T Cell Supplementary & Review Material Contents:

CD28 versus CTLA-4 in T cell activation. Helper T cells regulate themselves with an elegant switch mechanism. When it first encounters antigen-presenting cells, the naïve T cell expresses CD28, which engages CD80 and CD86[1] on the APC. CD28 transmits activation signals into the T cell. Within a few days, the T cell upregulates CTLA-4 on its surface. CTLA-4 transmits inhibitory signals into the T cell. What's important is that its affinity for CD80/CD86 is higher that that of CD28, so the inhibitory message predominates and the T cell shuts down. Lately, CTLA-4 is being called a "checkpoint" inhibitor of T cell activation.

So naturally, several groups have taken advantage of the T cell's natural "turn-on/turn-off" mechanism to develop therapeutic reagents. A fusion protein between CTLA-4 and the Fc of IgG (for good solubility and pharmacodynamics) can bind CD80/CD86 on APC, making these molecules unavailable to the costimulatory CD28 on T cells, and thus suppressing T cell activation. It's licensed for treatment of rheumatoid arthritis. The product is **abatacept**, made by Bristol-Meyers Squibb.
Manufacturer's site: www.Orencia.com

Ipilimumab is a fully human mAb against CTLA-4, which when it binds blocks the inhibitory signal; so it increases the responsiveness of activated T cells. It's licensed for use against malignant melanoma. Commonly patients make CTL against melanoma, but they are not highly effective; treatment of the patient with ipilimumab unblocks the CTLA-4 checkpoint, and the tumor-specific CTL become fully active.

Th17 (T_H17) cells are the newest Th subset. They were recognized as a separate type of Th cell in 2005. They make the proinflammatory cytokines IL-17 and IL-23, and have been shown to play a part in certain mouse autoimmunity models. They can also be found in lesions of human psoriasis and inflammatory bowel disease (*see* Autoimmunity). A monoclonal antibody against IL-23 (unfortunately also against IL-12, which shares a p40 chain with IL-23) is claimed to have some efficacy in psoriasis. There is a newer monoclonal selectively against IL-23's unique chain which looks good in early testing. Since Th17 are generally studied under conditions artificially manipulated to enhance their numbers, their true role and importance in human biology is not yet established. However, recent reports suggest a role for Th17 cells in resistance to infection by *Mycobacterium tuberculosis*, *Klebsiella pneumoniae*, and *Bordetella pertussis*.
Review: http://www.ncbi.nlm.nih.gov/pubmed/20044948

About their development: Th0 cells exposed to high concentrations of TGFβ upregulate FoxP3 and develop into Treg. If a high concentration of IL-6 is also present, FoxP3 is suppressed and the orphan relation to retinoic acid receptors ROR-γt is expressed instead, resulting in a Th17 cell. Like other Th, Th17 is self-stimulating, using autocrine IL-21.

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[1] CD80 is also called B7.1; CD86 is also B7.2. But the B7 names are no longer used that much.

SUMMARY: T_H CELL SUBSETS

T cell	Induced by	Cytokines made	Surface markers	Transcription factors	Main functions
Th1	"DC1" IL-12	IL-2 IFN-γ (TNF-β)	CD4	T-bet Stat4	●IFN-γ polarizes macrophages into M1, activates, attracts them ●IL-2 helps CTL get activated by Ag
Th2	"DC2" IL-4	IL-4, IL-5, IL-6, IL-10, IL-13	CD4	GATA-3	●IL-4, 13 polarize macrophages into M2, activates, attracts them ●IL-4, 5 attract eosinophils
Th17	TGFβ + IL-6 IL-21 IL-23	IL-17 IL-21 IL-22	CD4	ROR-γt	IL-17, 22 attracts, activate multiple inflammatory cells
Tfh	?	A variety of Th1 and Th2 cytokines	CD4; CXCR5 for homing to follicles	BCL-6	IL-2, IFN-γ, IL-4 made by different subsets help B cells switch isotypes
Treg	TGFβ	TGF-β IL-10	CD4 CD25 $CD127^{low}$	Foxp3	Suppresses Th1, Th2, Th17, Tfh by contact and soluble factors (IL-10, TGF-β)

"DC1" and "DC2" refer to dendritic cells polarized by exposure to the appropriate cytokine/chemokine soup to favor differentiation of Th0 into Th1 or Th2, respectively. CD1 make the well-known Th1-polarizing IL-12. Not everyone uses this terminology.