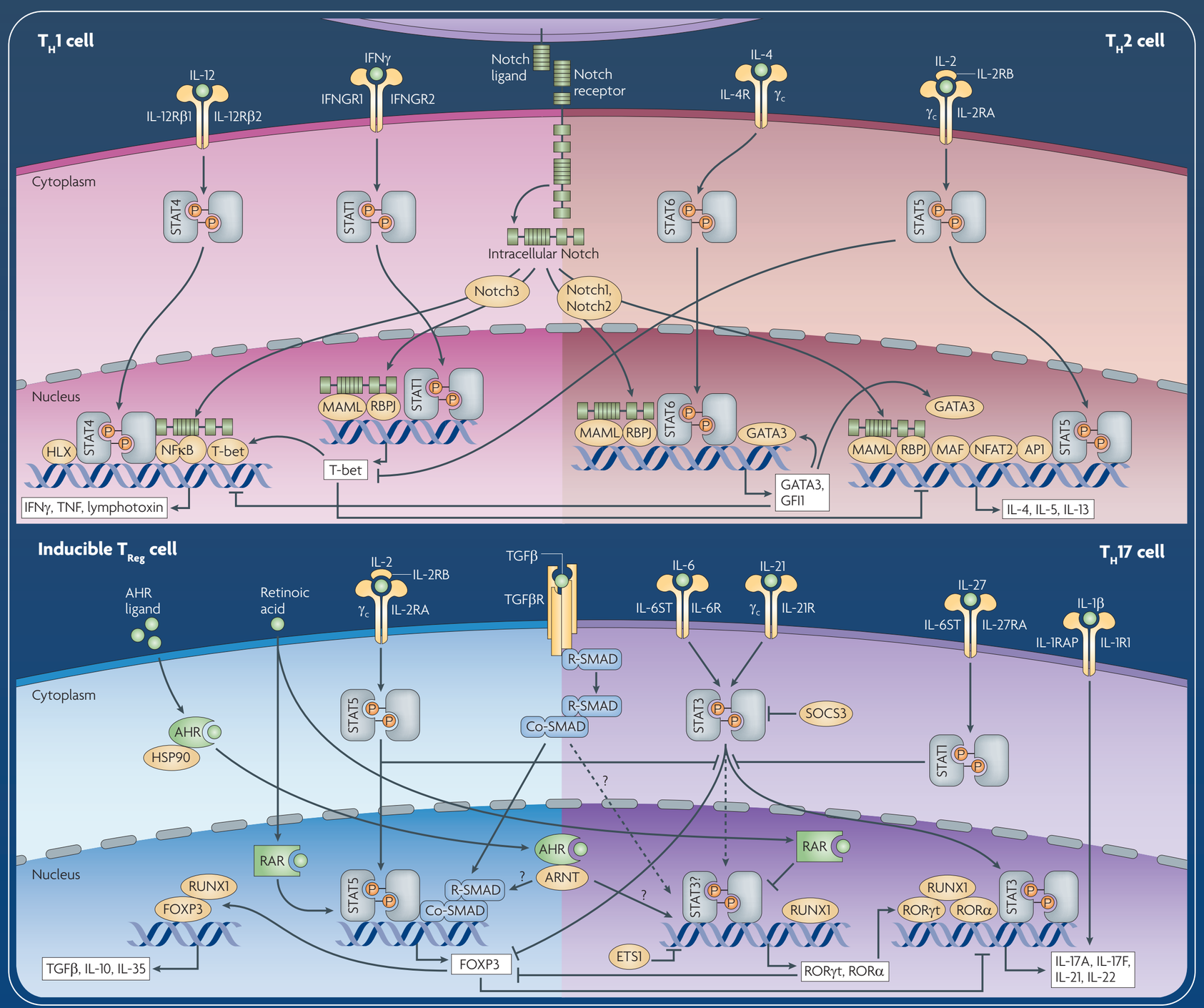


Subset flexibility and plasticity

At present, lineage commitment is defined by the signature cytokines that differentiated cells secrete (IFNγ, IL-4 and IL-17 for T_H1, T_H2 and T_H17 cells, respectively). However, additional complexity is becoming evident. For example, although T_{Reg} cells are thought to be immunosuppressive, all CD4+ T-cell subsets can produce the immunoregulatory cytokine IL-10, which is crucial for dampening immune responses. Furthermore, T_H17 cells can also produce IFNγ, and so the relationship between T_H1 cells and T_H17 cells is currently being intensively scrutinized. Similarly, although T_H17 cells produce IL-21 and IL-22, it also seems that under some circumstances, T cells can produce IL-21 or IL-22 without producing IL-17 (not shown). Another complication is that models that imply the selective expression of master regulators might not be appropriate. For example, FOXP3 and RORγt can be co-expressed and can interact. Functionally, it seems that some T_{Reg} cells can be induced to become T_H17 cells. So, an important issue in the field is whether each CD4+ T-cell subset should be viewed as a terminally differentiated lineage or whether the subsets retain some flexibility. The extent to which some aspects of T-cell subsets are firmly fixed and others remain plastic is the subject of intense investigation.

CD4+ T-cell differentiation

Following contact with antigen-presenting cells (APCs), signals generated by the T-cell receptor (TCR) and co-stimulatory molecules initiate the process by which naive CD4+ T cells begin to differentiate towards one of several fates. In the context of an appropriate signal through the TCR, the cytokine milieu that is generated by APCs is an important factor that influences differentiation. IL-12 activates STAT4 and drives naive CD4+ T cells to become T_H1 cells, which produce IFNγ. Signals from the TCR, as well as from IL-12 and IFNγ (acting through STAT4 and STAT1, respectively), increase the expression of the transcription factor T-bet, which promotes IFNγ production and commitment to the T_H1-cell lineage. T_H1 cells are important for host defence against intracellular bacteria. Naive CD4+ T cells are induced to become T_H2 cells through the secretion of IL-4 by innate immune cells, which signals through STAT6. This leads to expression of the transcription factor GATA3, in turn resulting in the production of IL-4, IL-5 and IL-13, which are important for host defence against helminths and contribute to the pathogenesis of asthma and allergy. T_{Reg} cells can develop from thymic CD4+ T-cell precursors in the presence of TGFβ and IL-2. These are termed natural T_{Reg} cells (not shown). In the periphery, naive CD4+ T cells can also be converted to become inducible T_{Reg} cells by signalling through STAT5 in the presence of TGFβ, which results in upregulation of the transcription factor FOXP3. T_{Reg} cells secrete low levels of IL-2 and IFNγ, and instead they produce high levels of IL-10, IL-35 and TGFβ. Retinoic acids, which are abundant in the liver and intestine, increase FOXP3 expression. T_{Reg} cells have an important role in peripheral self tolerance and immune suppression. T_H17 cells develop from naive CD4+ T cells in response to IL-6, IL-21, TGFβ and IL-1β. IL-6 and IL-21 activate STAT3, which increases the expression of the transcription factors RORγt and RORα, which in turn promote the expression of IL-17A, IL-17F, IL-21 and IL-22. IL-23 seems to stabilize and increase the pathogenicity of T_H17 cells. T_H17 cells are important for host defence against extracellular bacteria and are involved in mediating autoimmune disease.



Abbreviations

γ_c, common cytokine receptor γ-chain; AHR, aryl hydrocarbon receptor; AP1, activator protein 1; ARNT, aryl receptor nuclear transporter; CCL20, CC-chemokine ligand 20; Co-SMAD, co-mediator SMAD; FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; GFI1, growth-factor independent 1; HLX, H2.0-like homeobox 1; HSP90, heat-shock protein 90; IFNγ, interferon-γ; IL, interleukin; IL-1RAP, IL-1 receptor accessory protein; IL-6ST, IL-6 signal transducer; IRF, interferon-regulatory factor; MAML, Mastermind-like; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; RA, retinoic acid; RAR, retinoic acid receptor; RBPJ, recombination-signal-binding protein for immunoglobulin-κ J region (also known as CSL); ROR, retinoic-acid-receptor-related orphan receptor; R-SMAD, receptor-regulated SMAD; RUNX, Runt-related transcription factor; SMAD, mothers against decapentaplegic homologue; SOCS3, suppressor of cytokine signalling 3; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β; TNF, tumour-necrosis factor.

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