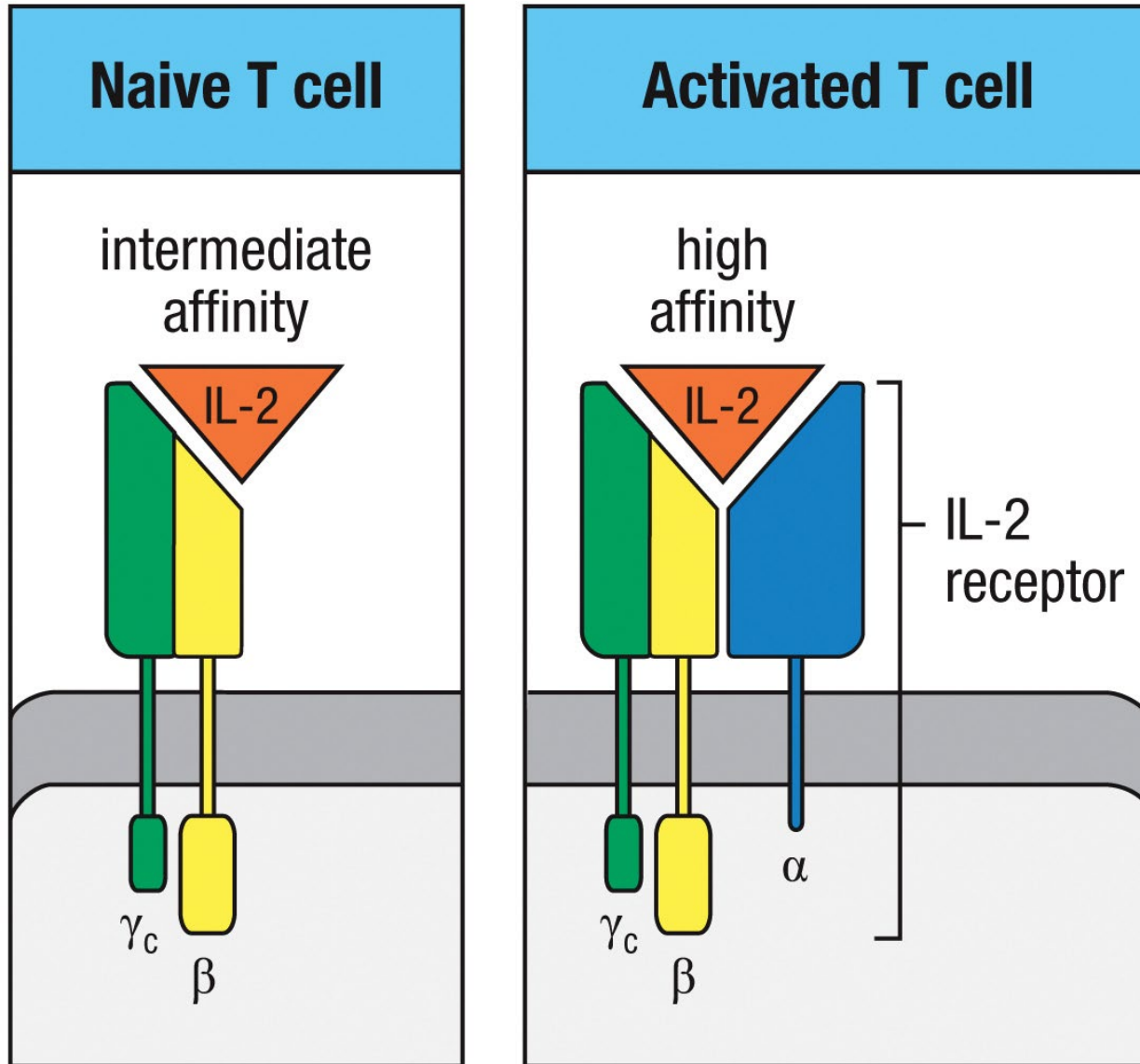


IL-2 Promotes Cell Growth and Differentiation



Outline

T cell mediated immunity

- T cell differentiation
- T cell-mediated cytotoxicity
- Macrophage activation by T_H1 cells
- Peripheral Tolerance

Effector T Cells

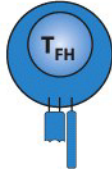
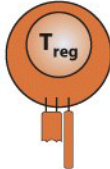
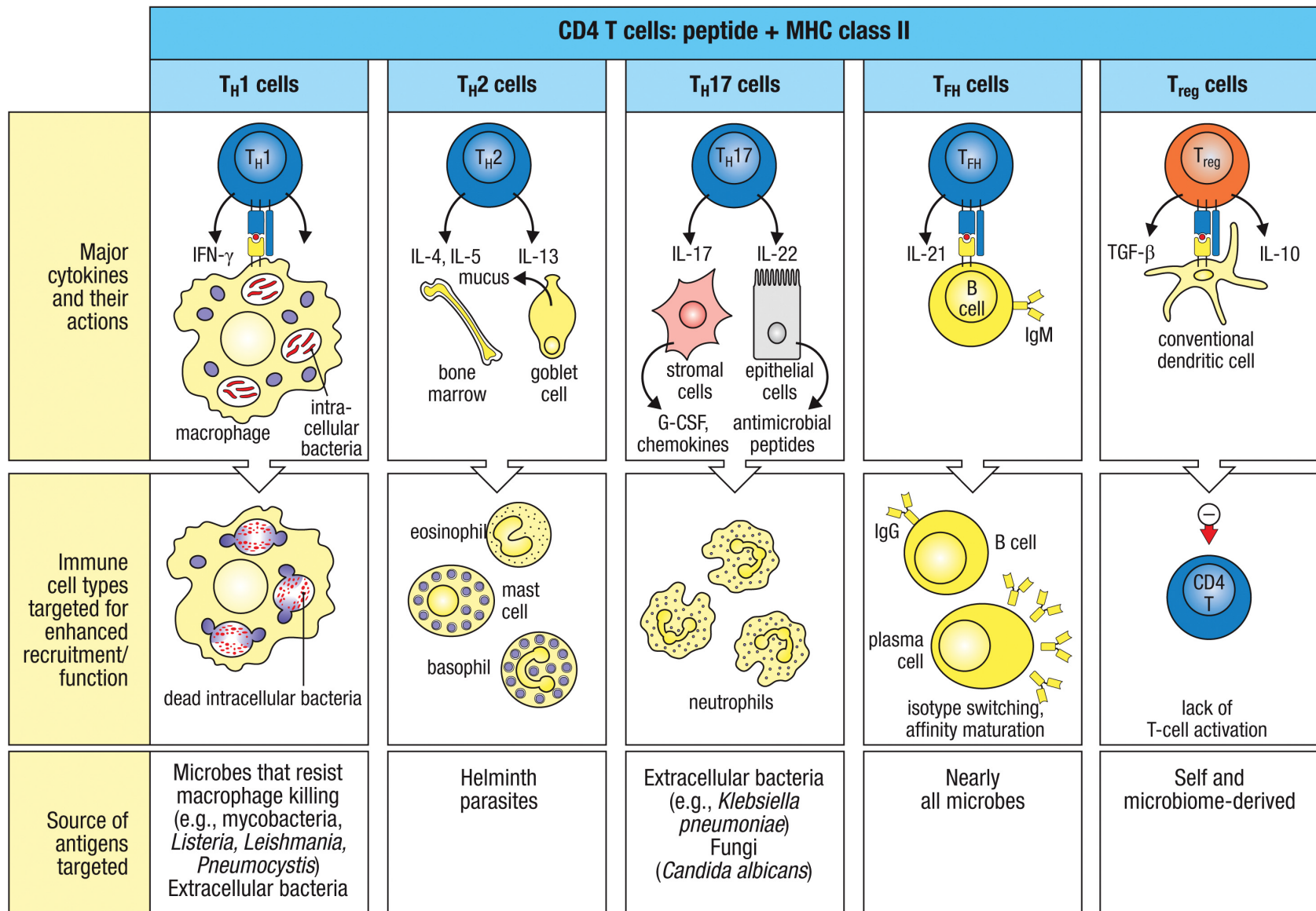
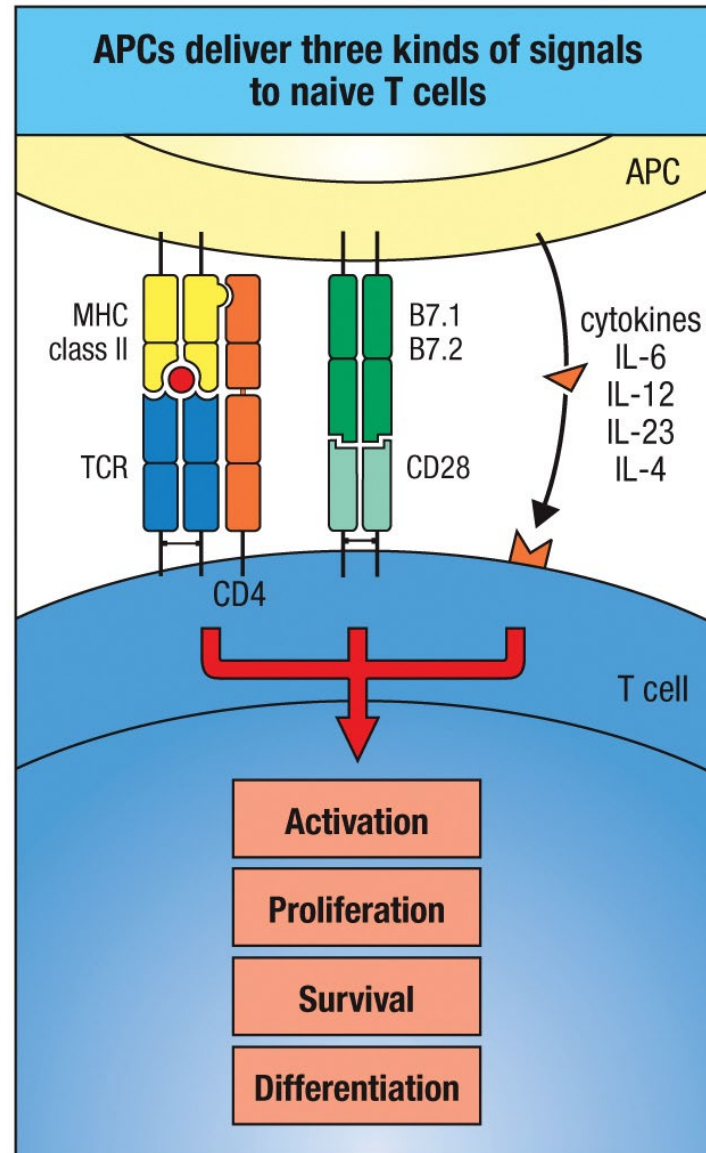
	CD8 cytotoxic T cells	CD4 T _H 1 cells	CD4 T _H 2 cells	CD4 T _H 17 cells	T _{FH} cells	CD4 regulatory T cells (various types)
Types of effector T cell						
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response Promote barrier integrity (skin, intestine)	B-cell help Isotype switching Antibody production	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, <i>Listeria</i> , <i>Leishmania donovani</i> , <i>Pneumocystis carinii</i>) Extracellular bacteria	Helminth parasites	<i>Klebsiella pneumoniae</i> Fungi (<i>Candida albicans</i>)	All types	

Figure 9.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

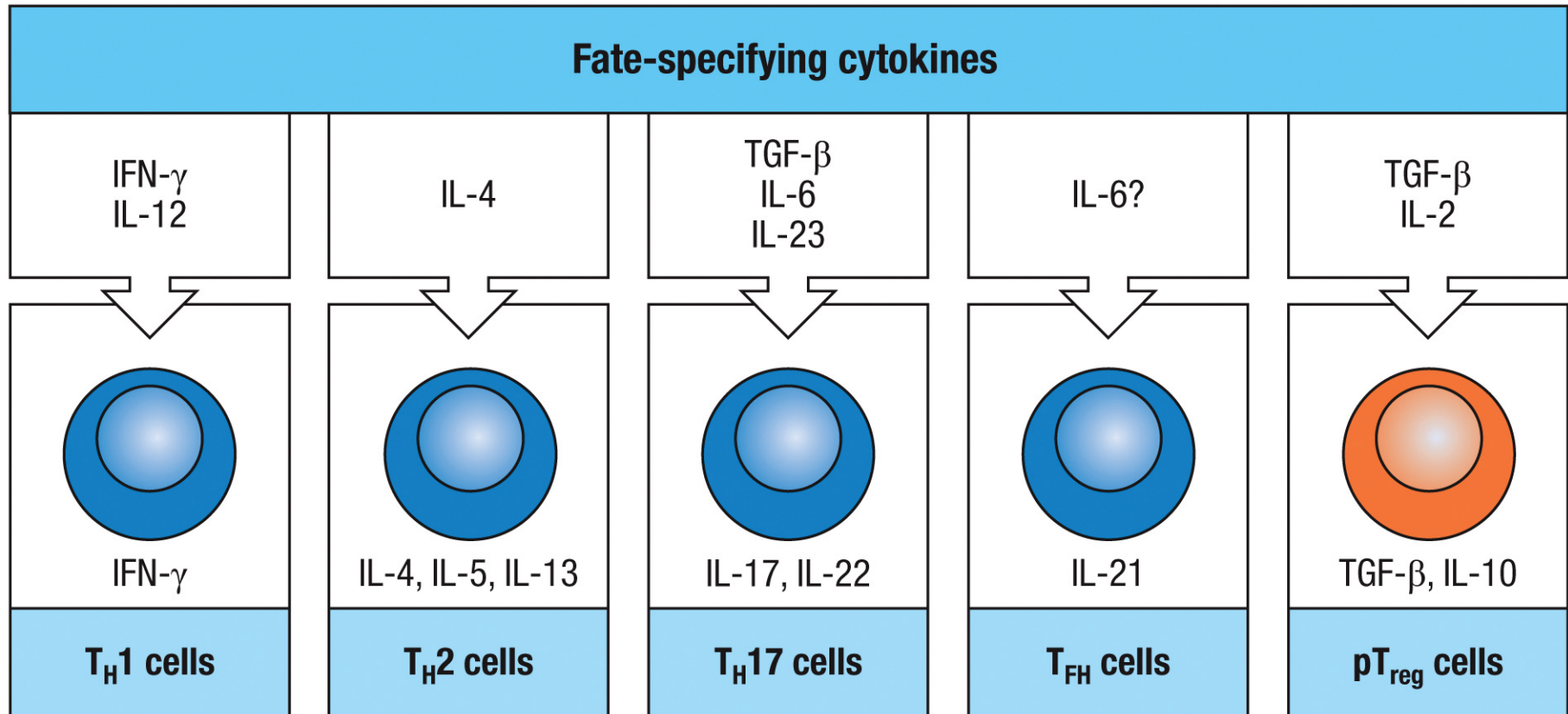
Different Types of T-Cells Are Specialized to Deal with Different Classes of Pathogens



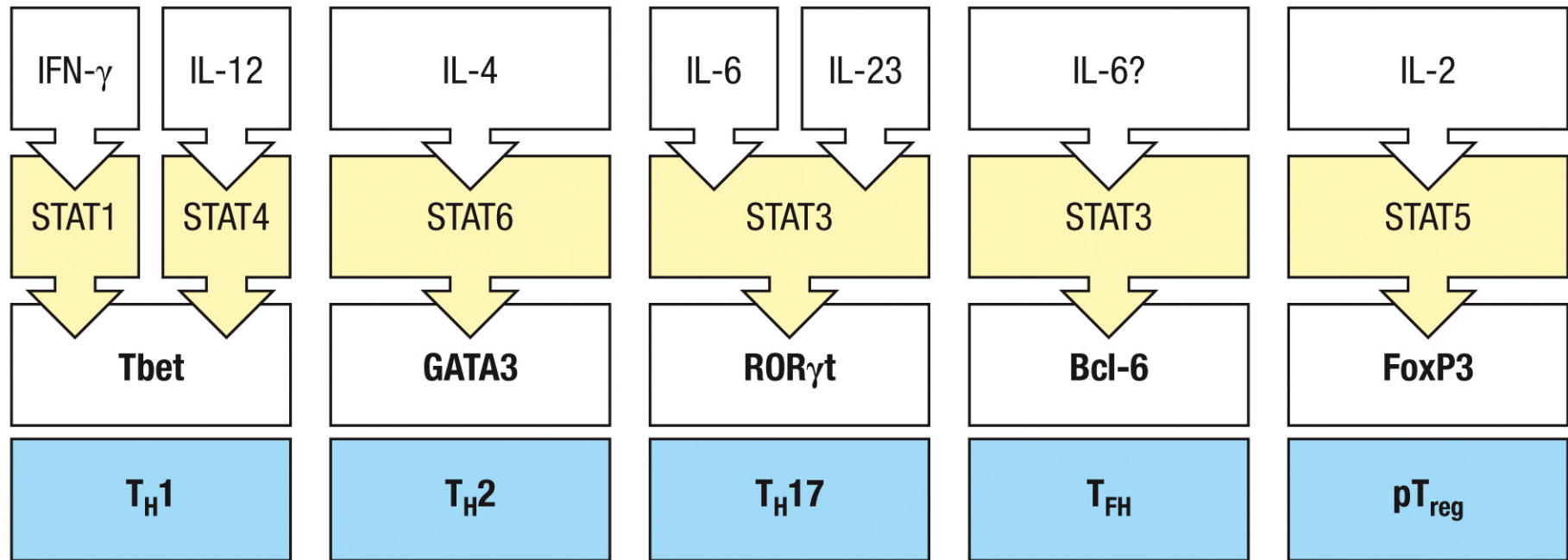
Activation of Naïve T Cells

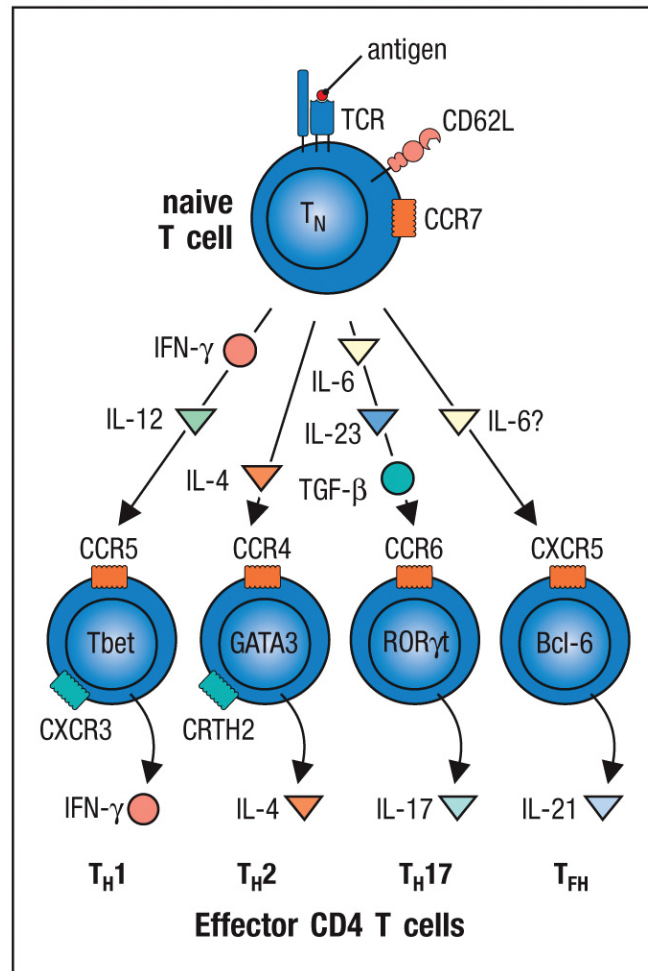


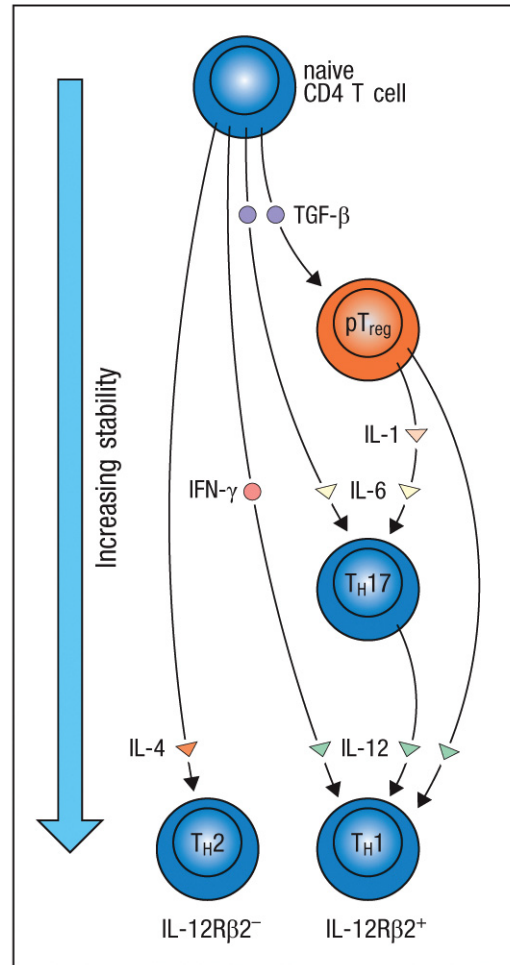
Signal 3



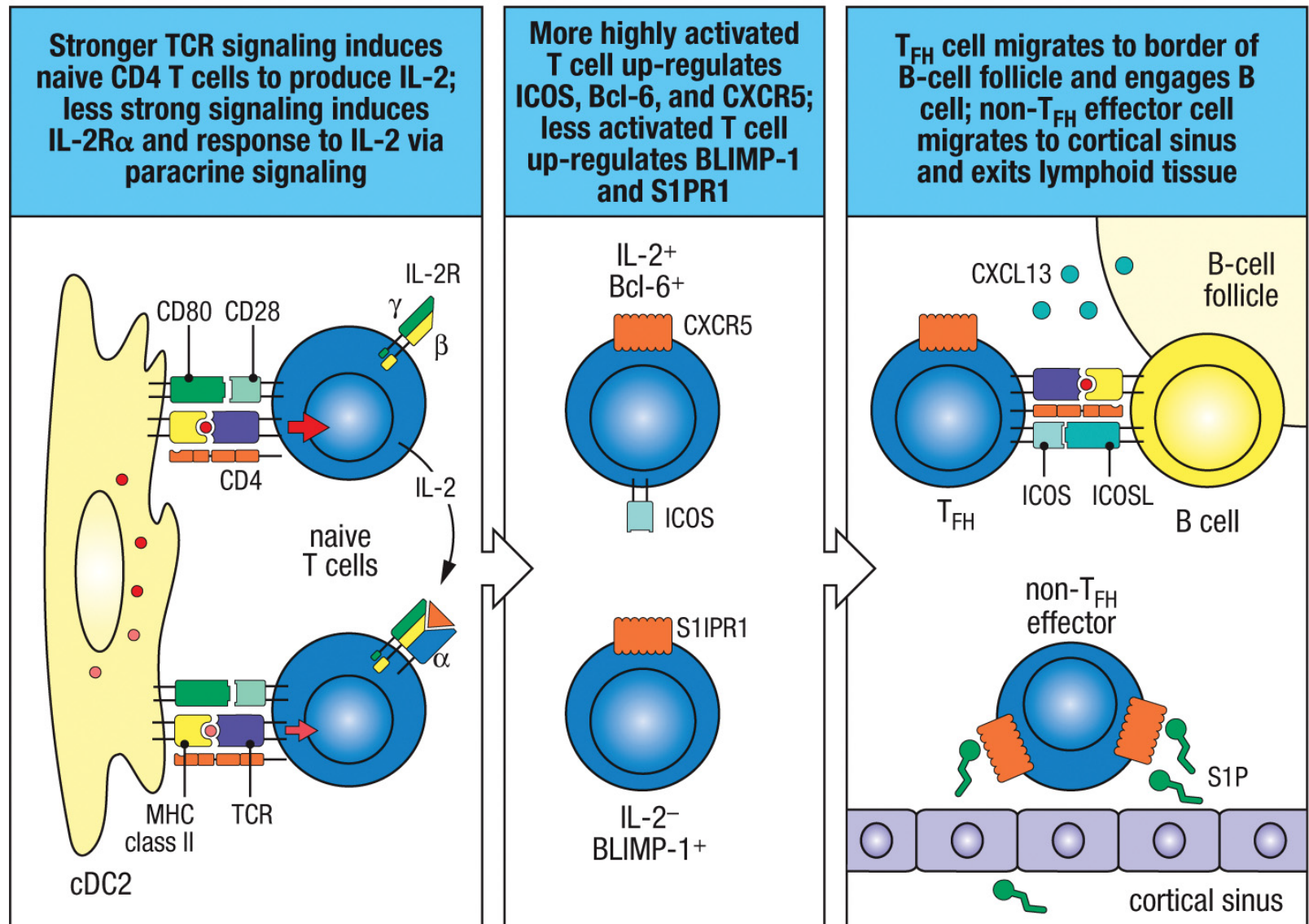
STAT Family of Transcription Factors



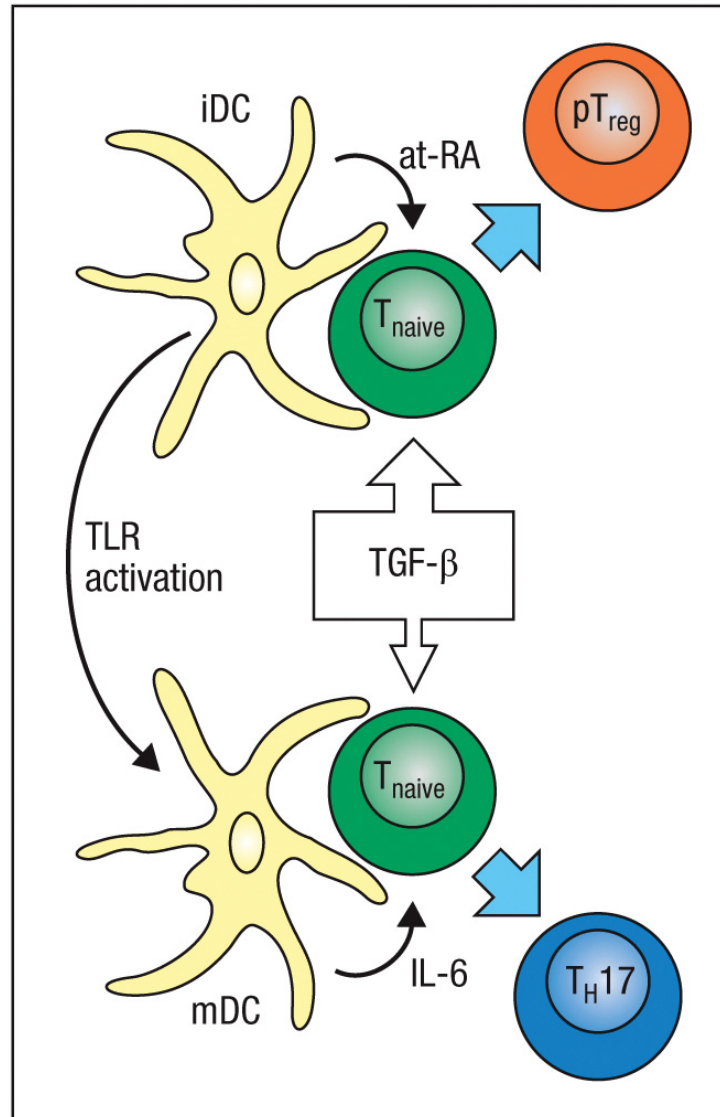




Strength of TCR Signalling



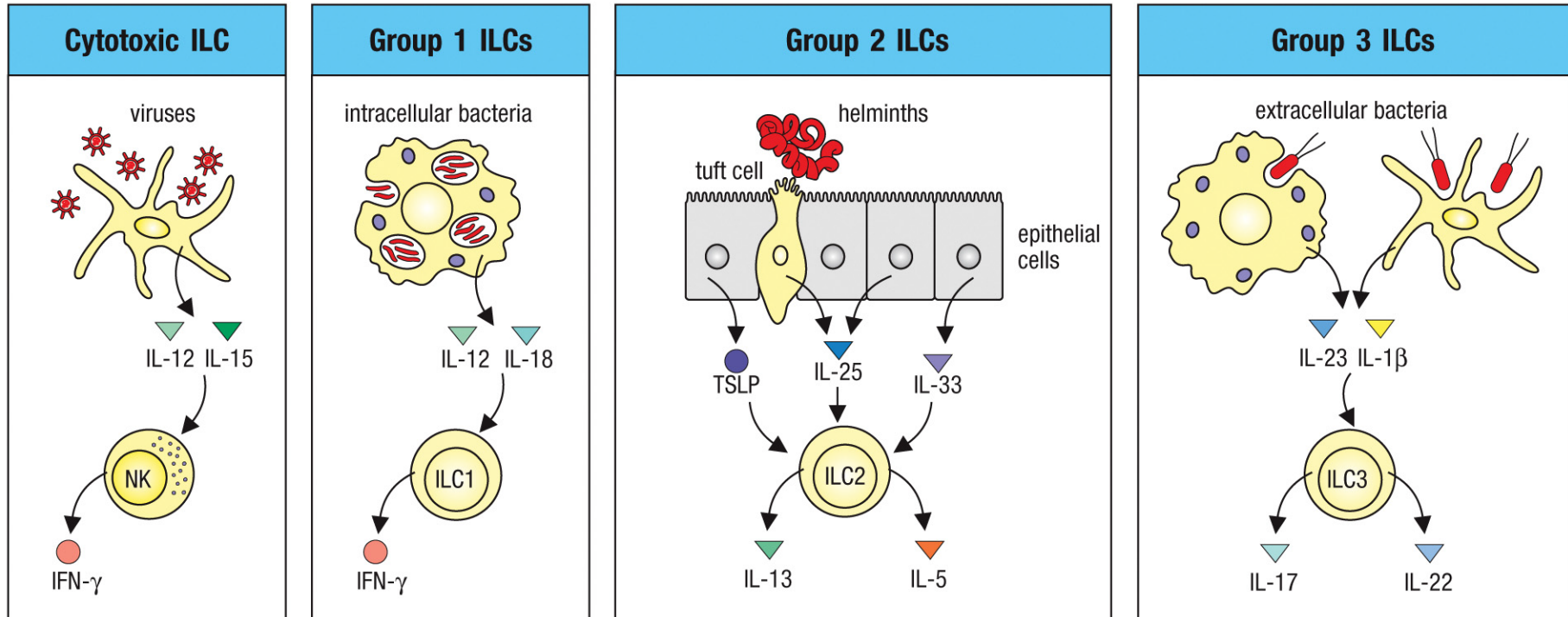
Infection Status Determines the Fate of T Cells



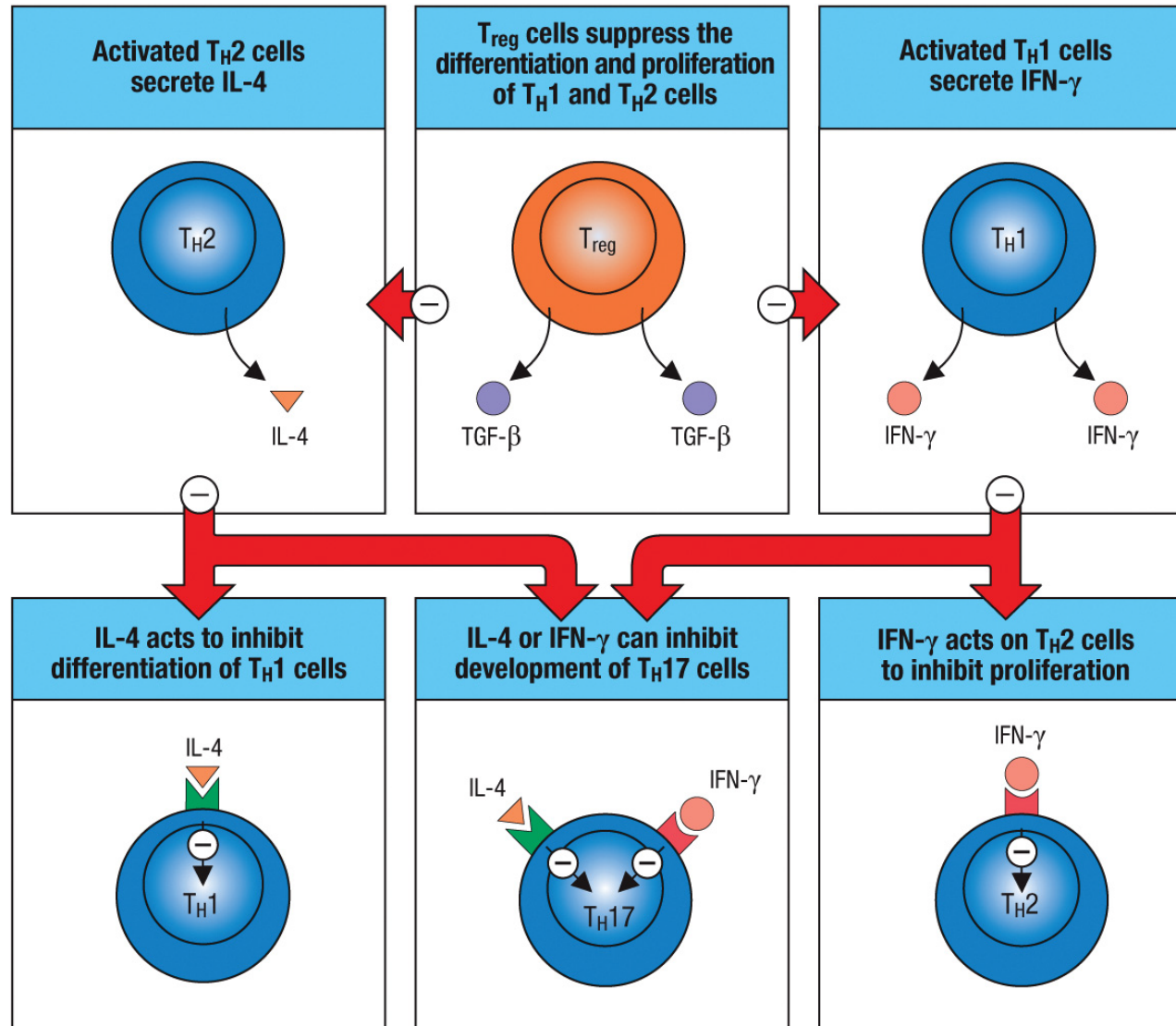
Induced regulatory T cells

All-tran retinoic acid

Innate Lymphoid Cells (ILCs)



Cytokines Sustain Specific T Cell Responses in the Periphery



T Cells Secret Cytokines

Pro-inflammatory

CD8 T cells: peptide + MHC class I						CD4 T cells: peptide + MHC class II			
Cytotoxic (killer) T cells		T _H 1 cells		T _H 2 cells		T _H 17 cells		T _{FH} cells	
Cytotoxic effector molecules	Others	Macrophage- activating effector molecules	Others	Barrier immunity- activating effector molecules	Others	Barrier immunity- activating effector molecules, neutrophil recruitment	Others	B-cell help	Others
Perforin Granzymes Granulysin Fas ligand	IFN- γ LT- α TNF- α	IFN- γ GM-CSF TNF- α CD40 ligand Fas ligand	IL-3 LT- α CXCL2 (GRO β)	IL-4 IL-5 IL-13 CD40 ligand	IL-3 GM-CSF IL-10 TGF- β CCL11 (eotaxin) CCL17 (TARC)	IL-17A IL-17F IL-22 CD40 ligand	IL-3 TNF- α GM-CSF CCL20	IL-21 IL-4 CD40 ligand	TNF- α LT- α CXCL13

Effects of T-Cell Cytokines

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hematopoietic cells	Other tissue cells	
Interleukin-2 (IL-2)	Naive, T _H 1, some CD8	Stimulates growth and J-chain synthesis	Growth and differentiation	–	–	–	↓T-cell responses IBD
Interferon- γ (IFN- γ)	T _H 1, T _{FH} , CTL	Differentiation IgG2a synthesis (mouse)	Inhibits T _H 2 and T _H 17 cell differentiation	Activation, ↑MHC class I and class II	Activates NK cells	Antiviral ↑MHC class I and class II	Susceptible to mycobacteria, some viruses
Lymphotoxin- α (LT- α , TNF- β)	T _H 1, some CTL	Inhibits	Kills	Activates, induces NO production	Activates neutrophils	Kills fibroblasts and tumor cells	Absence of lymph nodes Disorganized spleen
Interleukin-4 (IL-4)	T _H 2, T _{FH}	Activation, growth IgG1, IgE ↑MHC class II induction	Growth, survival	Promotes marginal zone macrophage activation	↑Growth of mast cells	–	No T _H 2
Interleukin-5 (IL-5)	T _H 2	Mouse: Differentiation IgA synthesis	–	–	↑Eosinophil growth and differentiation	–	Reduced eosinophilia
Interleukin-13 (IL-13)	T _H 2	IgG1, IgE class switch	–	Promotes marginal zone macrophage	–	↑Production of mucus (goblet cell)	Impaired helminth expulsion

Effects of T-Cell Cytokines

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hematopoietic cells	Other tissue cells	
Interleukin-17 (IL-17)	T _H 17, T _{FH}	Promotes IgG2a, IgG2b, IgG3 (mouse)	–	–	Stimulates neutrophil recruitment	Stimulates fibroblasts and epithelial cells to secrete chemokines	Impaired antibacterial defense
Interleukin-22 (IL-22)	T _H 17	–	–	–	–	Stimulates mucosal epithelium and skin to produce antimicrobial peptides	Impaired antibacterial defense
Interleukin-21 (IL-21)	T _{FH} , some T _H 1, T _H 17, CTL	Stimulates B-cell growth, germinal center formation, IgG class switching	Promotes CTL memory	–	–	–	Deficient antibody responses
Transforming growth factor- β (TGF- β)	T _{reg} , T _{FH}	Inhibits growth IgA switch factor	T _H 17 and iT _{reg} differentiation, inhibits T _H 1 and T _H 2	Inhibits activation	Activates neutrophils	Inhibits/ stimulates cell growth	Death at ~10 weeks
Interleukin-10 (IL-10)	T _{reg} , some T _H 1, T _H 2, T _H 17, CTL	↑MHC class II	Inhibits T _H 1	Inhibits cytokine release	Co-stimulates mast cell growth	–	IBD

Effects of T-Cell Cytokines

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hematopoietic cells	Other tissue cells	
Transforming growth factor- β (TGF- β)	T_{reg} , T_{FH}	Inhibits growth IgA switch factor	T_H17 and iT_{reg} differentiation, inhibits T_H1 and T_H2	Inhibits activation	Activates neutrophils	Inhibits/ stimulates cell growth	Death at ~10 weeks
Interleukin-10 (IL-10)	T_{reg} , some T_H1 , T_H2 , T_H17 , CTL	$\uparrow$ MHC class II	Inhibits T_H1	Inhibits cytokine release	Co-stimulates mast cell growth	–	IBD
Interleukin-3 (IL-3)	T_H1 , T_H2 , T_H17 , some CTL	–	–	–	Growth factor for progenitor hematopoietic cells (multi-CSF)	–	–
Tumor necrosis factor- α (TNF- α)	T_H1 , T_H17 , some T_H2 , some CTL	–	–	Activates, induces NO production	–	Activates microvascular endothelium	Susceptibility to Gram + sepsis
Granulocyte– macrophage colony-stimulating factor (GM-CSF)	T_H1 , T_H17 , some T_H2 , some CTL	Differentiation	Inhibits growth?	Activation Differentiation to dendritic cells	$\uparrow$ Production of granulocytes and macrophages (myelopoiesis) and dendritic cells	–	–

Question

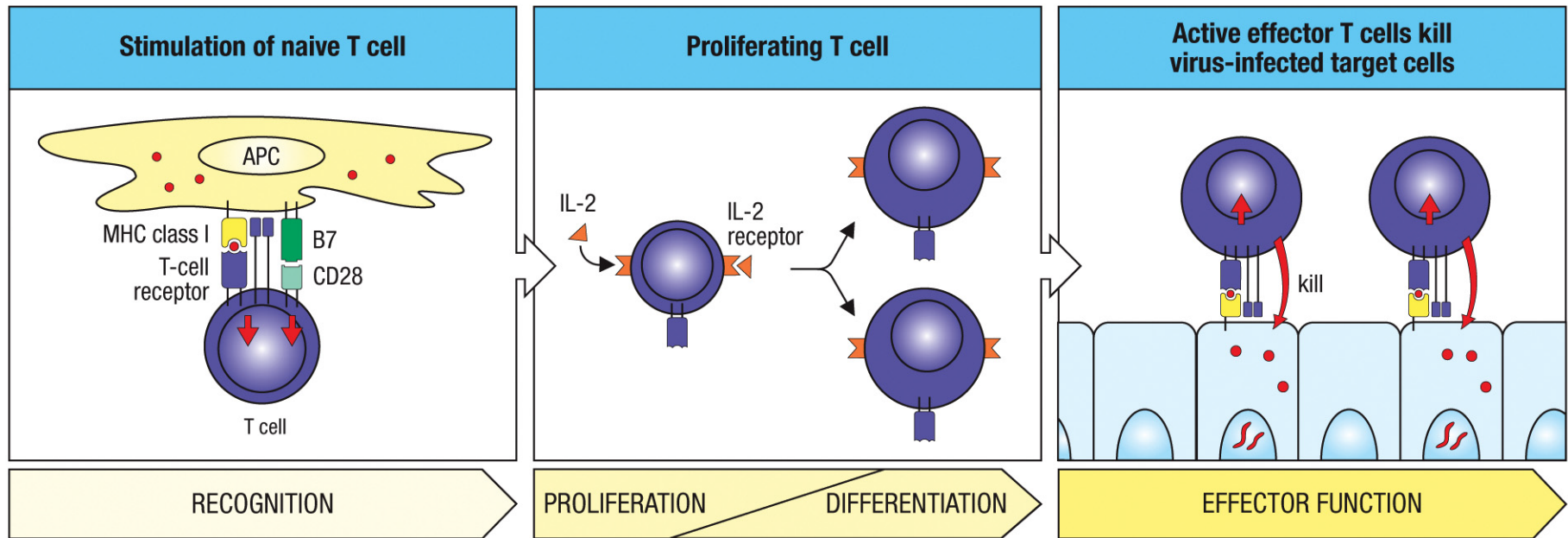
- What are the major subtypes of CD4+ T cells? And their function?
- Which cytokines are required to promote their differentiation, respectively?

Outline

T cell mediated immunity

- T cell differentiation
- T cell-mediated cytotoxicity
- Macrophage activation by T_H1 cells
- Peripheral Tolerance

CD8 T Cells

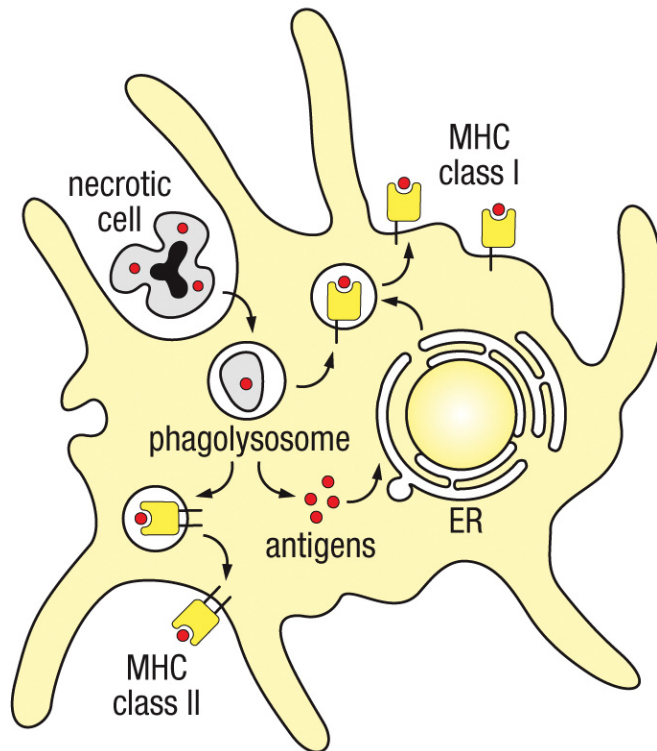


Priming
In lymph nodes

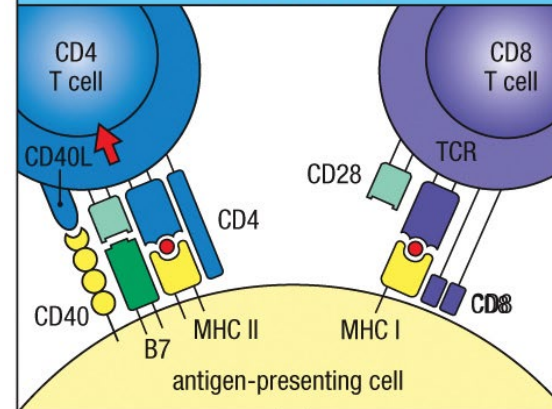
At infection site

Most CD8 T-Cell Responses Require CD4 T-Cells

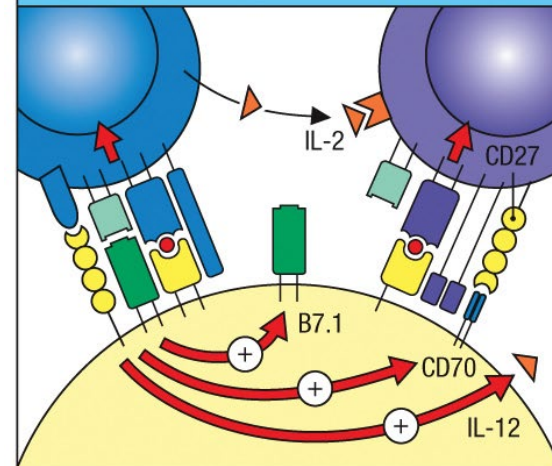
Antigens taken up by cDC1 during cross-presentation may activate both naive CD8 and CD4 T cells



APC stimulates effector CD4 T cell to induce the expression of CD40L and IL-2



Stimulation of APC through CD40 increases B7 and CD70, which both co-stimulate the naive CD8 T cell, and also increases APC production of IL-12



CD8 T-Cell Memory Requires CD4 T-Cells

With a pathogen that induce an severe acute infection, effector T cells are generated, but not the memory T cells.

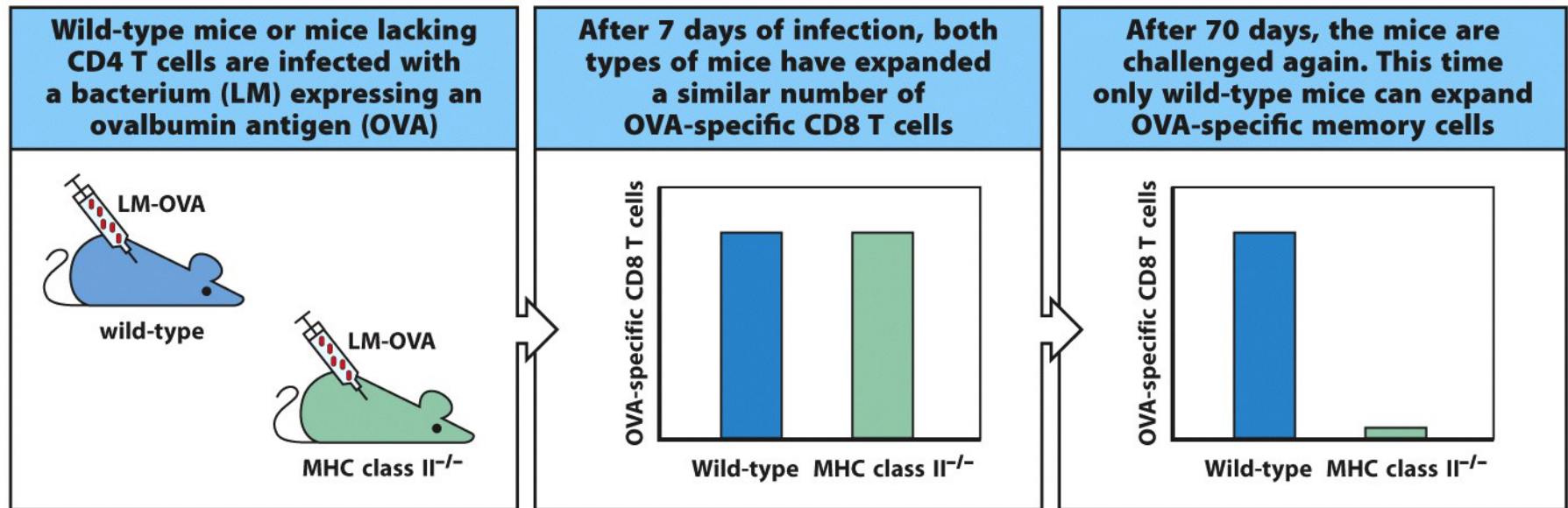
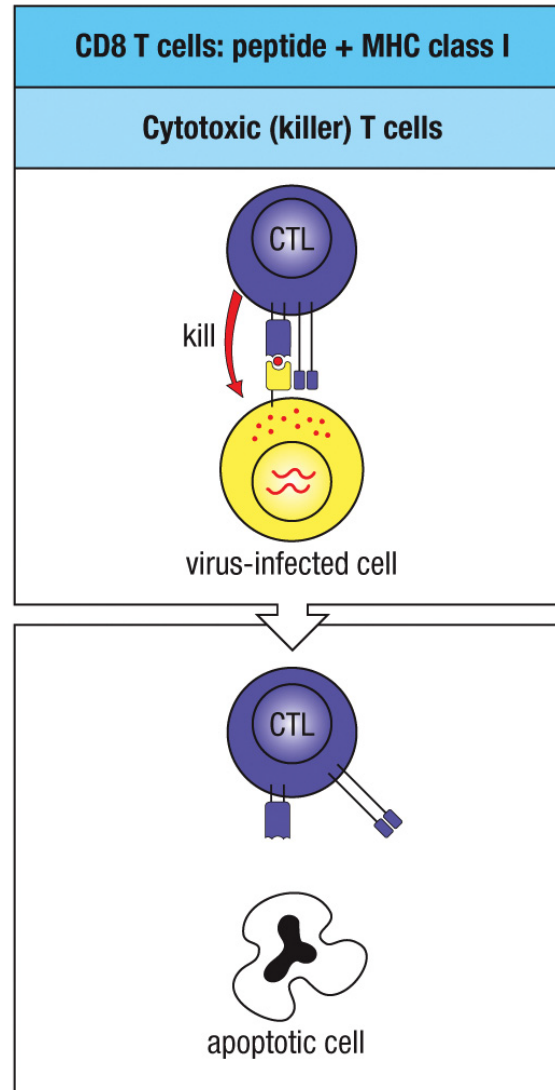


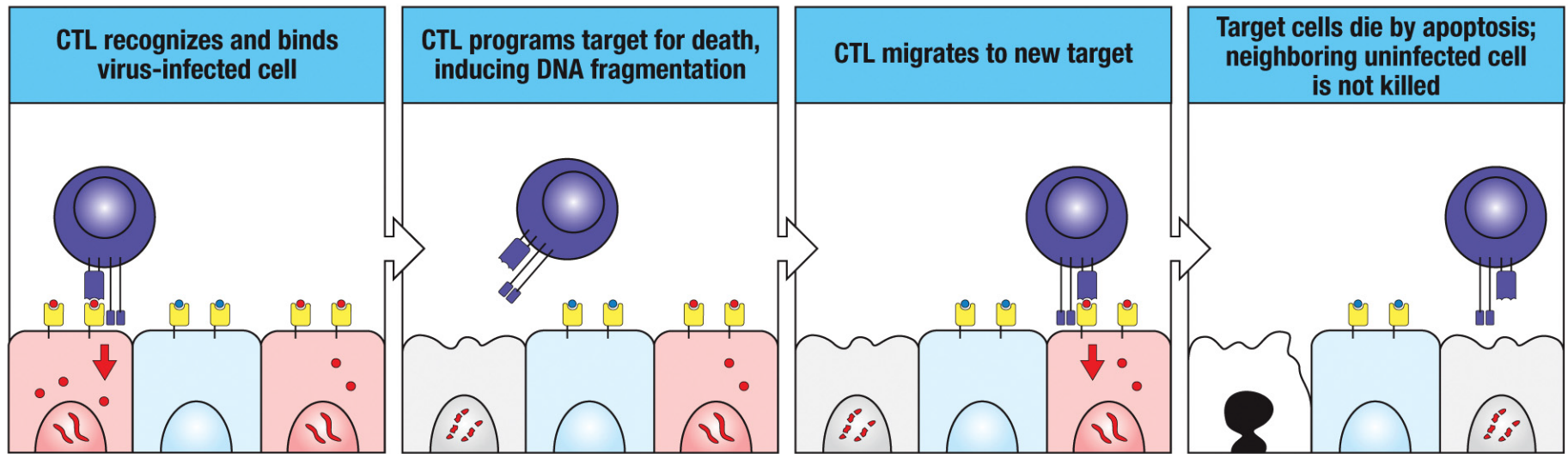
Figure 11.26 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

CD8 T Cells

Target killing does not require co-stimulation

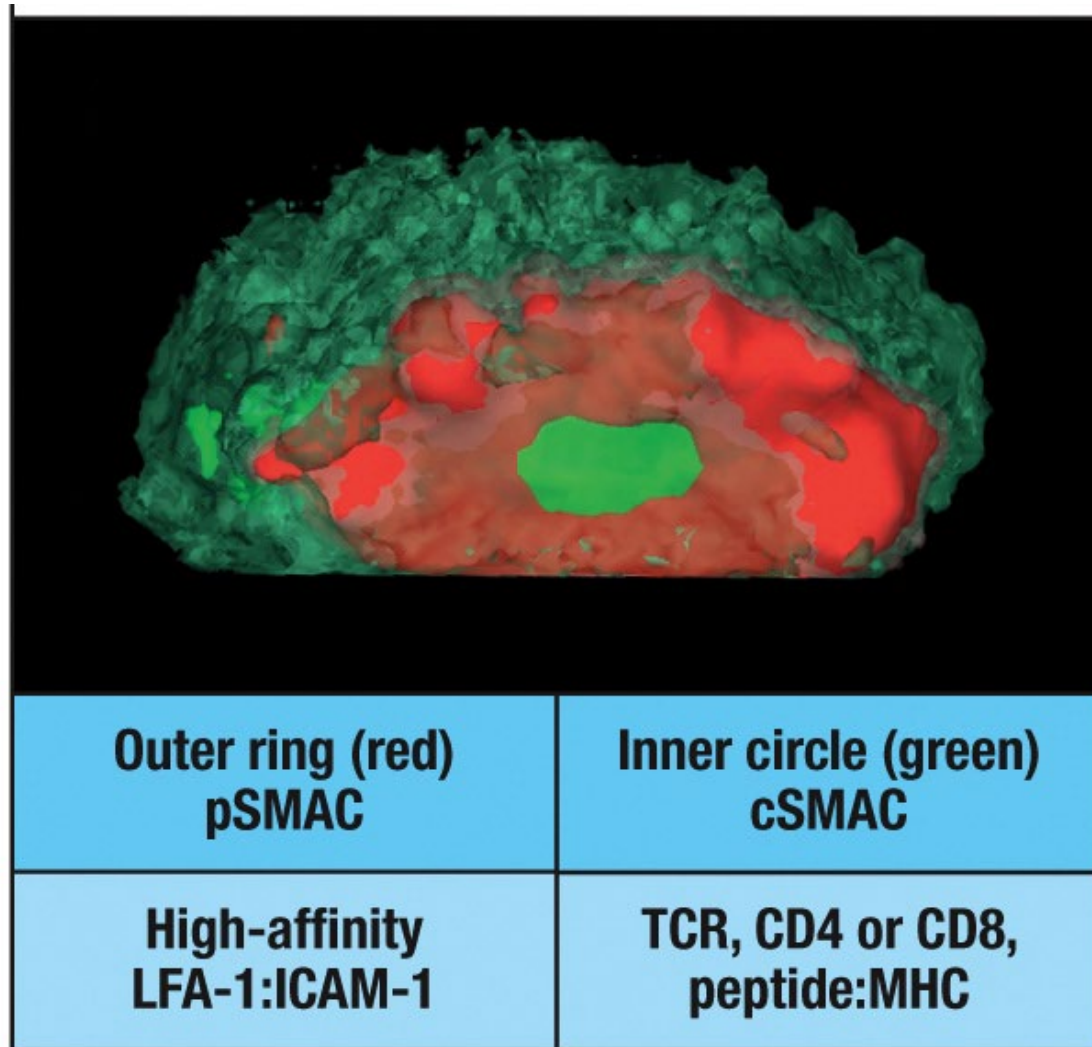


Cytotoxic T Cells are Serial Killers



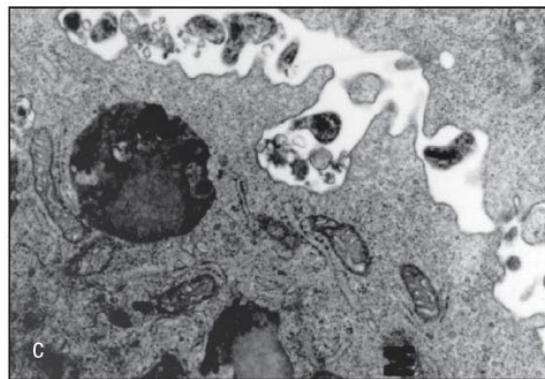
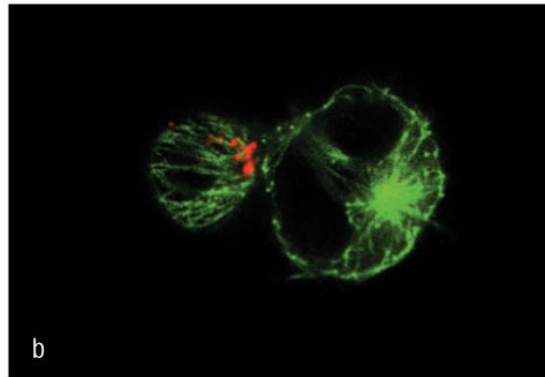
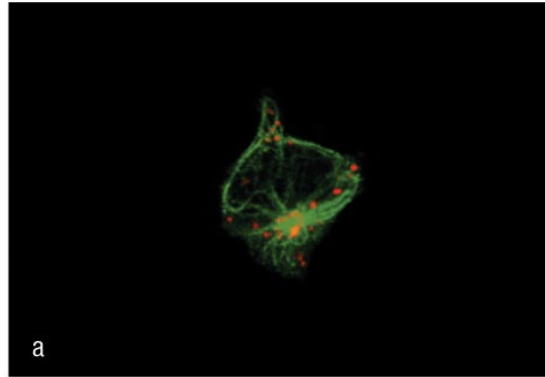
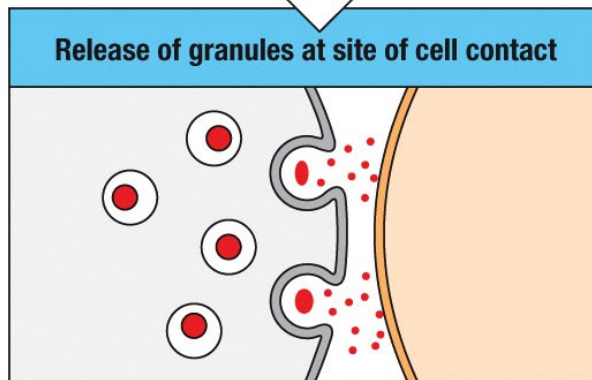
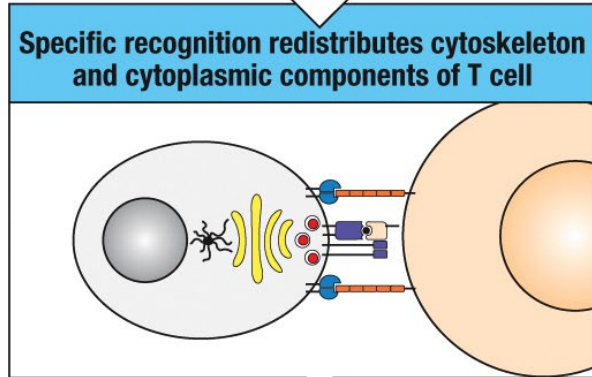
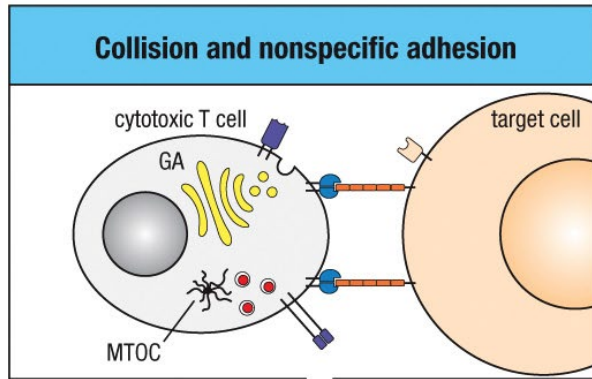
Immunological Synapse

supramolecular adhesion complex



Photograph courtesy of Avi Kupfer

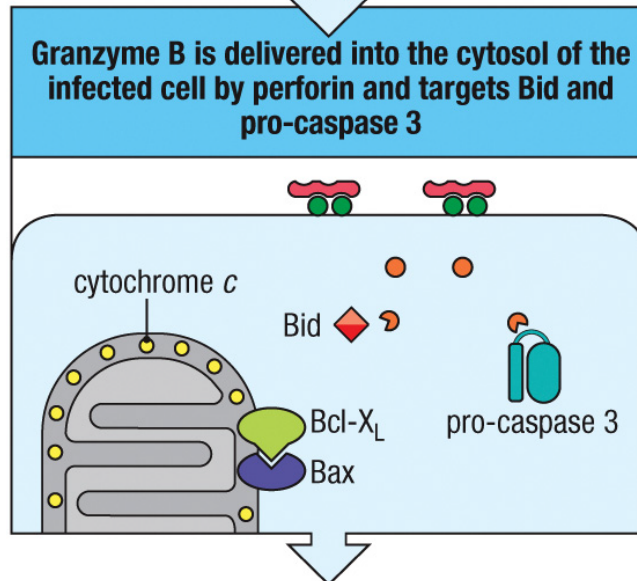
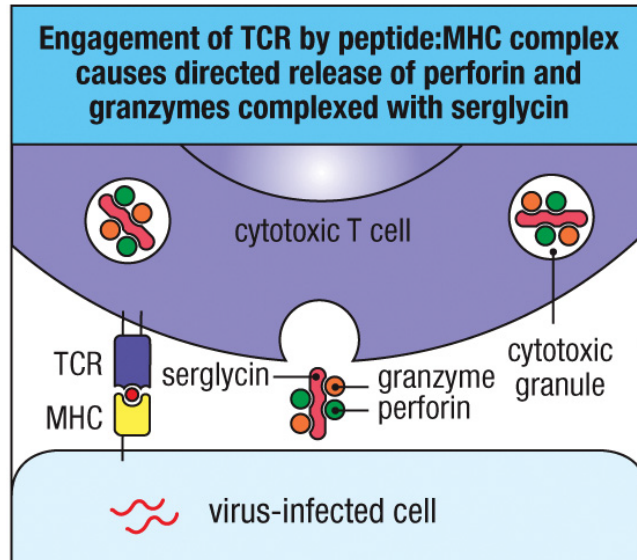
Polarization of T-Cells During Antigen Recognition



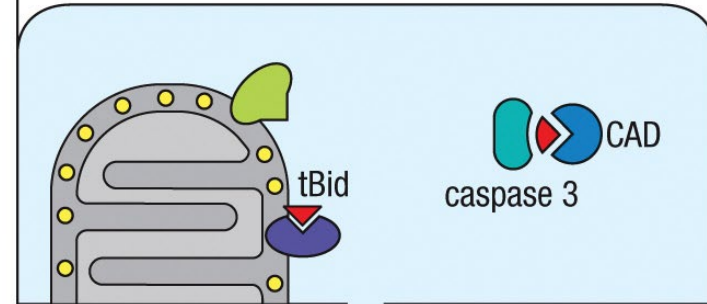
(a, b): Gillian Griffiths; (c): Photo courtesy of Eckhard Podack via Kristin Podack

Cytotoxic granules
Microtubules

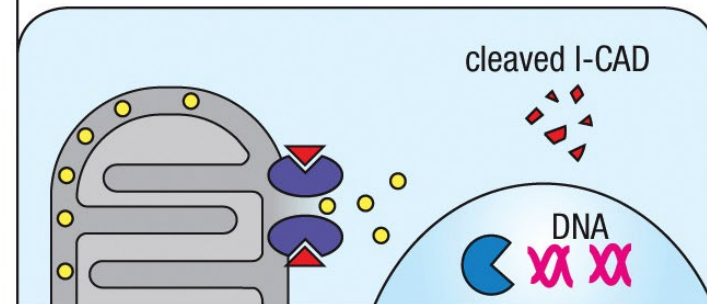
Granzyme Induced Apoptosis



Truncated Bid (tBid) displaces Bcl-X_L as it binds Bax, inducing Bax oligomerization. Activated caspase 3 cleaves I-CAD, releasing caspase-activated DNase (CAD)



Release of cytochrome *c* into cytosol via Bax pores activates the apoptosome, further activating caspase 3 and cleaving I-CAD to induce DNA fragmentation



Question

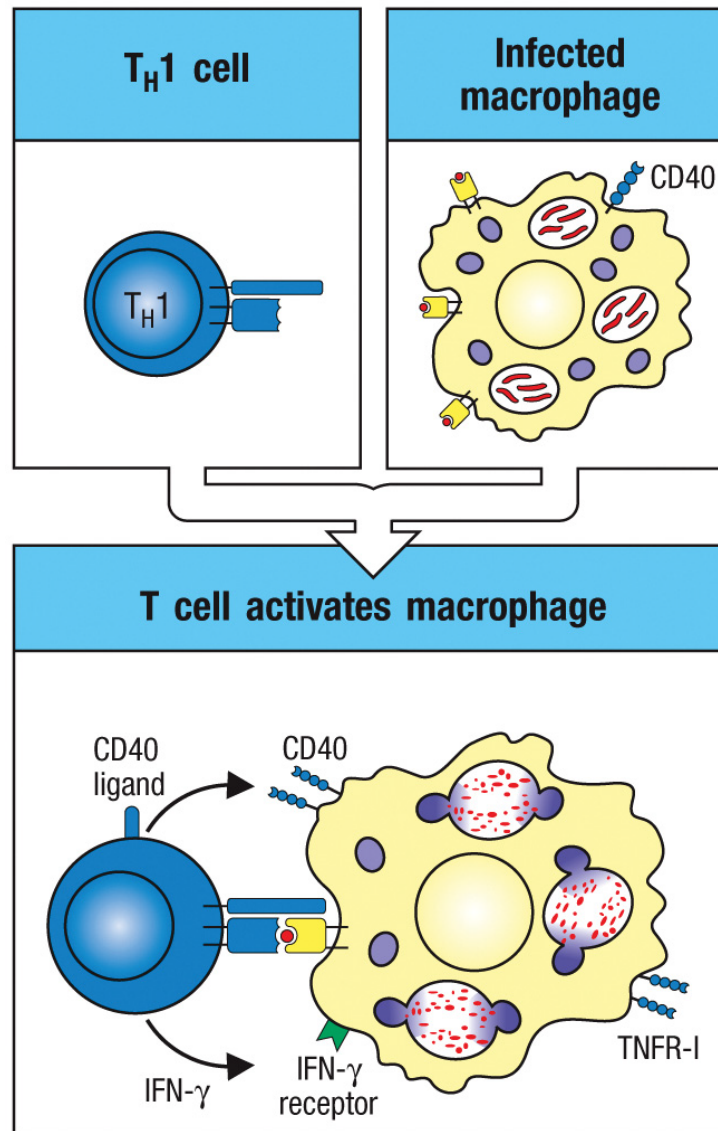
- How do CD4 T cells help CD8 T cells to become activated in the lymph node?

Outline

T cell mediated immunity

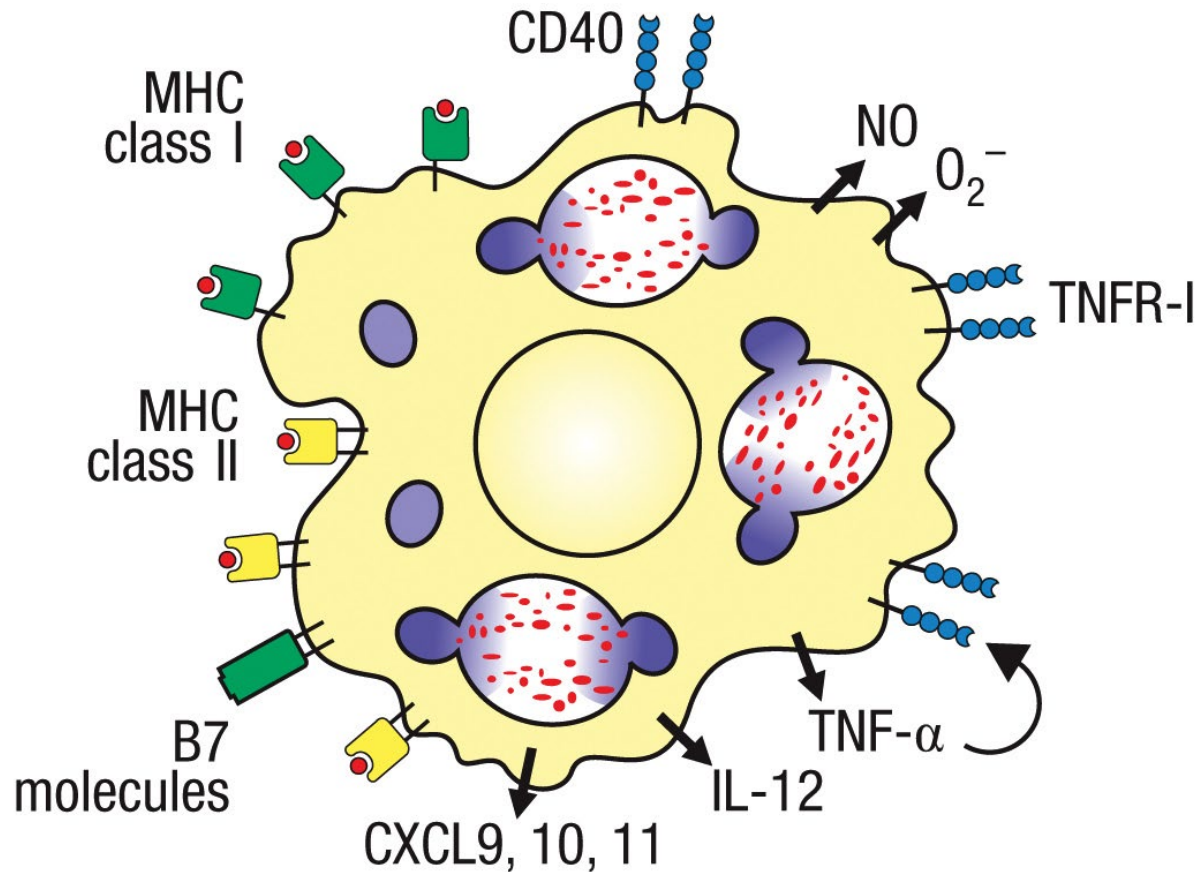
- T cell differentiation
- T cell-mediated cytotoxicity
- Macrophage activation by T_H1 cells
- Peripheral Tolerance

T_H1 Cells Activate Infected Macrophages

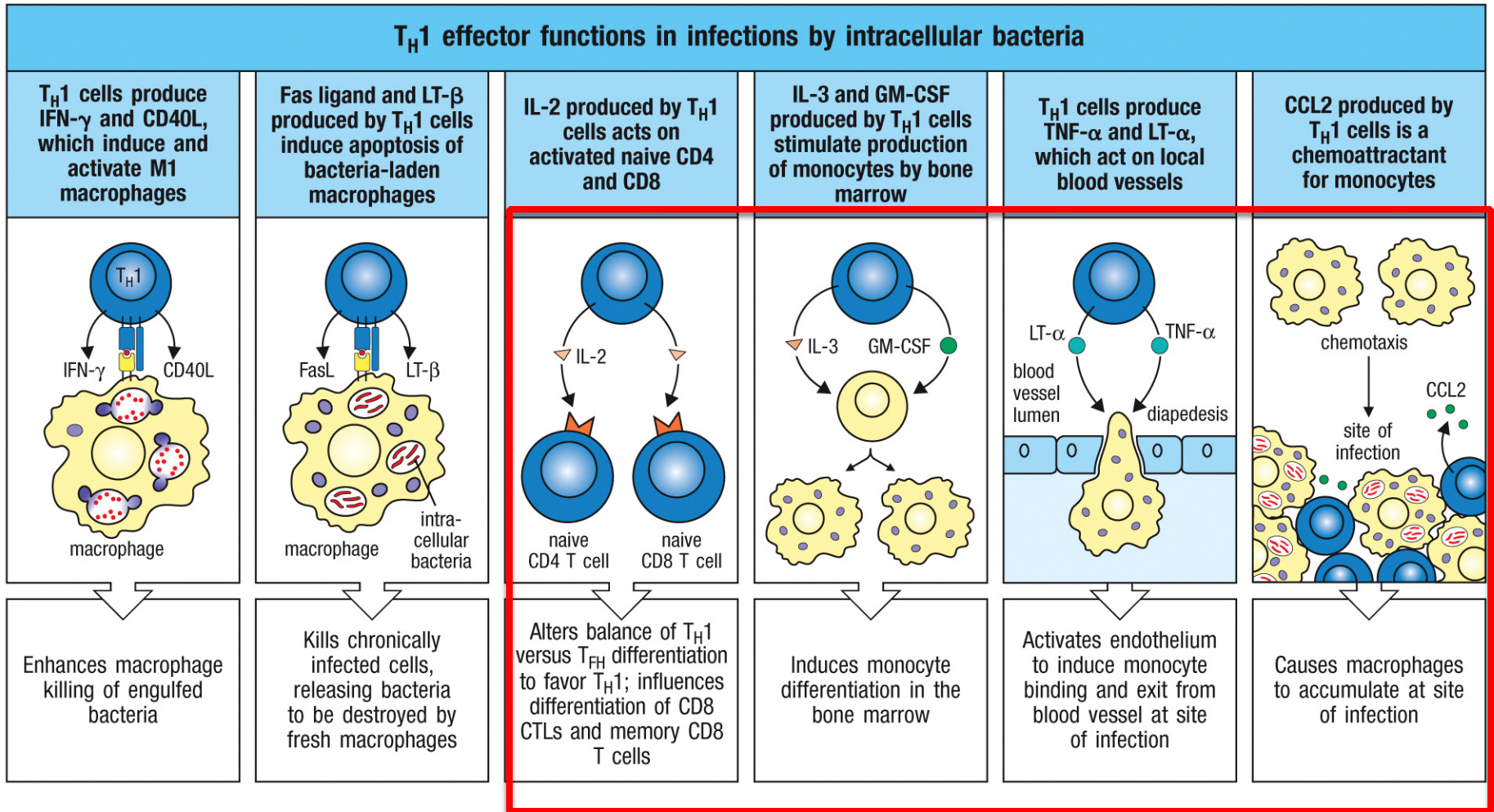


Macrophages Activated by T_H1 Cells Are Highly Microbicidal

Activated M1 macrophage



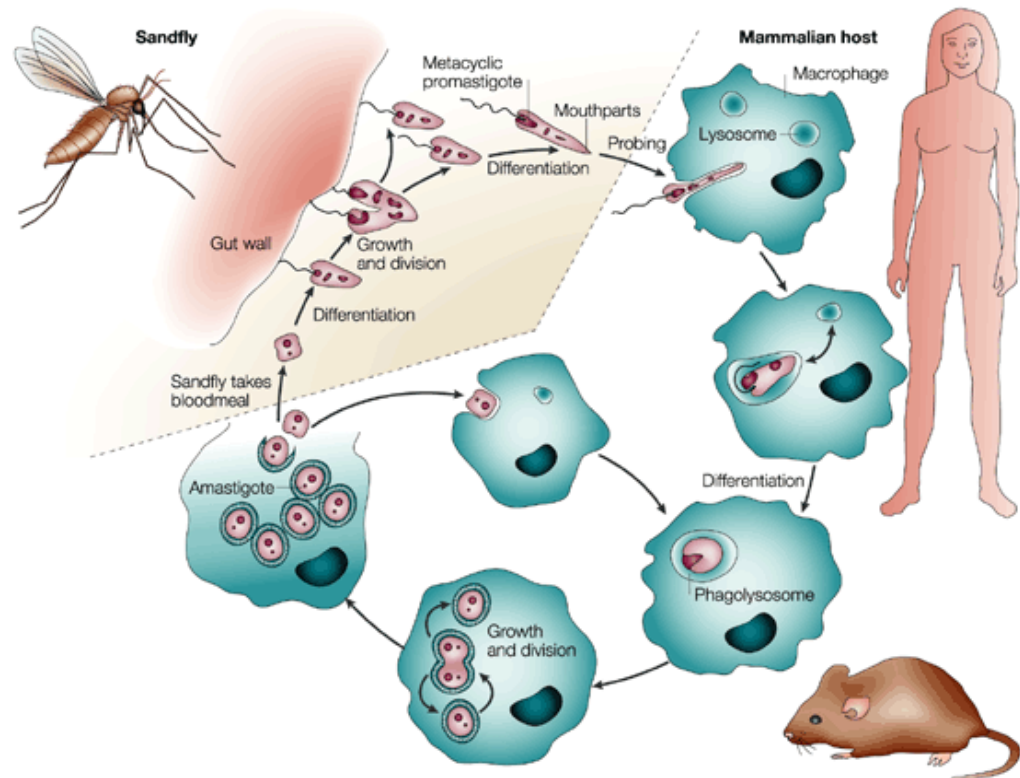
Responses to Intravascular Pathogens Are T_H1 Dependent



Increase the number of effector cells at infection site
Proinflammatory

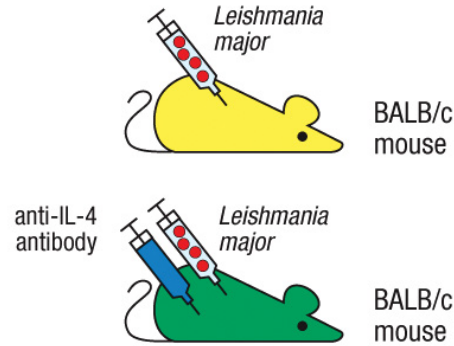
Leishmania major

- *L. major* is an intracellular pathogen which infects the macrophages and dendritic cells.

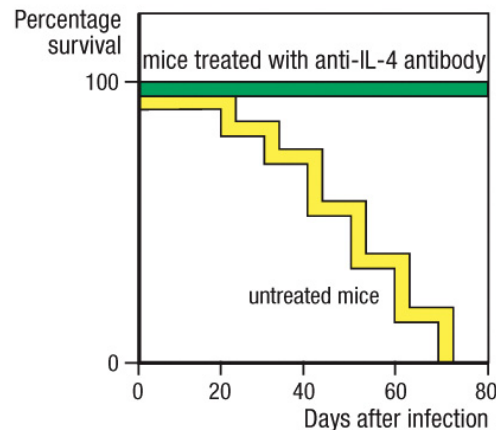


Responses to Intravascular Pathogens Are T_H1 Dependent

BALB/c mice are infected with *Leishmania major*, either with or without administration of an antibody that blocks IL-4



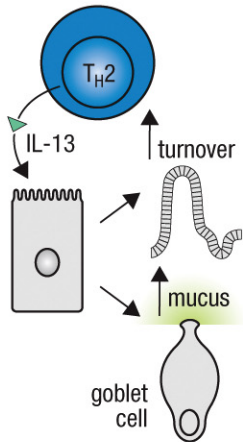
Untreated BALB/c mice develop a T_H2 response that impairs elimination of the infection and leads to death. Mice treated with anti-IL-4 antibody develop a T_H1 response that eliminates the parasite and they survive



T_H2 Cells in Helminth Infection

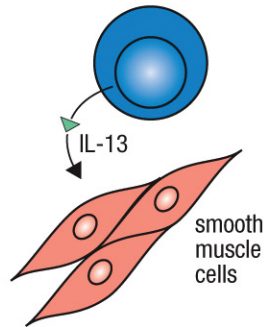
T_H2 cell effector functions in helminth infections

T_H2 cells produce IL-13, which induces epithelial cell repair and mucus



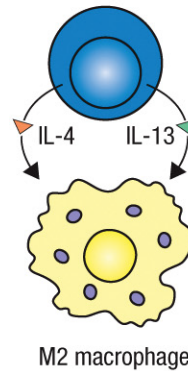
Increased cell turnover and movement helps shedding of parasitized epithelial cells. Mucus prevents adherence and accelerates loss of parasite

IL-13 produced by T_H2 cells increases smooth muscle contractility that enhances worm expulsion



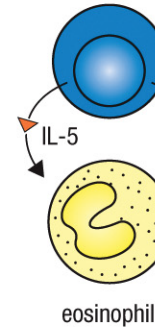
Increased contractility of mucosal smooth muscle enhances worm expulsion

T_H2 cells recruit and activate M2 macrophages via IL-4 and IL-13



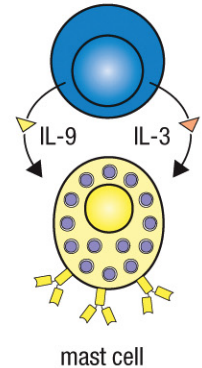
Products of arginase-1 expressed by M2 macrophages increase smooth muscle contraction and enhance tissue remodeling and repair

IL-5 produced by T_H2 cells recruits and activates eosinophils



Eosinophils produce MBP, which kills parasites. They can also mediate ADCC using parasite-specific Ig

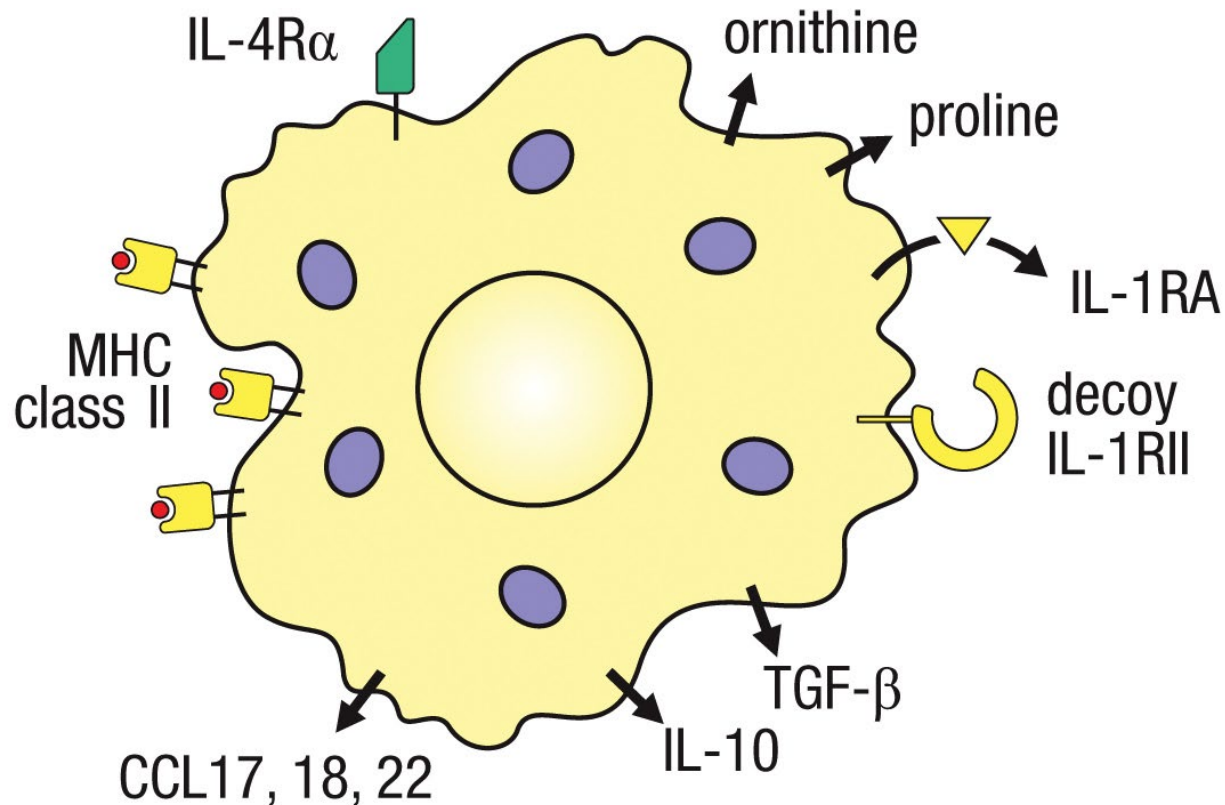
T_H2 cells drive mast cell recruitment via IL-3, IL-9. Specific IgE arms mast cells against helminths



Mast cells produce mediators such as histamine, TNF- α , and MMCP. These recruit inflammatory cells and remodel the mucosa

M2 Macrophages

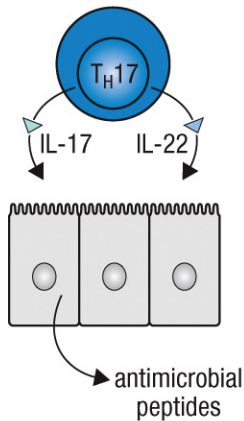
Alternatively activated, M2 macrophage



T_H17 Cells in Extracellular Bacterial Infection

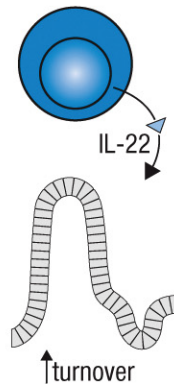
T_H17 effector functions in infections by extracellular bacteria

IL-17 and IL-22 produced by T_H17 cells induce the production of antimicrobial peptides by epithelial cells



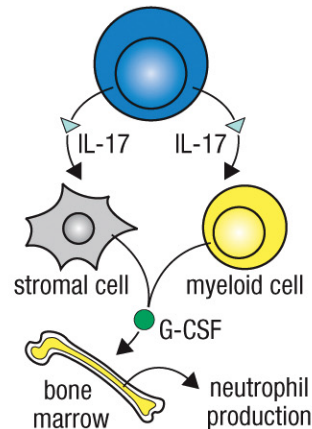
Direct killing or growth inhibition of bacteria attached to the epithelium

IL-22 produced by T_H17 cells increases epithelial cell turnover



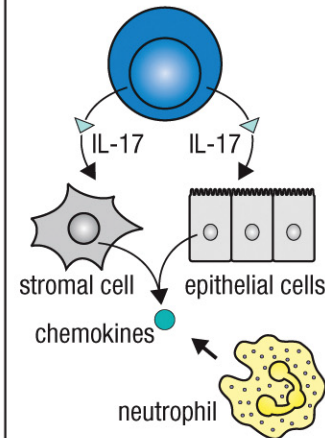
Increased epithelial cell division and shedding impairs bacterial colonization

IL-17 produced by T_H17 cells activates stromal cells and myeloid cells to produce G-CSF, which stimulates neutrophil production in bone marrow



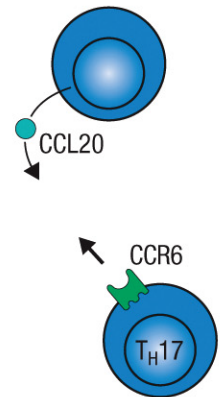
Increases numbers of circulating neutrophils to sustain supply of short-lived innate effectors at infection site

IL-17 produced by T_H17 cells activates stromal cells and epithelial cells to produce chemokines that recruit neutrophils



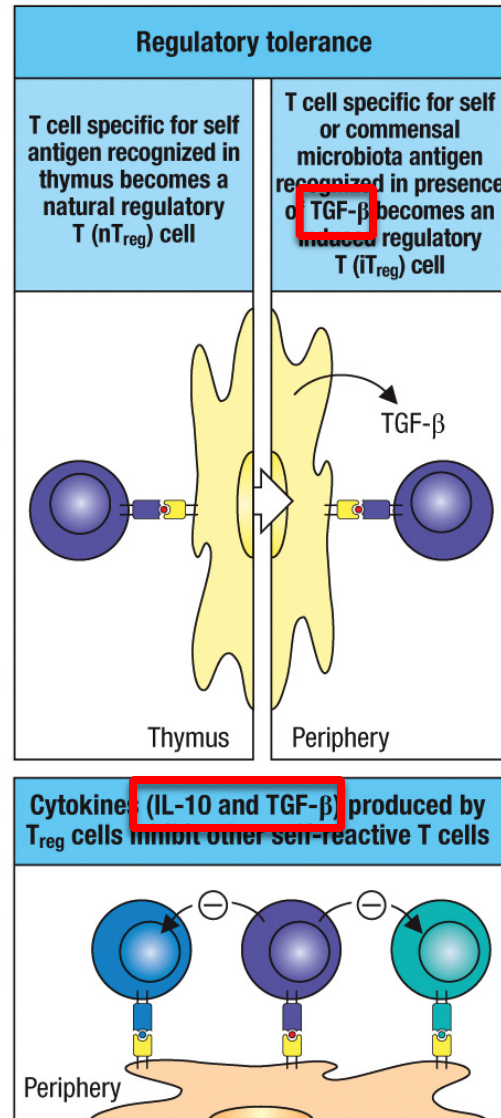
Recruitment of neutrophils to the site of infection

CCL20 produced by T_H17 cells is a chemoattractant for other T_H17 cells



Increased recruitment of T_H17 cells to site of infection

Regulatory T Cells



IPEX: Case Study

Patient:

- atopic dermatitis shortly after birth
- diarrhea and type I diabetes
- Enlarged lymph nodes and autoantibodies

Family history:

- A sibling died in infancy

Diagnosis:

- Missense mutation in FOXP3 gene

IPEX



Figure 18.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

IPEX

- IPEX: Immune dysregulation, polyendocrinopathy, enteropathy X- linked disease
 - Lack of T reg
 - Targeting self organs
 - Endocrine, platelet, skin, etc

Question

- Can IPEX be treated with bone marrow transplantation ?
- A) yes
- B) no

Case Study-Lepromatous Leprosy

- Patient:
 - 18 year old female
 - Hypopigmentation
 - Hair loss
 - Nose bleed
 - Regional lepromatous leprosy
- Diagnosis:
 - Acid-fast bacilli from biopsy
- Treatment:
 - Drugs that kill *M. leprae*

Cutaneous Nodules

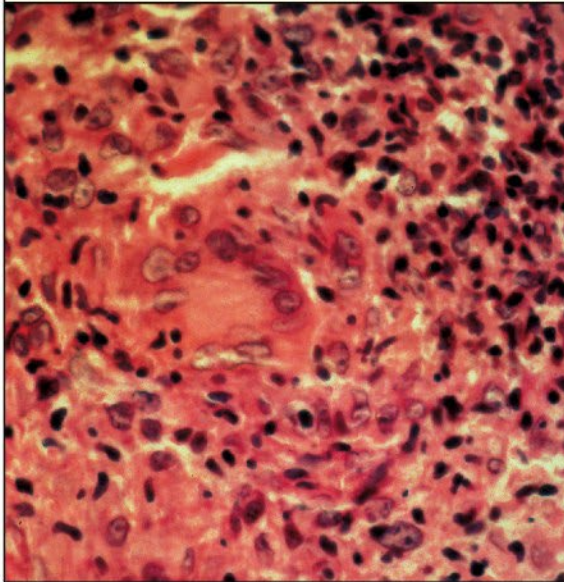


Figure 48.3 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Infection with *Mycobacterium leprae* can result in different clinical forms of leprosy

There are two polar forms, tuberculoid and lepromatous leprosy, but several intermediate forms also exist

Tuberculoid leprosy



Organisms present at low to undetectable levels

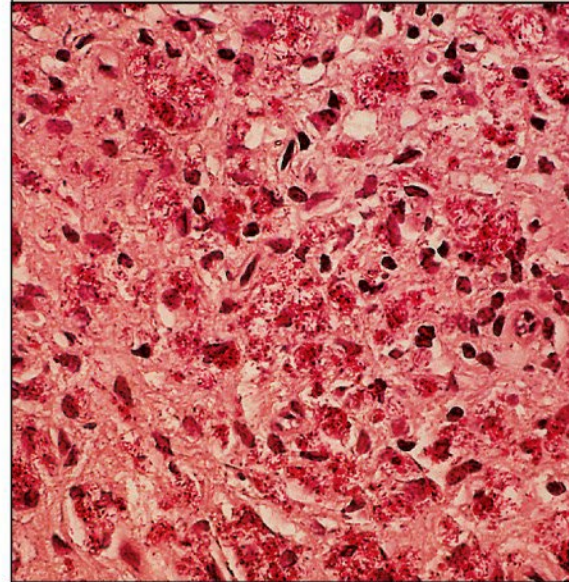
Low infectivity

Granulomas and local inflammation.
Peripheral nerve damage

Normal serum immunoglobulin levels

Normal T-cell responsiveness.
Specific response to *M. leprae* antigens

Lepromatous leprosy



Organisms show florid growth in macrophages

High infectivity

Disseminated infection.
Bone, cartilage, and diffuse nerve damage

Hypergammaglobulinemia

Low or absent T-cell responsiveness.
No response to *M. leprae* antigens

Figure 48.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Two Types of Leprosy

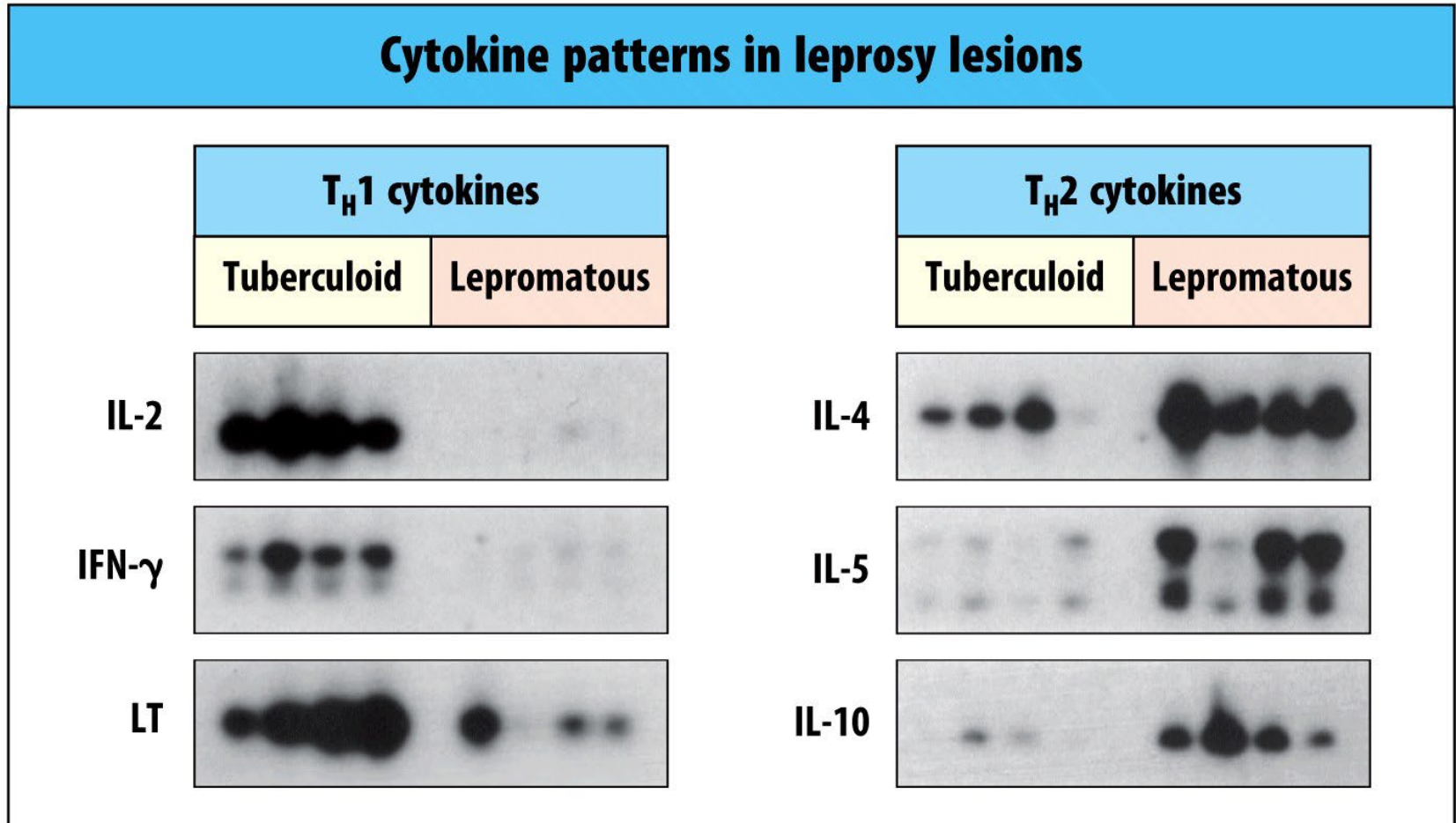


Figure 48.5 Case Studies in Immunology, 6ed. (© Garland Science 2012)

What's Wrong with the Patient?

- Mounting of a Th2 response with does not contain an infection in macrophage phagosomes.

Question

- What can you do to tweak the Th1 vs Th2 response?