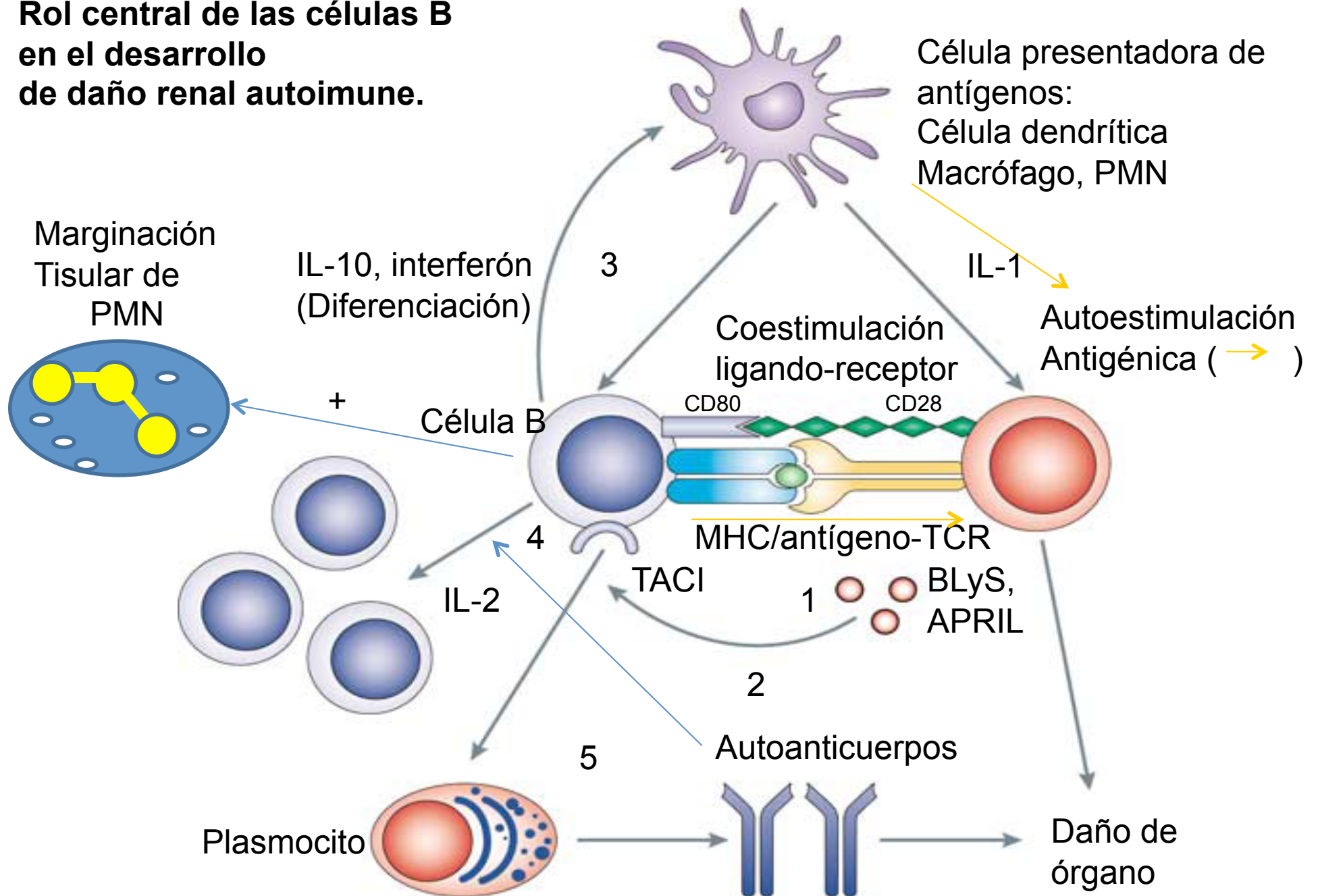


**Rol central de las células B en
el desarrollo de daño renal autoimune.**

Rol central de las células B en el desarrollo de daño renal autoinmune.

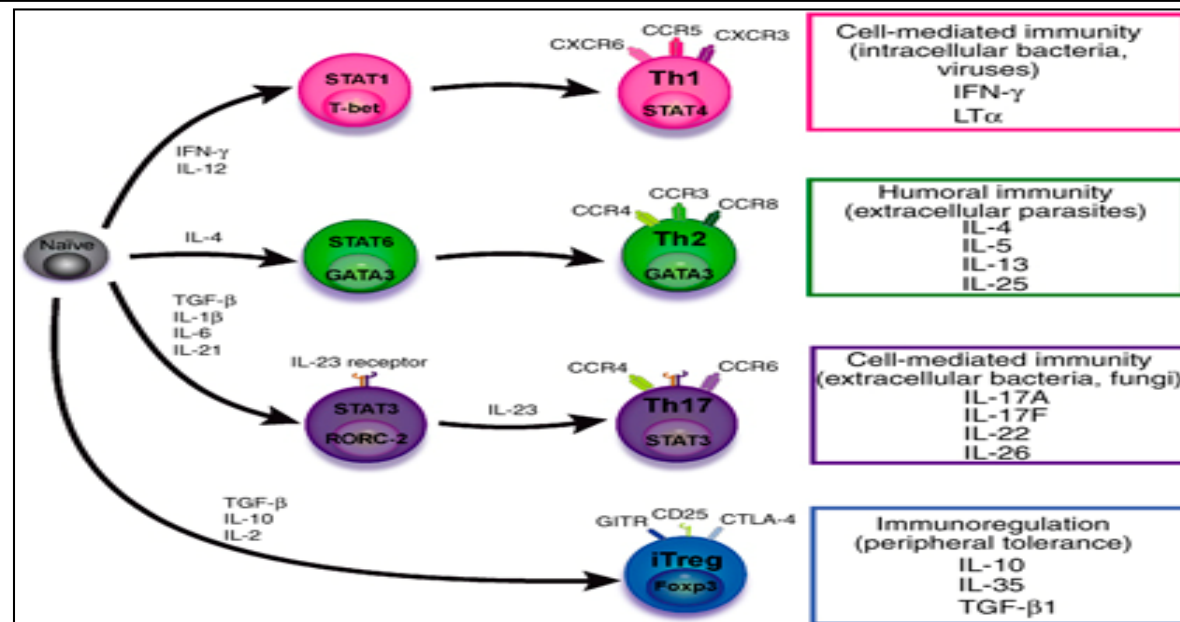


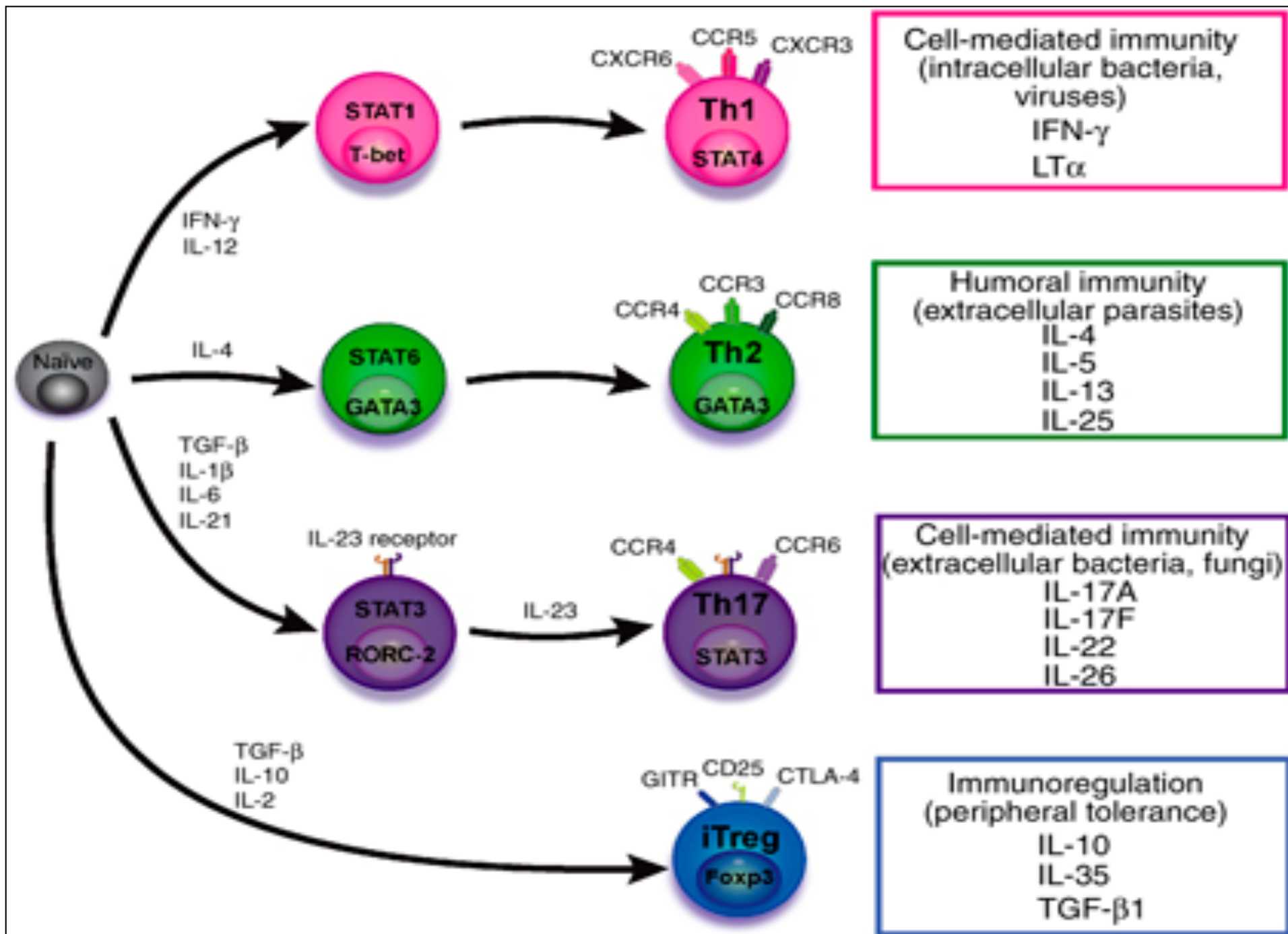
Naive CD4 T cells are activated after interaction of T cell receptors with antigen/MHC (signal 1) and co-stimulation (signal 2).

Depending on the fine texture of the inflammatory milieu in which antigen activation takes place, these newly activated T cells commit to one of several CD4 subset phenotypes.

In addition to the classical Th1 and Th2 CD4 phenotypes, regulatory (Treg) and Th17 phenotypes have been more recently identified and characterized.

Whereas effector T cells such as the Th1, Th2, and Th17 phenotypes exert injurious, cytopathic effects on tissues, the Treg phenotype restrains or “regulates” effector T cell-mediated tissue injury.





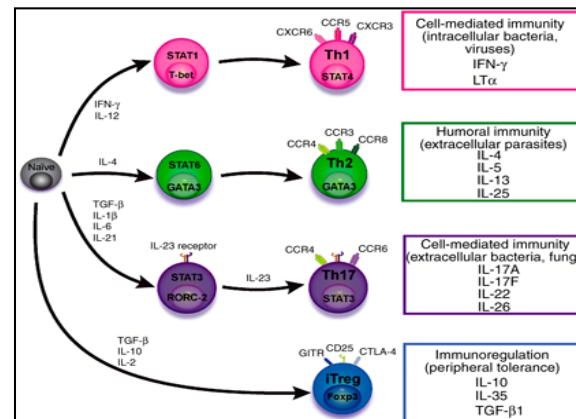
Naive CD4 cells T commit to the tissue destructive, -IFN–expressing Th1 program when signals 1 and 2 are delivered in a milieu rich in IL-12, a product of certain stimulated antigen-presenting cells.

In contrast, antigen activation conducted in an IL-4 –rich environment leads to commitment to the Th2 phenotype.

Commitment to the Th1 or Th2 phenotype rests with expression of a distinctive DNA-binding lineage specification factor by CD4 T cells.

Expression of the t-bet specification factor commits newly antigen-activated and IL-12–stimulated CD4 T cells to the Th1 phenotype.

In contrast, expression of GATA 3 commits newly antigen-activated and IL-4 –stimulated T cells to the Th2 phenotype.1 Until recently, it was thought, upon antigen activation, helper T cells became either Th1 or Th2 T cells.



IL-2–producing Th1 and IL-4 –producing Th2 are considered terminally differentiated phenotypes.

Once they commit, there is no “going back.”

Th1 and Th2 cells were once held responsible for diametrically opposing functions in tissue injury.

Th1 cells were the most potent mediator and principle architects of CD4-dependent tissue-destructive reactions, whereas Th2 cells were thought to protect antigen-bearing tissues from Th1 cells.

Although this scenario is easy to remember, Th1 cells attack while Th2 cells protect “foreign” tissues, it is not altogether true.

Th1 cells, IFN-gamma or IL-2 (Th1 cell products) are not required for rejection.

Rejection of MHC-mismatched allografts can be caused by T cells in the Th2 mode.

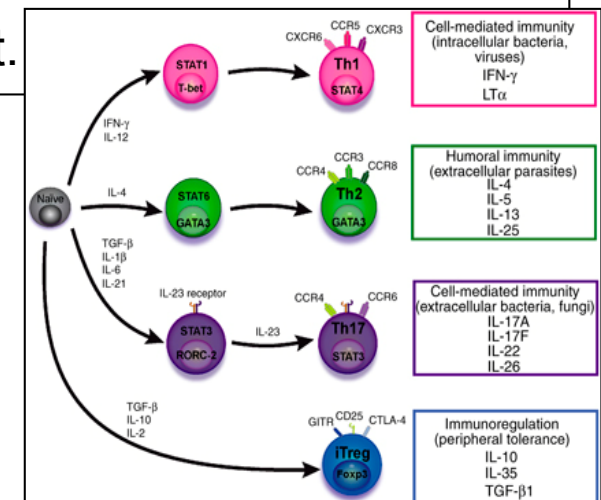
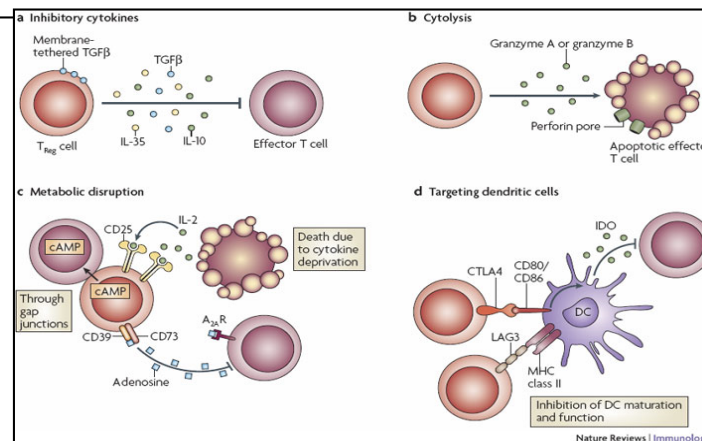
CD4 Tregs, not Th2 cells, are crucially important in restraining the destructive effects of cytopathic T cells.

In keeping with new dogma that CD4 T cells take cues from the cytokine environment, a TGF-beta dominant environment leads naive CD4 T cells to commit to the regulatory phenotype.

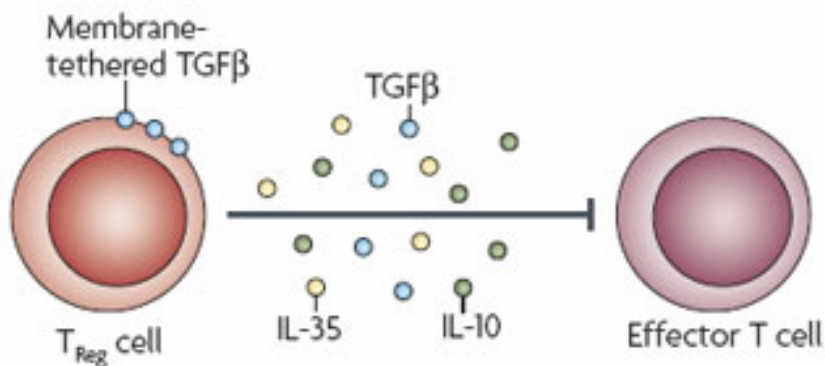
Indeed, this commitment is obtained by the TGF-beta triggered expression of the lineage-unique Foxp3 lineage specification factor.

Whereas newly antigen-activated and TGF-beta stimulated, mature, naive CD4 T cells are induced to express the Treg phenotype, a population of Foxp3 “natural” Tregs also emerge from the thymus with potent regulatory properties.

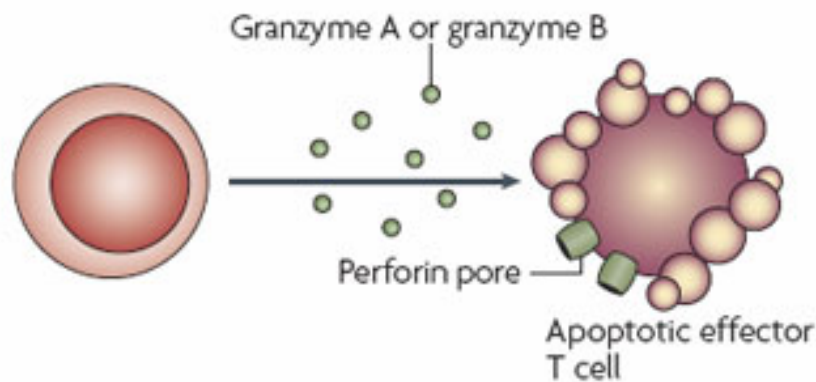
Hence, two populations, induced and natural Tregs, exist.



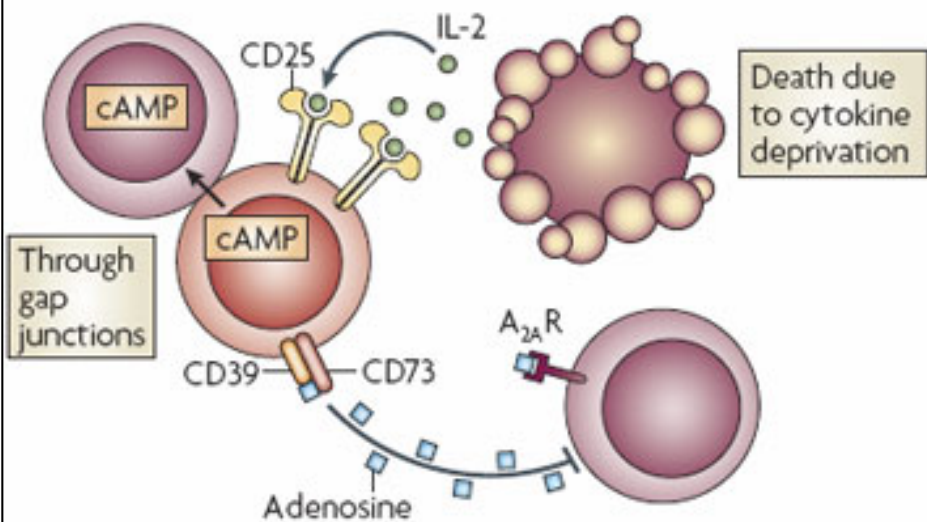
a Inhibitory cytokines



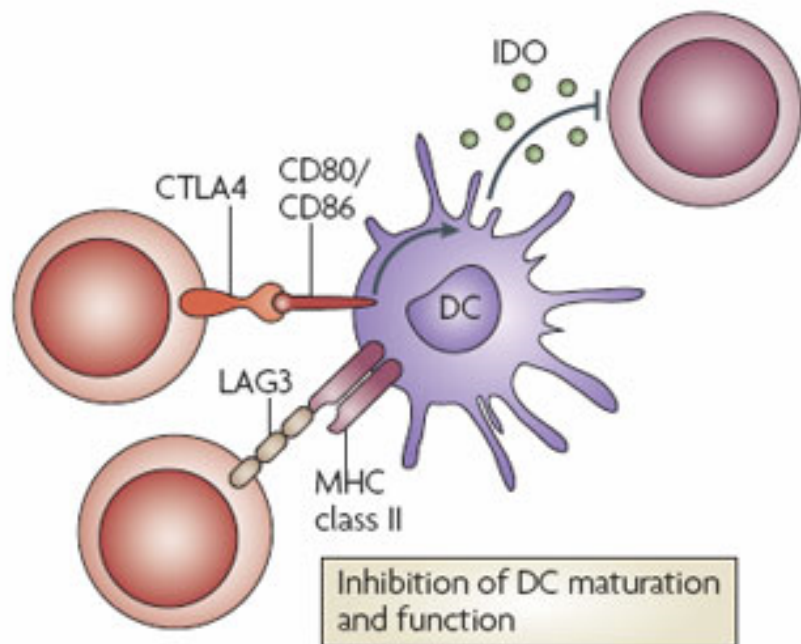
b Cytolysis



c Metabolic disruption



d Targeting dendritic cells

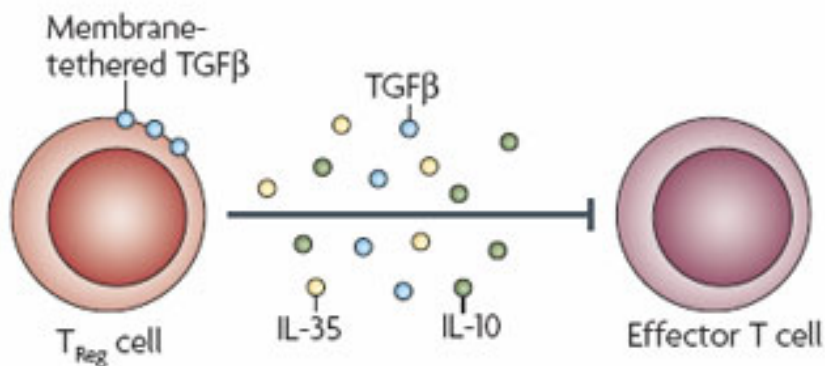


Humans born with loss-of-function or deletional mutations of Foxp3 rapidly develop devastating forms of autoimmunity.

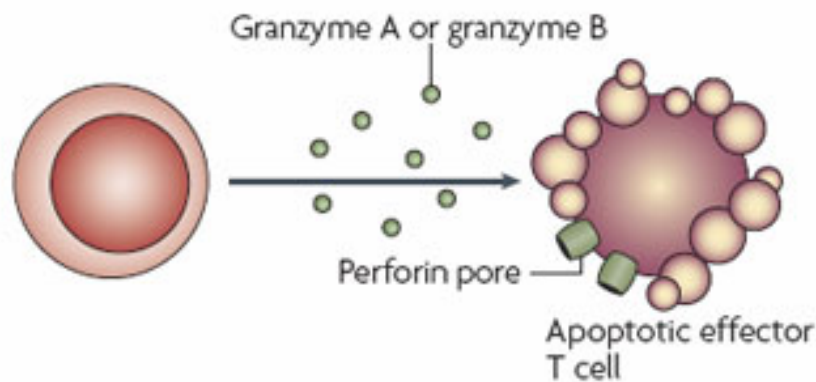
There can be no doubt that Foxp3 Tregs are crucial to the development and maintenance of tolerance.

The means by which Tregs restrain effector T cells from destroying antigen-bearing tissue seems multifactorial and includes cell– cell interactions with both effector T cells and dendritic cells as well as release of immunosuppressive cytokines, such as TGF-beta and IL-10, and the generation of adenosine catalyzed by subset-specific expression of ectoenzymes.

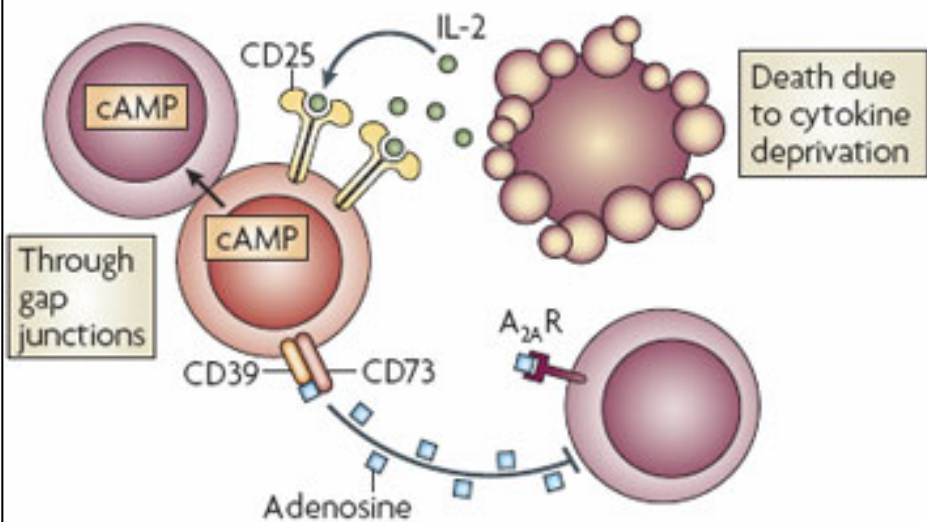
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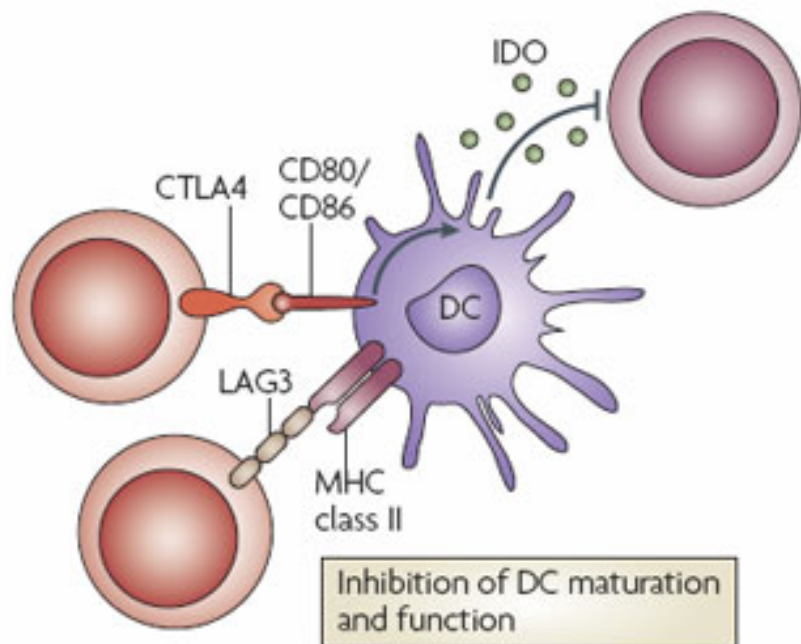
b Cytolysis



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Remarkably, TGF- beta, in the presence of IL-6, IL-12, promotes commitment of naive murine and human CD4 T cells to the highly cytopathic Th17 phenotype.

In humans, other proinflammatory cytokines, including TNF- alpha and IL-1 in addition to IL-6, elicit a similar effect.

Indeed, the presence of these proinflammatory cytokines precludes commitment of naive CD4 T cells to the regulatory phenotype.

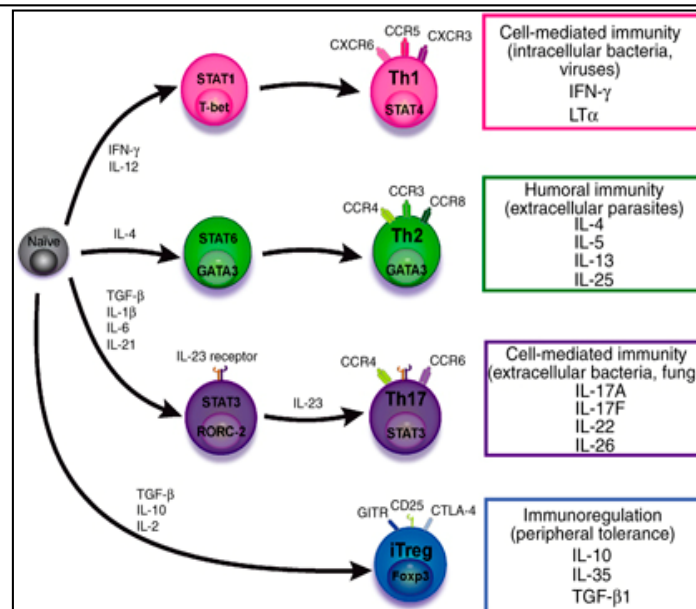
Th17 cells participate in extremely inflamed forms of T cell– dependent tissue injury.

Within these toxic environments, the ability of Foxp3 T cells to restrain effector T cells from executing tissue injury is severely compromised.

Owing to the violence of Th17-dependent tissue injury, a means to target Th17 selectively for therapy is a potentially important unmet need.

The precise role of Th17 cells in rejection is under study.

Preliminary experiments suggest, as is the case in autoimmune diseases, that Th17 cells participate in rejection.

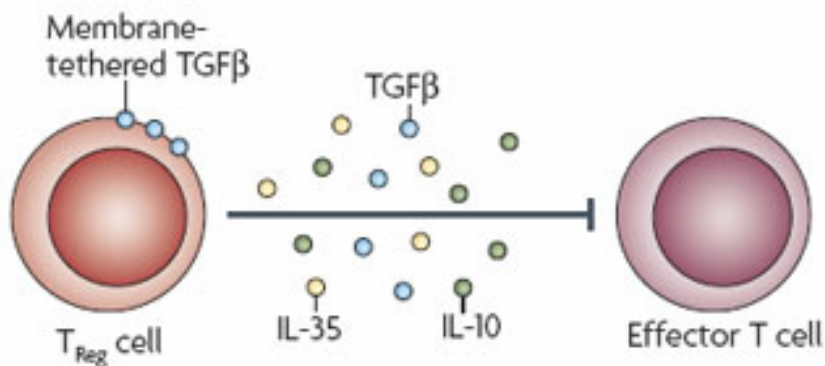


The pivotal role of particular cytokines in dictating the precise nature of the commitments of naive T cells undergoing antigen activation is now clear for the Th17 as well as for the Treg, Th1, and Th2 phenotypes.

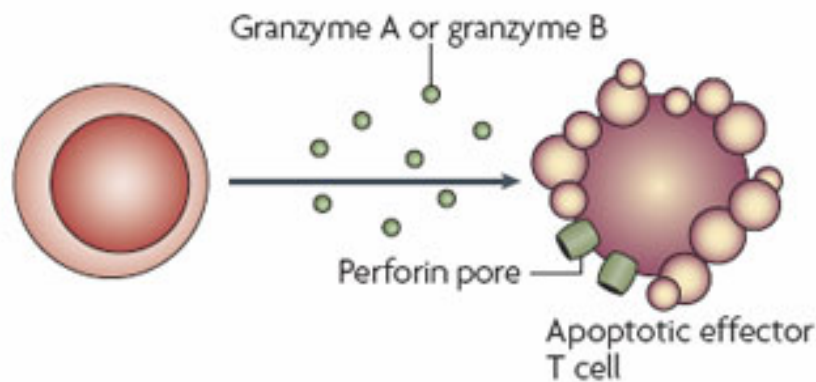
Thus, the role of cytokines in directing differentiation or commitment to the Th17 and Treg phenotypes is new but also classical in the sense that cytokines are widely known to influence the expression of lineage-determining specification-type transcription factors.

Unprecedented is the recent discovery that the cytokine and inflammatory milieu in which Tregs and Th17 cell function alters the molecular and functional phenotype of these committed, presumably terminally differentiated T cells.

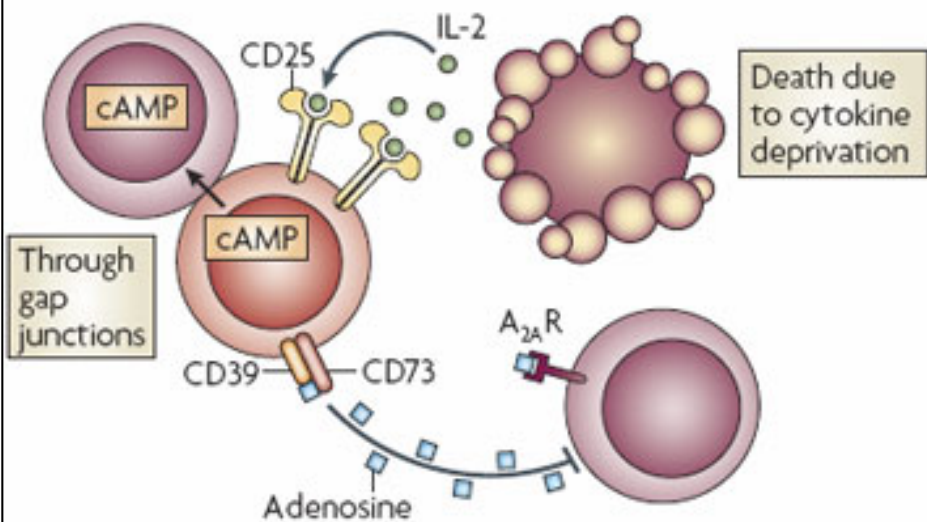
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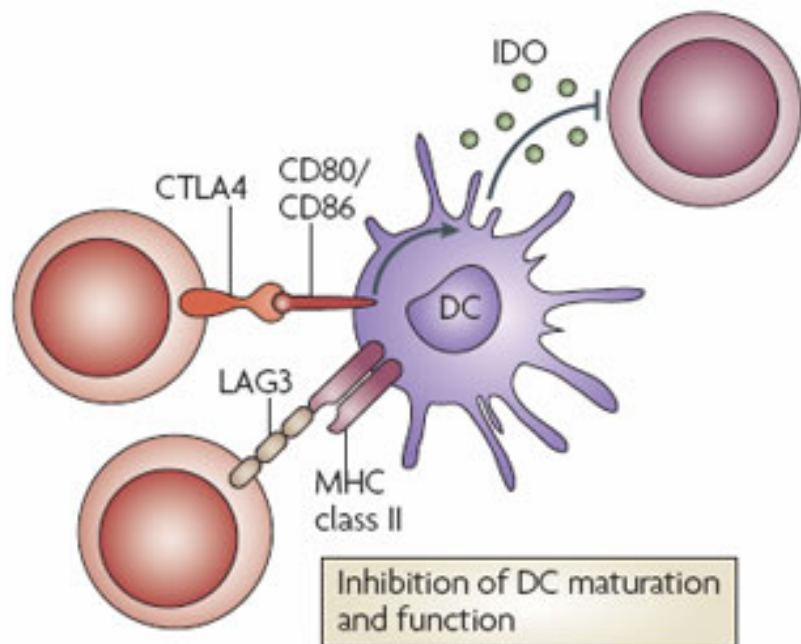
b Cytolysis



c Metabolic disruption



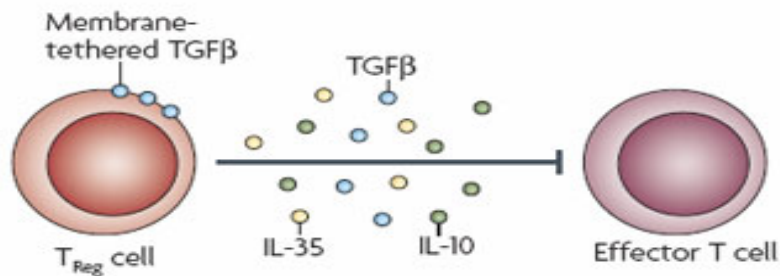
d Targeting dendritic cells



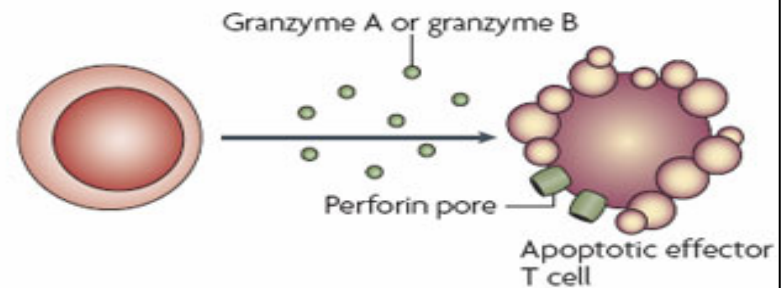
Depiction of the various regulatory T (T_{Reg})-cell mechanisms centred around four basic modes of action.

a | Inhibitory cytokines include interleukin-10 (IL-10), IL-35 and TGF-beta

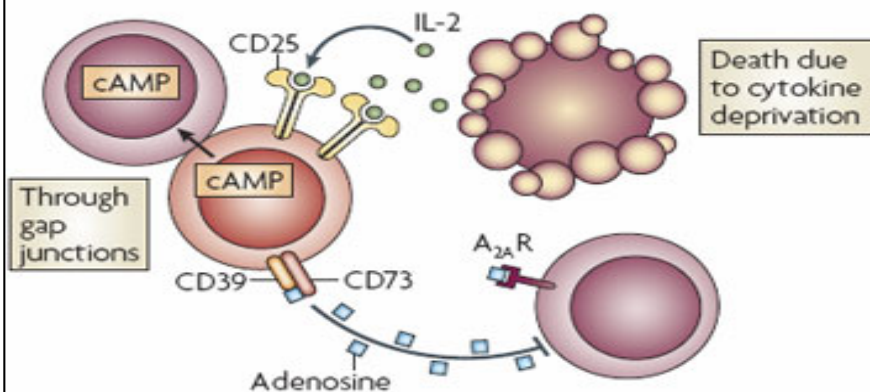
a Inhibitory cytokines



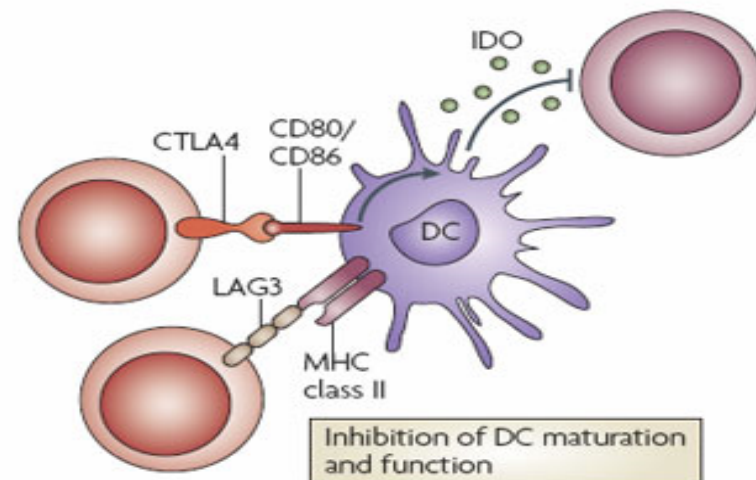
b Cytolysis



c Metabolic disruption

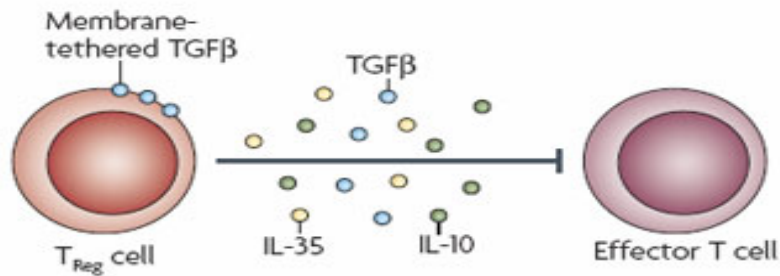


d Targeting dendritic cells

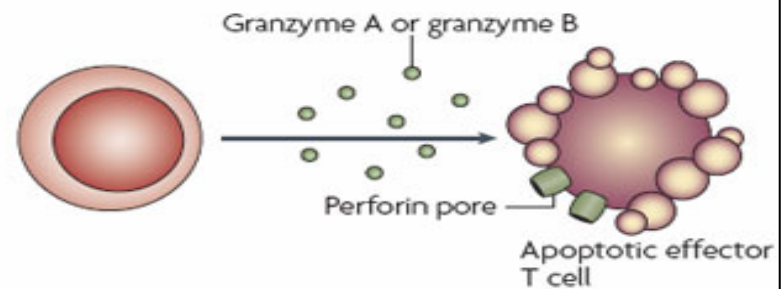


b | Cytolysis includes granzyme-A- and granzyme-B-dependent and perforin-dependent killing mechanisms.

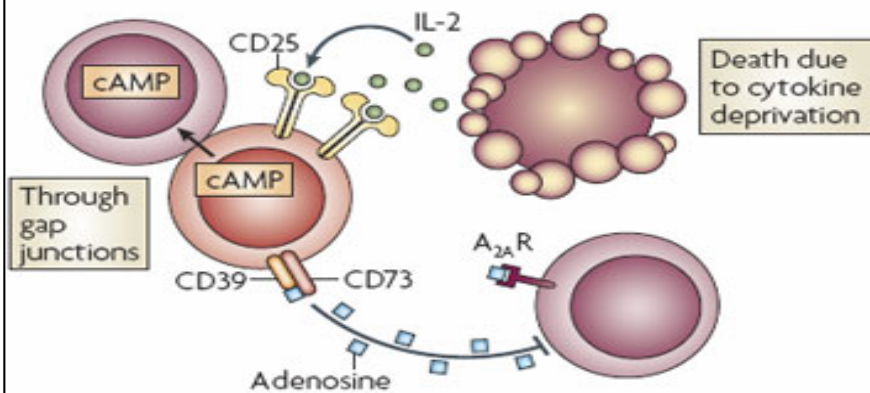
a Inhibitory cytokines



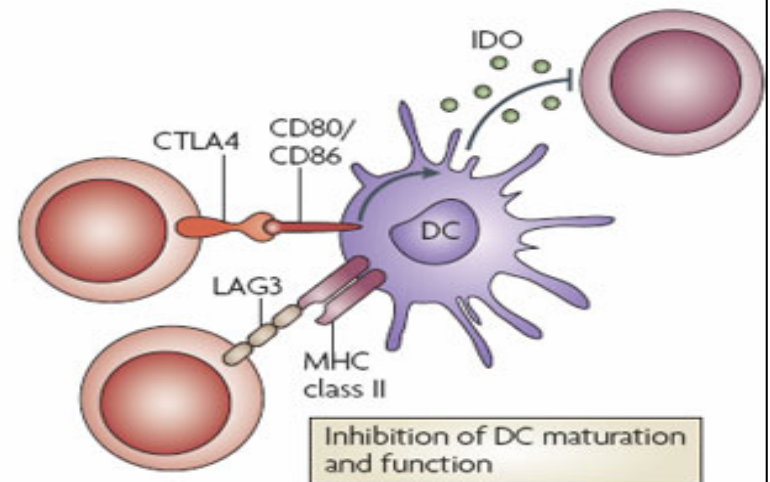
b Cytolysis



c Metabolic disruption

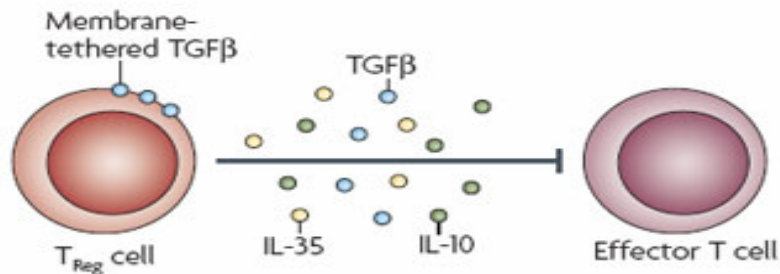


d Targeting dendritic cells

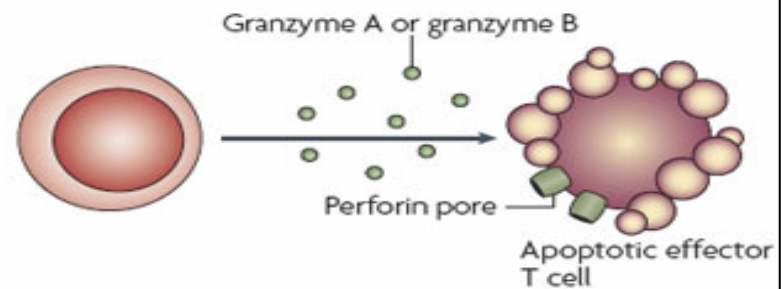


c | Metabolic disruption includes high-affinity CD25 (IL-2 receptor)-dependent cytokine-deprivation-mediated apoptosis, cAMP-mediated inhibition, and CD39- and/or CD73-generated, adenosine receptor 2A ($A_{2A}R$)-mediated immunosuppression.

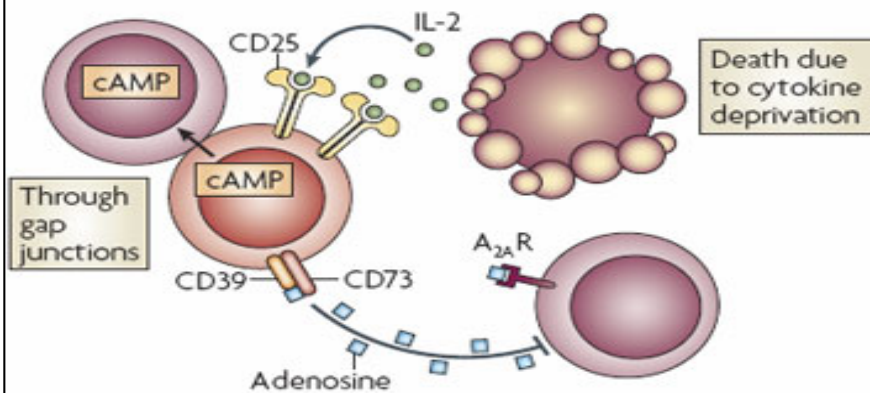
a Inhibitory cytokines



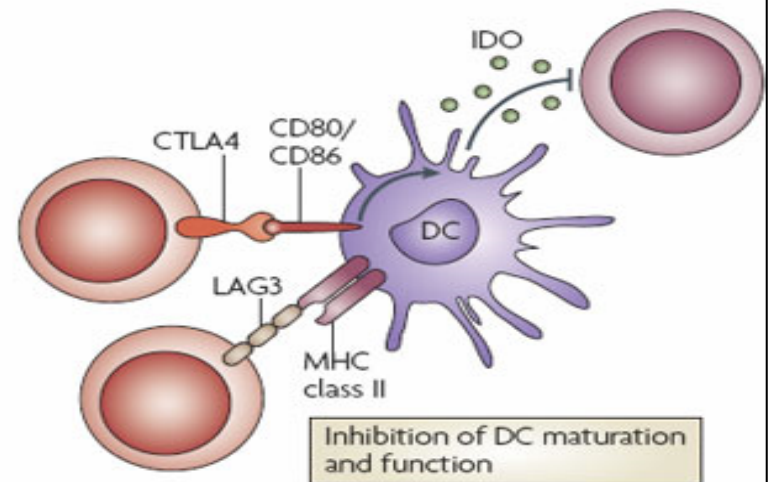
b Cytolysis



c Metabolic disruption

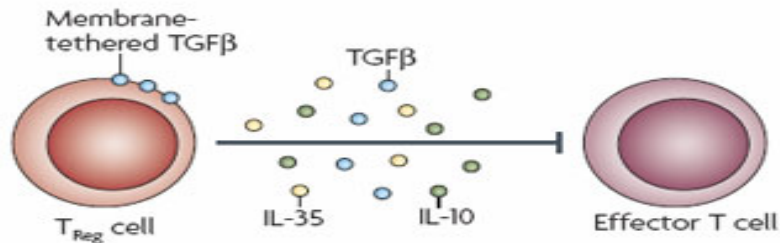


d Targeting dendritic cells

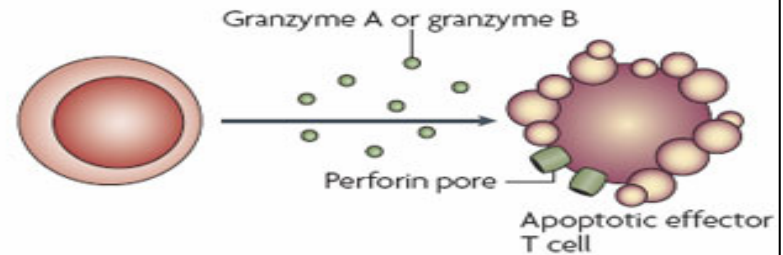


d | Targeting dendritic cells (DCs) includes mechanisms that modulate DC maturation and/or function such as lymphocyte-activation gene 3 (LAG3)–MHC-class-II-mediated suppression of DC maturation, and cytotoxic T-lymphocyte antigen-4 (CTLA4)–CD80/CD86-mediated induction of indoleamine 2,3-dioxygenase (IDO), an immunosuppressive molecule made by DCs.

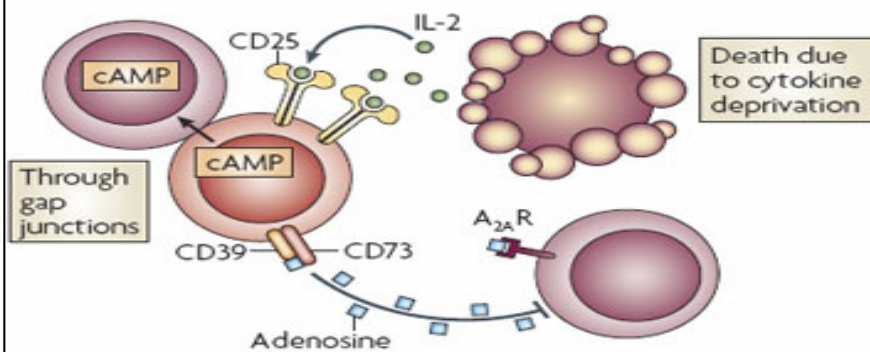
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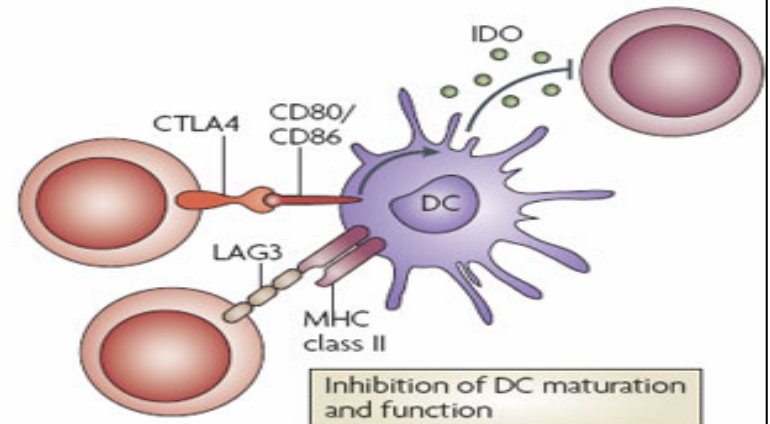
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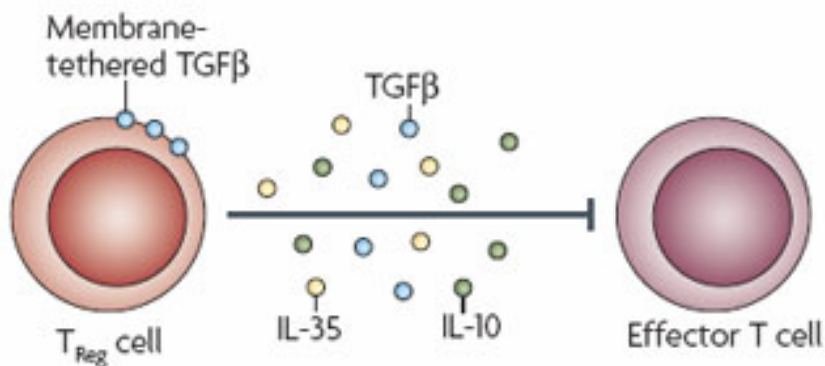
c Metabolic disruption



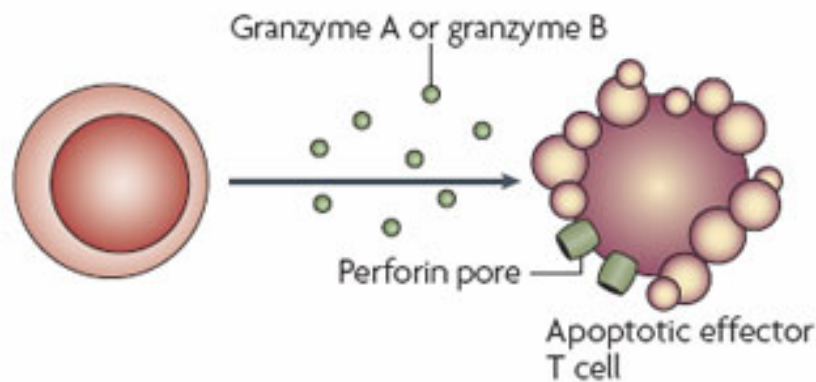
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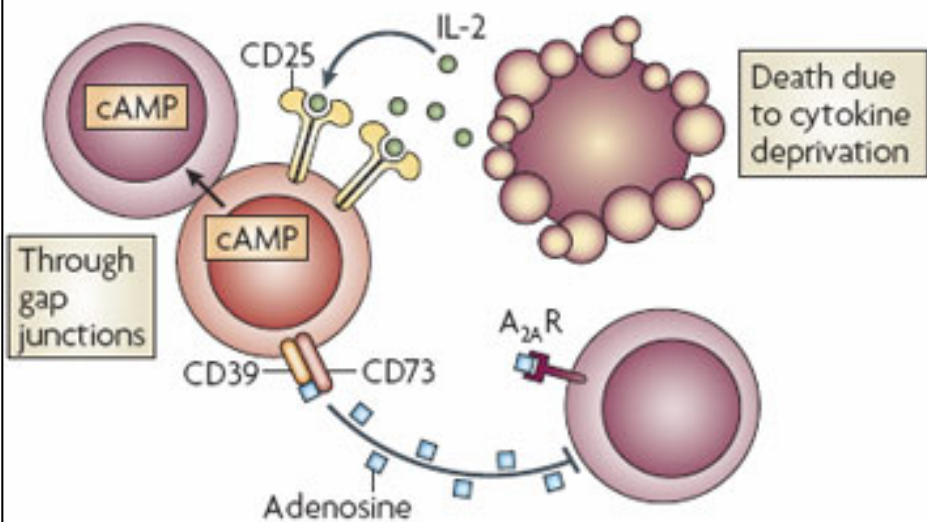
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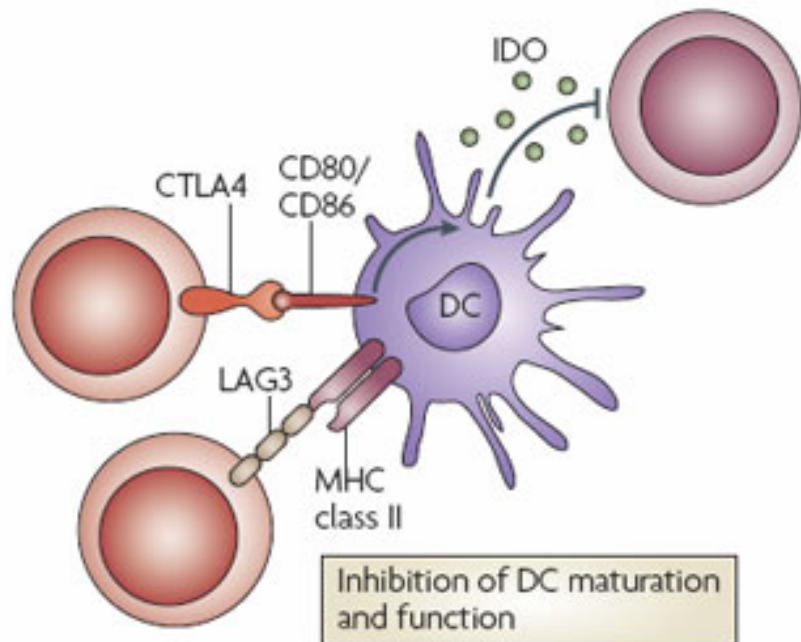
b Cytolysis

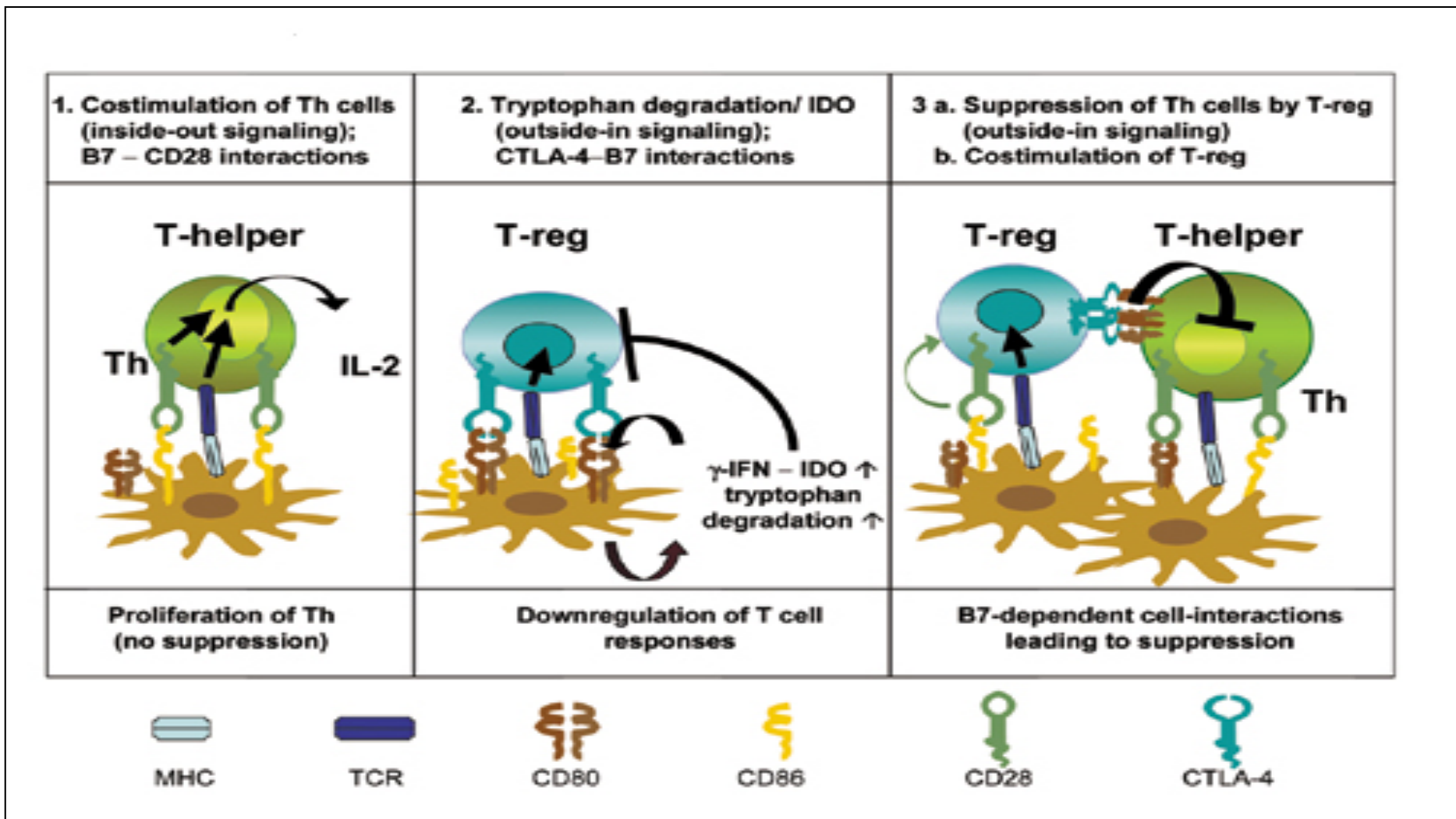


c Metabolic disruption

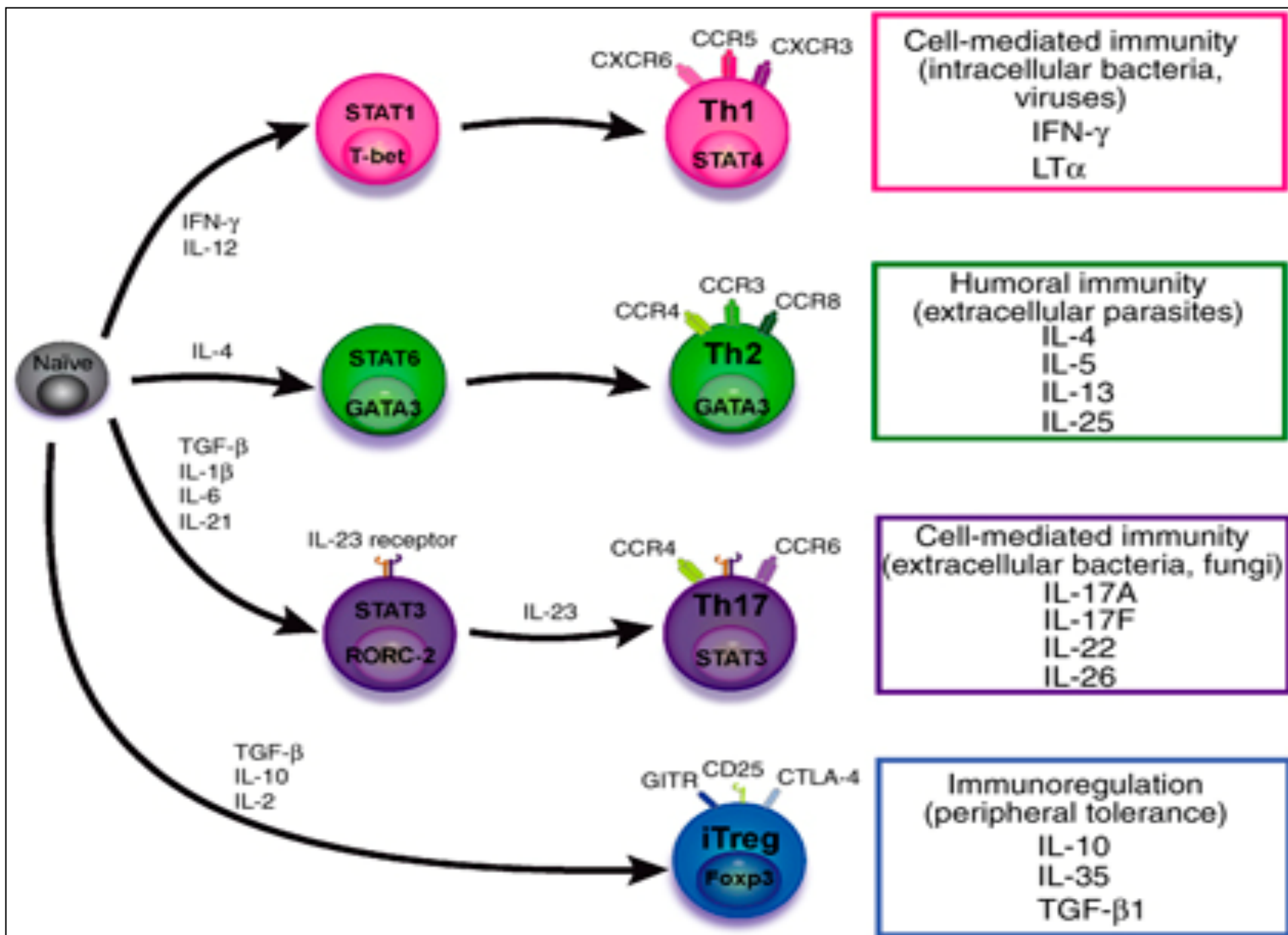


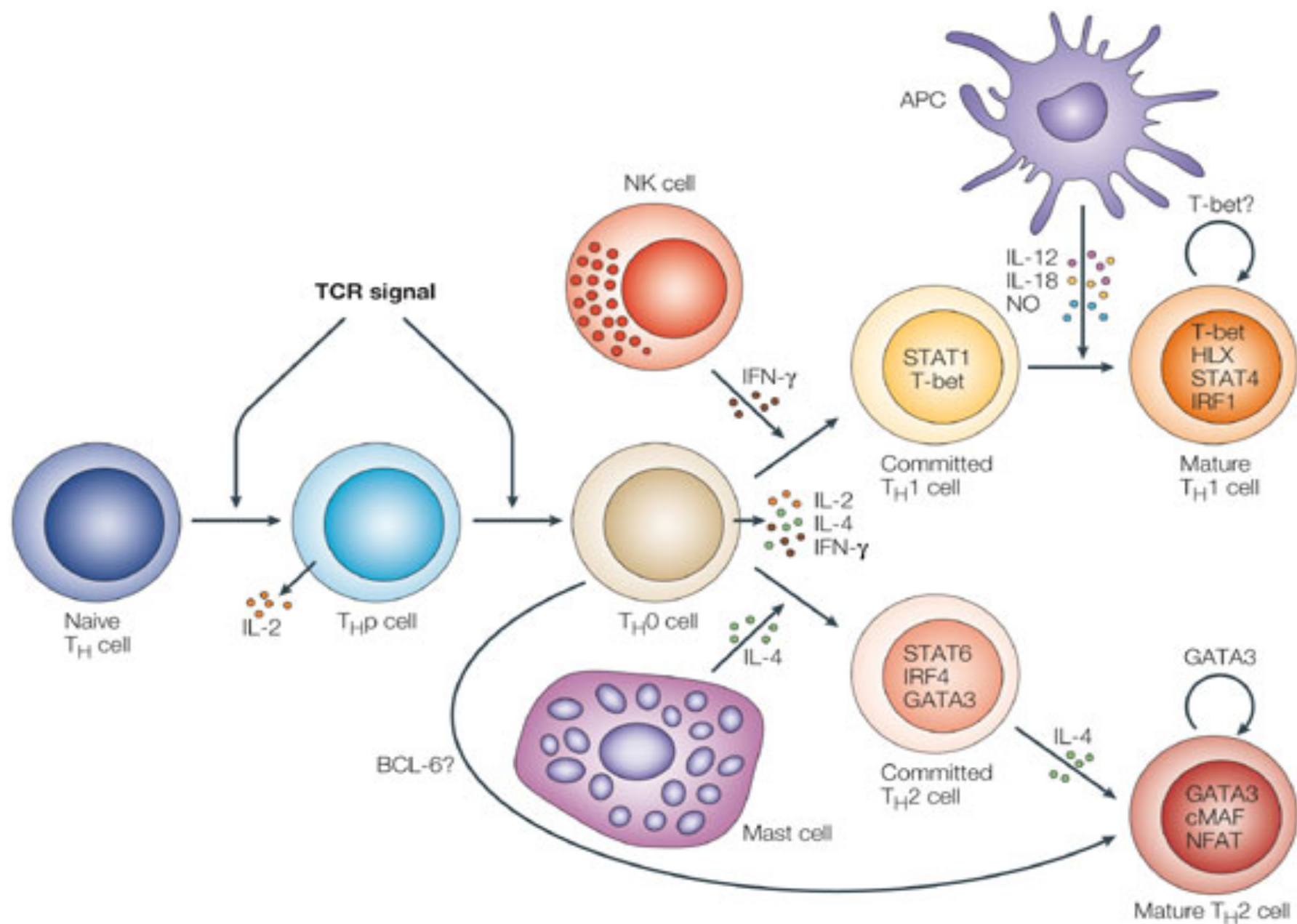
d Targeting dendritic cells





B7-mediated pathways of immune regulation. T-reg, regulatory T cells; Th, T helper; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; TCR, T cell receptor; IDO, indoleamine 2,3-dioxygenase.





Model for T helper (Th) or T regulatory (Treg) differentiation from naïve CD4⁺ T cells.

Th1 cells differentiate in the presence of IL-12, and require activation of the master regulator transcription factor, T-beta, through STAT1.

Fully committed Th1 cells express chemokine receptors, CXCR6, CXCR3, and CCR5, and produce IFN-gamma and lymphotoxin through STAT4.

They are involved in cell-mediated immunity against intracellular bacteria and viruses.

Th2 cells depend on the presence of IL-4, STAT6, and GATA-3, and release IL-4, IL-5, IL-13, and IL-25. Th2 cells express chemokine receptors, CCR3, CCR4, and CCR8, and are important in humoral immunity against parasites and helminthes.

Th17 cells require a combination of TGF- beta and proinflammatory cytokines (IL-1 , IL-6, and/or IL-21) to differentiate from naïve CD4⁺, and RORC-(variant) acts as the key transcriptional regulator.

Upregulation of the IL-23 receptor makes these cells responsive to IL-23.

Human Th17 cells produce IL-17A, IL-17F, IL-22, and IL-26, and are important in host protection against extracellular pathogens and in autoimmunity. Their surface markers include chemokine receptors, CCR4, CCR6, and CD161.

In addition to effector T cells, naïve CD4⁺ T cells can also differentiate into induced Treg (iTreg) in the presence of IL-2 and TGF-beta or IL-10.

iTreg produces immunosuppressive cytokines, TGF-beta, IL-10, and IL-35, and express surface markers, GITR, CD25, and CLTA-4.

Similar to thymus-derived naturally occurring Treg (nTreg), iTreg also expresses the master regulator transcription factor, Foxp3.

T_H1 cells produce IFN-gamma, IL-2 and lymphotoxin, whereas T_H2 cells produce IL-4, -5, -6, -10 and -13

T_H1 and T_H2 cells originate from precursor T_H (T_{Hp}) cells, which secrete IL-2 but not IL-4 or IFN-gamma. These cells then differentiate into T_H0 cells, which produce both T_H1 and T_H2 cytokines.

IL-4 drives T_H0 cells to differentiate towards the T_H2 -cell phenotype by activating signal transducer and activator of transcription 6 (STAT6), which in turn upregulates the expression of GATA-binding protein 3 (GATA3)

GATA3 is crucial for chromatin changes that stabilize the T_H2 -cell phenotype, and it cooperates with growth-factor independent 1 (GFI1) in triggering T_H2 -cell Proliferation.

Differentiation into T_H2 cells occurs independently of IL-4 or STAT6 in mice that are deficient in B-cell lymphoma 6 (BCL-6).

Differentiation into T_H1 cells depends on IL-12-mediated activation of STAT4 which in turn supports IFN-gamma production. IFN-gamma signals induce STAT1 to activate the transcription factor T-beta, which cooperates to increase expression of IFN-gamma and the α -subunit of the IL-12 receptor (IL-12R α 2).

T_H0 cells that are destined to become T_H2 cells downregulate expression of IL-12R α 2.

Cytokines that cooperate with IL-12 include IL-18, -23 and -27. In a positive-feedback loop, IFN-gamma drives T_H1-cell responses independently of IL-12.

IFN-gamma supports the differentiation of human T_H cells into T_H1 cells.

As well as cytokines, nitric oxide (NO), which is produced by inducible NO synthase, promotes differentiation into T_H1 cells, by upregulating expression of IL-12R.

Also, the type of dendritic cell (DC) that is encountered by the uncommitted T_H cell is relevant: B220⁺ plasmacytoid DCs, which produce IFN-gamma, and conventional CD8⁺ B220⁻ DCs, which produce IL-12, both trigger T_H1 responses. By contrast, conventional CD8⁻ B220⁻ DCs prime T_H2 responses.

APC, antigen-presenting cell; IRF, IFN-regulatory factor; NK, natural killer; TCR, T-cell receptor.