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T cells: the usual subsets

Chen Dong and Gustavo J. Martinez

T cells have important roles in immune responses and function by directly secreting soluble mediators or through cell contact-dependent mechanisms. Many T cell subsets have been characterized. Although effector T cells were originally considered to be terminally differentiated, a growing body of evidence has challenged this view and suggested that the phenotype of effector T cells is not completely fixed but is more flexible or plastic. T cells can have 'mixed' phenotypes (that is, have characteristics usually associated with more than one T cell subset) and can interconvert from one subset phenotype to another, although instructive signalling can lead to long-term fixation of cytokine memory. T cell plasticity can be important for adaptation of immune responses in different microenvironments and might be particularly relevant for host defence against pathogens that colonize different tissues. Distinct T cell subsets, or differentiation states, can be identified based on the cell surface markers expressed and/or the effector molecules produced by a particular T cell population. This Poster summarizes our current understanding of the surface markers, transcriptional regulators, effector molecules and functions of the different T cell subsets that participate in immune responses. Further knowledge of how these T cell subsets are regulated and cooperate with each other will provide us with better tools to treat immune-related diseases.

Cytotoxic T cell

Surface phenotype	αβ TCR, CD3, CD8
Transcription factors	EOMES, T-bet, BLIMP1
Effector molecules secreted	Perforin, granzyme, IFNγ
Function	Cytotoxic; kill infected and transformed cells and thereby protect the host from viral infections and cancer. Direct killing is mediated by secretion of perforin and granzymes, which cause apoptosis of target cells.
Other features	In humans, mainly CD45RO$^+$. Some terminally differentiated CTLs in humans re-express CD45RA.

Exhausted T cell

Surface phenotype	CD3, CD8, PD1, TIM3, 1B11, LAG3
Transcription factors	BLIMP1
Function	Generated in response to chronic antigen-mediated TCR stimulation. These cells express inhibitory receptors and lack effector cytokine production; they therefore fail to mount effective antiviral immune responses.

Anergic T cell

Surface phenotype	αβ TCR, CD3, BTLA
Effector factors	GRAIL, CBL-B, ITCH, NEDD4
Function	These cells are generated following TCR activation in the absence of co-stimulatory signals, which leads them to become unresponsive to subsequent stimulatory signals. They are functionally inactive cells and fail to proliferate or produce IL-2. Their generation may be important for avoiding autoimmune responses.
Other features	Increased expression of p27KIP1, which leads to cell cycle arrest.

T_R1 cell

Surface phenotype	αβ TCR, CD3, CD4
Transcription factors	Not known
Effector molecules secreted	IL-10
Function	Immunosuppression mediated by IL-10 production. These cells are generated from naive T cells in the presence of TGFβ and IL-27 or in the presence of the immunosuppressive drugs vitamin D3 and dexamethasone.

Natural T_{Reg} cell

Surface phenotype	αβ TCR, CD3, CD4, CD25, CTLA4, GITR
Transcription factors	FOXP3, STAT5, FOXO1, FOXO3
Effector molecules secreted	IL-10, TGFβ, IL-35
Function	Mediate immunosuppression and tolerogenic responses through contact-dependent and -independent mechanisms. These cells are generated in the thymus.

Inducible T_{Reg} cell

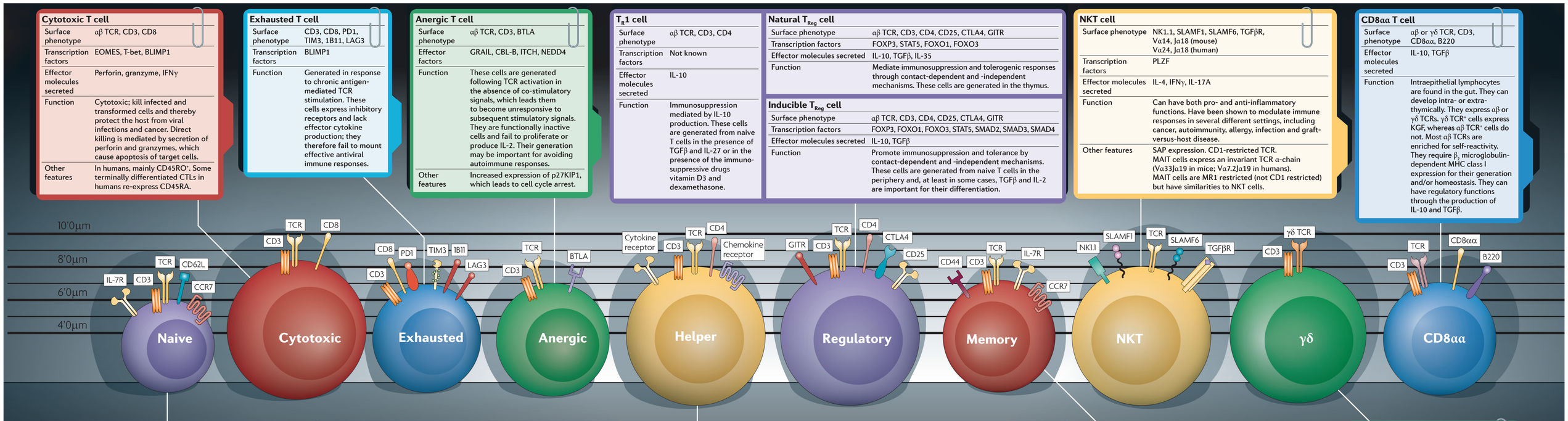
Surface phenotype	αβ TCR, CD3, CD4, CD25, CTLA4, GITR
Transcription factors	FOXP3, FOXO1, FOXO3, STAT5, SMAD2, SMAD3, SMAD4
Effector molecules secreted	IL-10, TGFβ
Function	Promote immunosuppression and tolerance by contact-dependent and -independent mechanisms. These cells are generated from naive T cells in the periphery and, at least in some cases, TGFβ and IL-2 are important for their differentiation.

NKT cell

Surface phenotype	NK1.1, SLAMF1, SLAMF6, TGFβR, Vα14, Jα18 (mouse) Vα24, Jα18 (human)
Transcription factors	PLZF
Effector molecules secreted	IL-4, IFNγ, IL-17A
Function	Can have both pro- and anti-inflammatory functions. Have been shown to modulate immune responses in several different settings, including cancer, autoimmunity, allergy, infection and graft-versus-host disease.
Other features	SAP expression. CD1-restricted TCR. MAIT cells express an invariant TCR α-chain (Vα33Jα19 in mice; Vα7.2Jα19 in humans). MAIT cells are MR1 restricted (not CD1 restricted) but have similarities to NKT cells.

CD8αα T cell

Surface phenotype	αβ or γδ TCR, CD3, CD8αα, B220
Effector molecules secreted	IL-10, TGFβ
Function	Intraepithelial lymphocytes are found in the gut. They can develop intra- or extra-thymically. They express αβ or γδ TCRs. γδ TCR$^+$ cells express KGF, whereas αβ TCR$^+$ cells do not. Most αβ TCRs are enriched for self-reactivity. They require β_2 microglobulin-dependent MHC class I expression for their generation and/or homeostasis. They can have regulatory functions through the production of IL-10 and TGFβ.



$CD4^+$ αβ T cell

Surface phenotype	αβ TCR, CD3, CD4, CCR7, CD62L^{hi}, IL-7R (CD127)
Transcription factors	THPOK
Function	Patrol through lymph nodes scanning peptide–MHC class II molecule complexes on APCs for the presence of their cognate antigen. Following activation by APCs, naive CD4$^+$ T cells differentiate into effector or regulatory T cells; activated naive T cells also give rise to memory T cells.
Other features	CD45RA expressed by human cells.

$CD8^+$ αβ T cell

Surface phenotype	αβ TCR, CD3, CD8, CCR7, CD62L^{hi}, IL-7R (CD127)
Transcription factors	RUNX3
Function	Patrol through lymph nodes scanning peptide–MHC class I molecule complexes for the presence of their cognate antigen. Following activation by APCs, they differentiate into CTLs and memory T cells.
Other features	CD45RA expressed by human cells.

T_H1 cell

Surface phenotype	αβ TCR, CD3, CD4, IL-12R, IFNγR, CXCR3
Transcription factors	T-bet, STAT4, STAT1
Effector molecules secreted	IFNγ, IL-2, LTα
Function	Promote protective immunity against intracellular pathogens. By secreting IFNγ, they induce activation of macrophages and upregulation of iNOS, leading to the killing of intracellular pathogens such as *Leishmania major*, *Listeria monocytogenes* and *Mycobacterium* spp. Their development is regulated by IL-12.

T_H2 cell

Surface phenotype	αβ TCR, CD3, CD4, IL-4R, IL-33R, CCR4, IL-17RB, CRTH2
Transcription factors	GATA3, STAT6, DEC2, MAF
Effector molecules secreted	IL-4, IL-5, IL-13, IL-10
Function	Promote humoral immune responses and host defence against extracellular parasites. However, they can also potentiate allergic responses and asthma. Their development and maintenance is regulated by IL-4, IL-25 and IL-33.
Other features	IRF4 is also an important transcription factor.

T_H9 cell

Surface phenotype	αβ TCR, CD3, CD4
Transcription factors	PU.1
Effector molecules secreted	IL-9, IL-10
Function	Involved in host defence against extracellular parasites, primarily nematodes. Despite their production of anti-inflammatory IL-10, they promote allergic inflammation. Their role in other inflammatory diseases still remains unclear as this subset has only recently been characterized.

T_H17 cell

Surface phenotype	αβ TCR, CD3, CD4, IL-23R, CCR6, IL-1R, CD161 (human only)
Transcription factors	RORγt, STAT3, RORα
Effector molecules secreted	IL-17A, IL-17F, IL-21, IL-22, CCL20
Function	Promote protective immunity against extracellular bacteria and fungi, mainly at mucosal surfaces. Also promote autoimmune and inflammatory diseases. Generated in the presence of TGFβ and IL-6 and/or IL-21 and are maintained by IL-23 and IL-1.
Other features	Also express BATF, IκBζ, IRF4 and AHR transcription factors. Human T_H17 cells also produce IL-26.

T_H22 cell

Surface phenotype	αβ TCR, CD3, CD4, CCR10
Transcription factors	AHR
Effector molecules secreted	IL-22
Function	Identified in inflammatory skin diseases. Their role in host defence remains unclear as this subset has only recently been characterized. Their identity as an independent T_H cell subset needs to be confirmed.

T_{FH} cell

Surface phenotype	αβ TCR, CD3, CD4, CXCR5, SLAM, OX40L, CD40L, ICOS, IL-21R, PD1
Transcription factors	BCL-6, STAT3
Effector molecules secreted	IL-21
Function	These cells are involved in promotion of germinal centre responses and provide help for B cell class switching.
Other features	SAP expression.

Central memory T cell

Surface phenotype	CCR7^{hi}, CD44, CD62L^{hi}, TCR, CD3, IL-7R (CD127), IL-15R
Transcription factors	BCL-6, BCL-6B, MBD2, BMI1
Effector molecules secreted	IL-2, CD40L Low levels IL-4, IFNγ, IL-17A
Function	Preferentially reside in secondary lymphoid organs, mounting recall responses to antigens. Even though these cells lack immediate effector functions, they rapidly proliferate and differentiate into effector T cells following antigen stimulation.

Effector memory T cell

Surface phenotype	CD62L^{low}, CD44, TCR, CD3, IL-7R (CD127), IL-15R, CCR7^{low}
Transcription factors	BLIMP1
Effector molecules secreted	Rapid and high production of inflammatory cytokines
Function	Preferentially found in peripheral tissues. They provide immediate protection upon antigen challenge through, for example, the rapid production of effector cytokines.

γδ T cell

Surface phenotype	γδ TCR, CD3
Effector molecules secreted	IFNγ, IL-17A, IL-17F, IL-22
Function	Enriched at epithelial surfaces and can have both pro- and anti-inflammatory functions, depending on the γδ TCR and the context. Have characteristics of both innate and adaptive immunity.
Other features	IFNγ- and IL-17A-producing cells are distinct populations that can be distinguished by CD27 and CCR6 expression. Innate immune recognition by expression of TLRs.

Abbreviations

AHR, aryl hydrocarbon receptor; APC, antigen-presenting cell; BATF, basic leucine zipper transcription factor, ATF-like; BCL-6, B cell lymphoma 6; BLIMP1, B lymphocyte-induced maturation protein 1; BTLA, B and T lymphocyte attenuator; CBL-B, Casitas B-lineage lymphoma B; CCL, CC-chemokine ligand; CCR, CC-chemokine receptor; CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T lymphocyte antigen 4; CXCR, CXC-chemokine receptor; EOMES, eomesodermin; FOX, forkhead box; GATA3, GATA-binding protein 3; GITR, glucocorticoid-induced TNF-receptor-related protein; GRAIL, gene related to anergy in lymphocytes; IκBζ, inhibitor of NF-κB-ζ; ICOS, inducible T cell co-stimulator; IFNγ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; IRF4, interferon-regulatory factor 4; ITCH, itchy homologue E3 ubiquitin protein ligase; J, joining region; KGF, keratinocyte growth factor; L, ligand; LAG3, lymphocyte activation gene 3; LTα, lymphotoxin-α; MAF, musculoaponeurotic fibrosarcoma oncogene; MAIT, mucosal-associated invariant T; MBD2, methyl-CpG-binding domain protein 2; MR1, MHC-related protein 1; NEDD4, neuronal precursor cell-expressed developmentally downregulated 4; NKT, natural killer T; p27KIP1, p27 kinase inhibitory protein 1; PD1, programmed cell death 1; PLZF, promyelocytic leukaemia zinc-finger; R, receptor; ROR, retinoic acid receptor-related orphan receptor; RUNX3, Runt-related transcription factor 3; SAP, SLAM-associated protein; SLAM, signalling lymphocytic activation molecule; SMAD, mothers against decapentaplegic homologue; STAT, signal transducer and activator of transcription; TCR, T cell receptor; T_{FH}, T follicular helper; TGFβ, transforming growth factor-β; THPOK, T_H-inducing POZ/Kruppel-like factor; T_H, T helper; TIM3, T cell immunoglobulin domain and mucin domain protein 3; TLR, Toll-like receptor; V, variable region.

Affiliations

Chen Dong and Gustavo J. Martinez are at the Department of Immunology, M.D. Anderson Cancer Center and Graduate School of Biomedical Sciences, University of Texas Health Science Center at Houston, Houston, Texas 77030, USA.

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