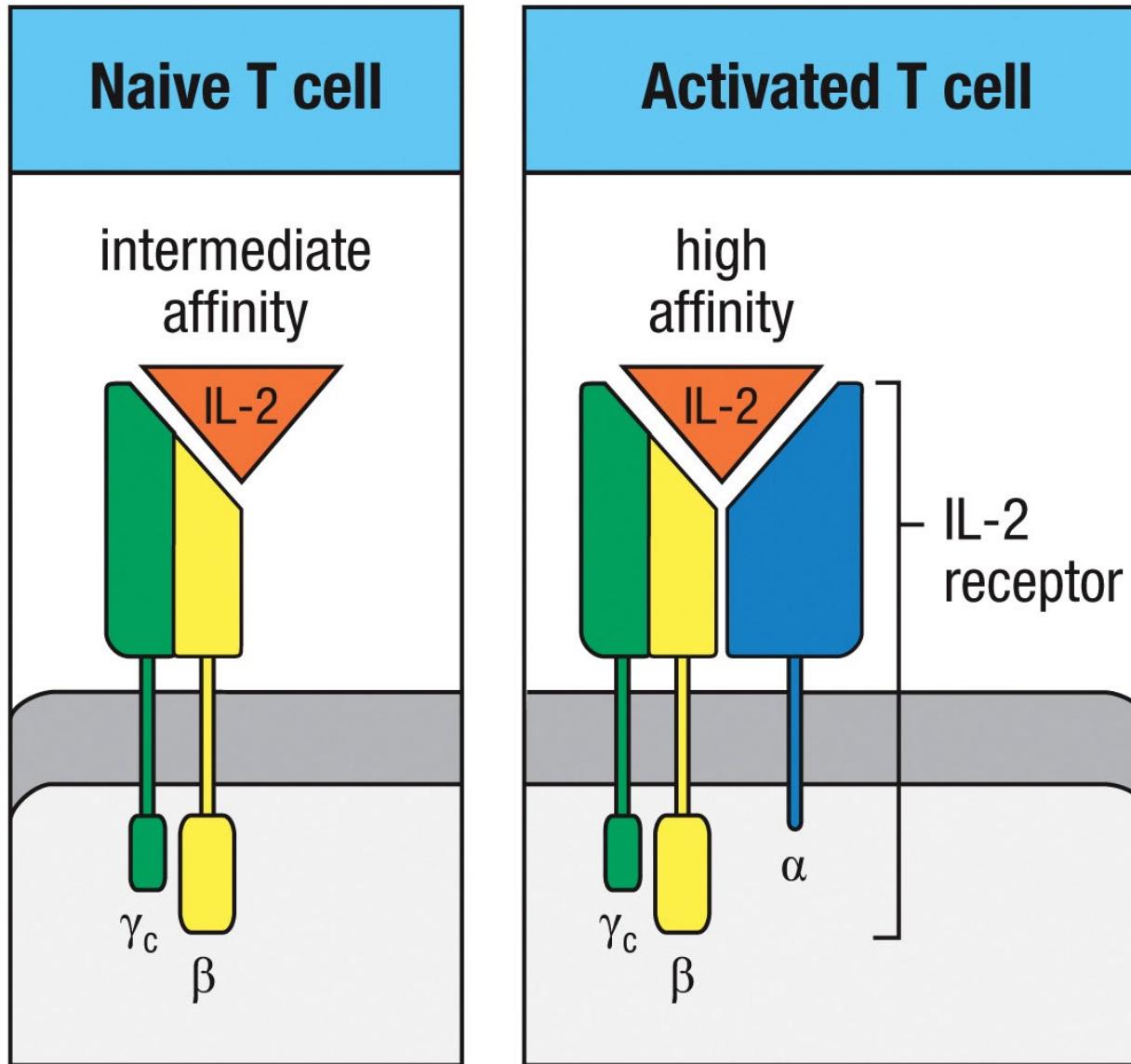


IL-2 Promotes Cell Growth and Differentiation



Outline

T cell mediated immunity

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

Effector T Cells

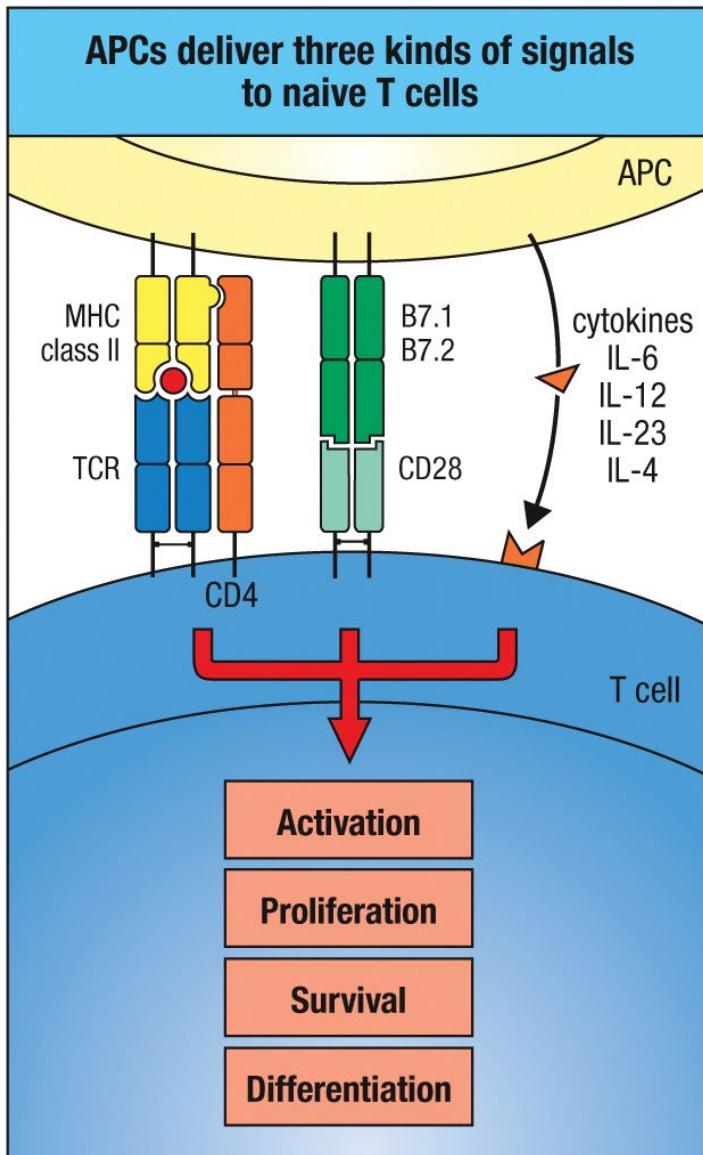
Types of effector T cell	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_{H17} cells	T_{FH} cells	CD4 regulatory T cells (various types)
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide 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)

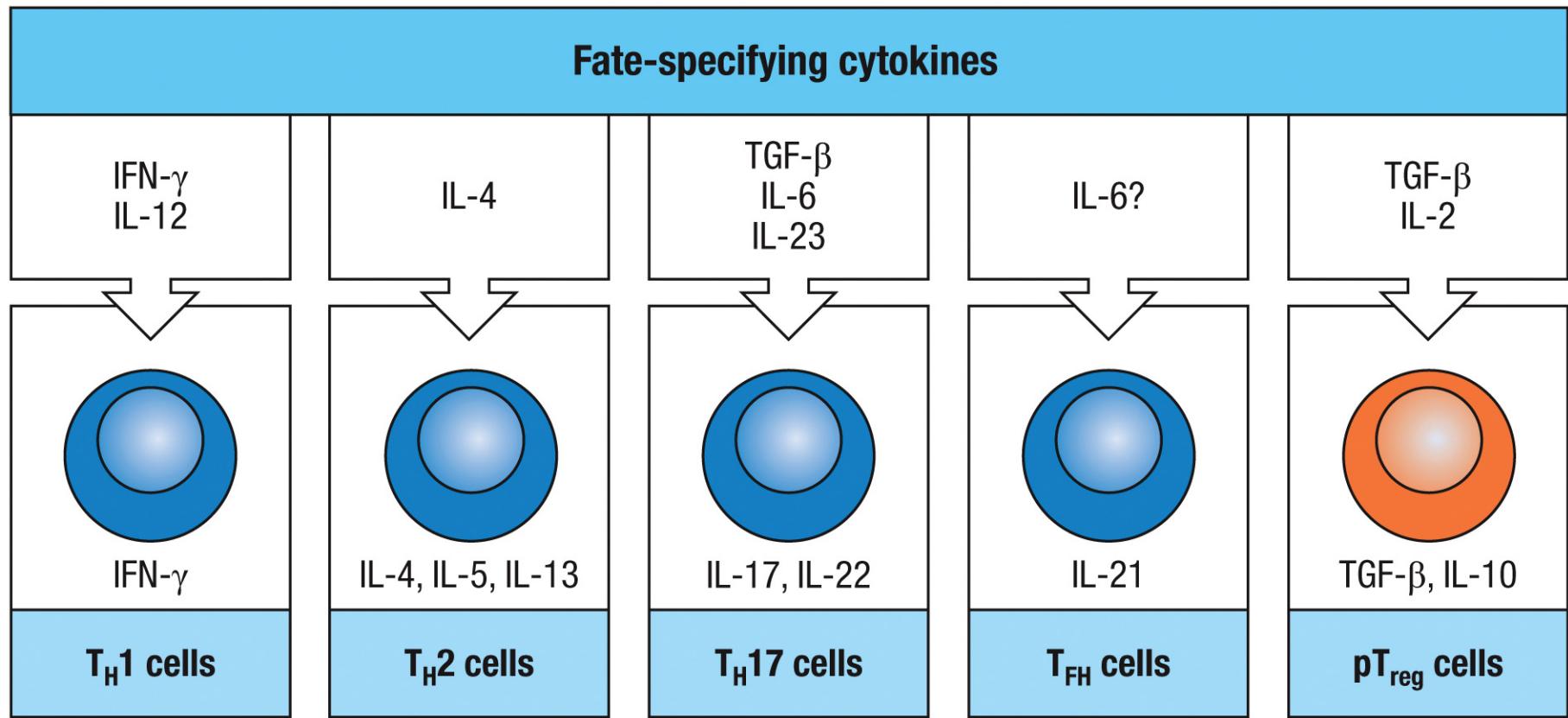
Different Types of T-Cells Are Specialized to Deal with Different Classes of Pathogens

	CD4 T cells: peptide + MHC class II				
	T _H 1 cells	T _H 2 cells	T _H 17 cells	T _{FH} cells	T _{reg} cells
Major cytokines and their actions	<p>T_H1</p> <p>IFN-γ</p> <p>macrophage</p> <p>intracellular bacteria</p>	<p>T_H2</p> <p>IL-4, IL-5 mucus</p> <p>bone marrow</p> <p>goblet cell</p>	<p>T_H17</p> <p>IL-17</p> <p>IL-22</p> <p>stromal cells</p> <p>G-CSF, chemokines</p> <p>epithelial cells</p> <p>antimicrobial peptides</p>	<p>T_{FH}</p> <p>IL-21</p> <p>B cell</p> <p>IgM</p>	<p>T_{reg}</p> <p>TGF-β</p> <p>conventional dendritic cell</p> <p>IL-10</p>
Immune cell types targeted for enhanced recruitment/ function	<p>dead intracellular bacteria</p> <p>eosinophil</p> <p>mast cell</p> <p>basophil</p> <p>neutrophils</p>			<p>IgG</p> <p>B cell</p> <p>plasma cell</p> <p>isotype switching, affinity maturation</p>	<p>CD4 T</p> <p>lack of T-cell activation</p>
Source of antigens targeted	<p>Microbes that resist macrophage killing (e.g., mycobacteria, <i>Listeria</i>, <i>Leishmania</i>, <i>Pneumocystis</i>)</p> <p>Extracellular bacteria</p>	<p>Helminth parasites</p>	<p>Extracellular bacteria (e.g., <i>Klebsiella pneumoniae</i>)</p> <p>Fungi (<i>Candida albicans</i>)</p>	<p>Nearly all microbes</p>	<p>Self and microbiome-derived</p>

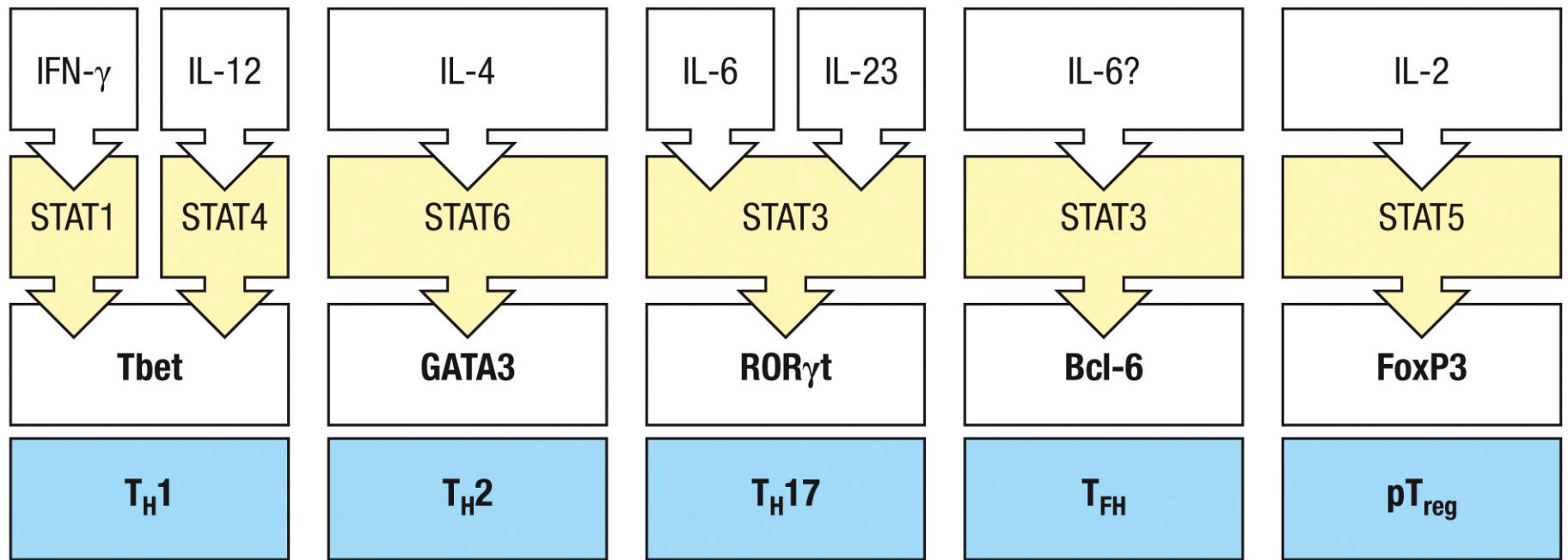
Activation of Naïve T Cells

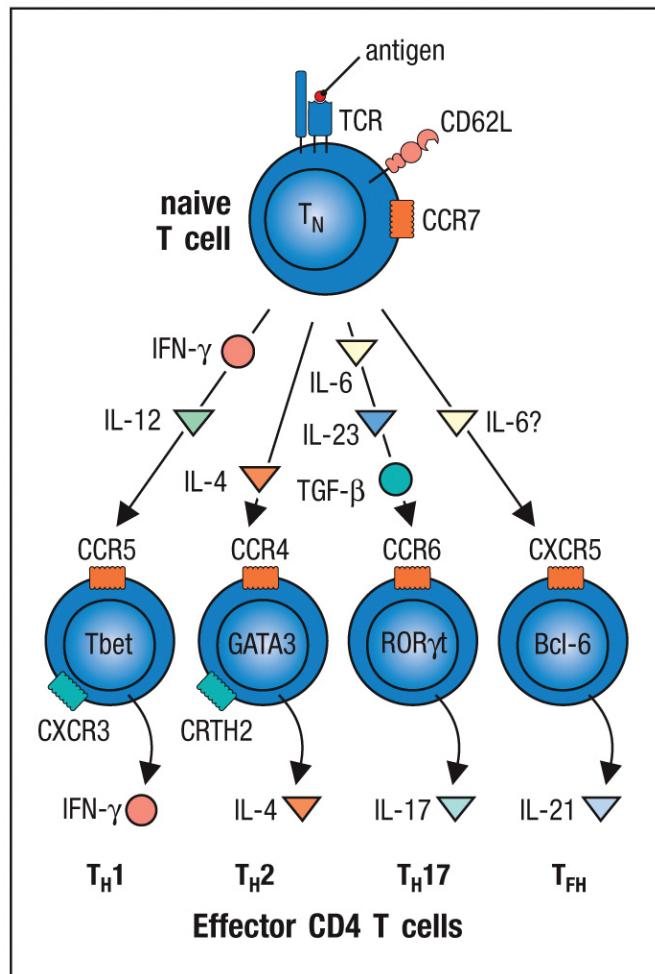


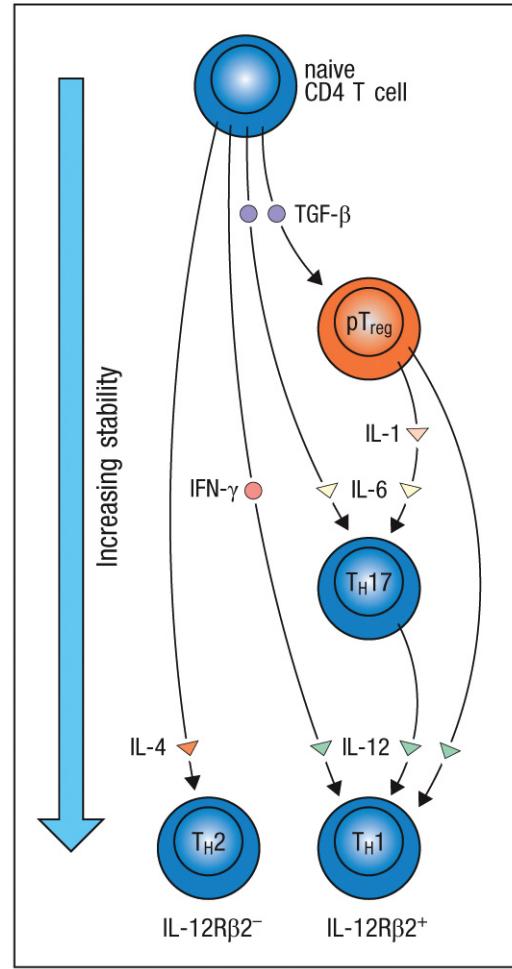
Signal 3



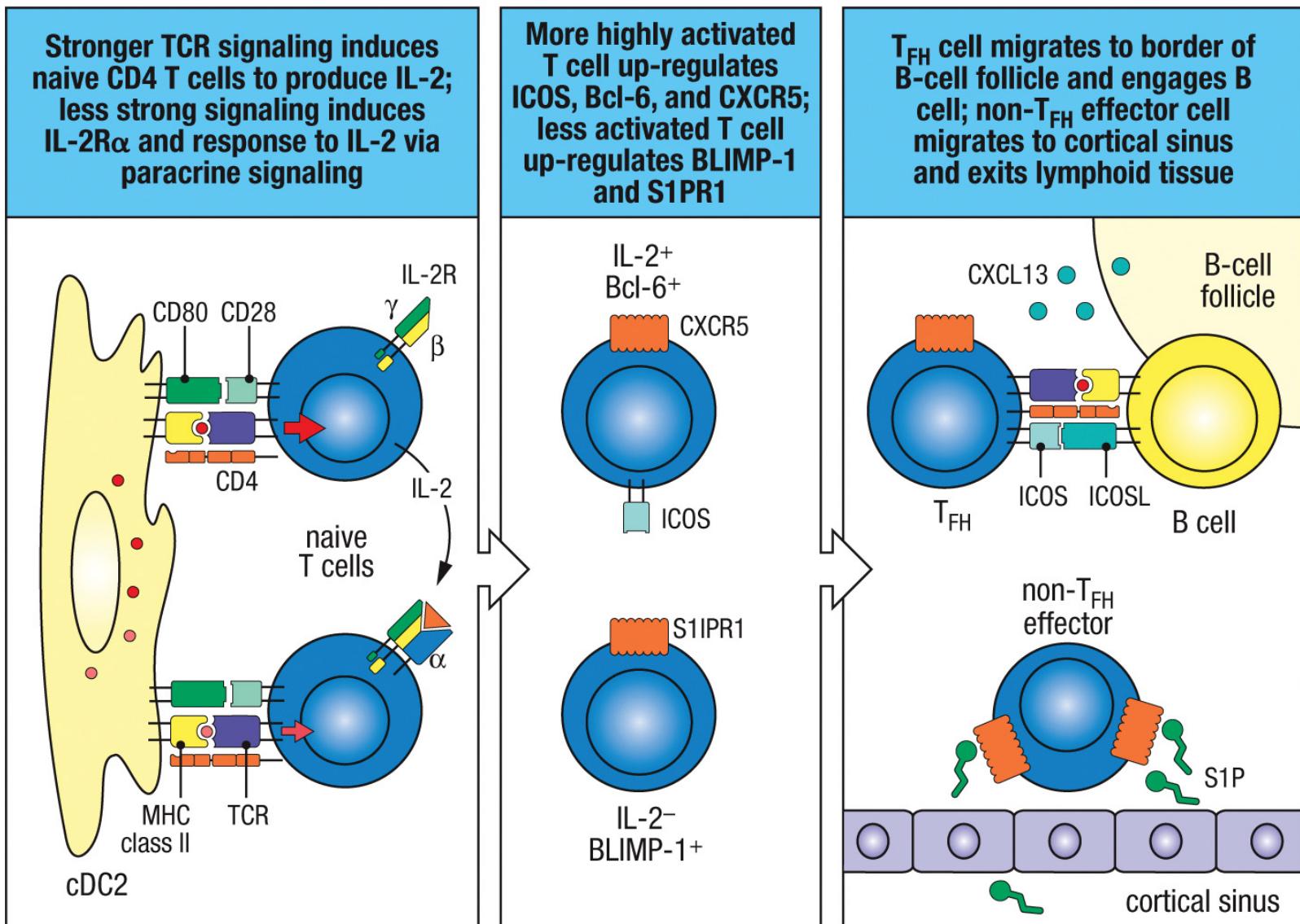
STAT Family of Transcription Factors



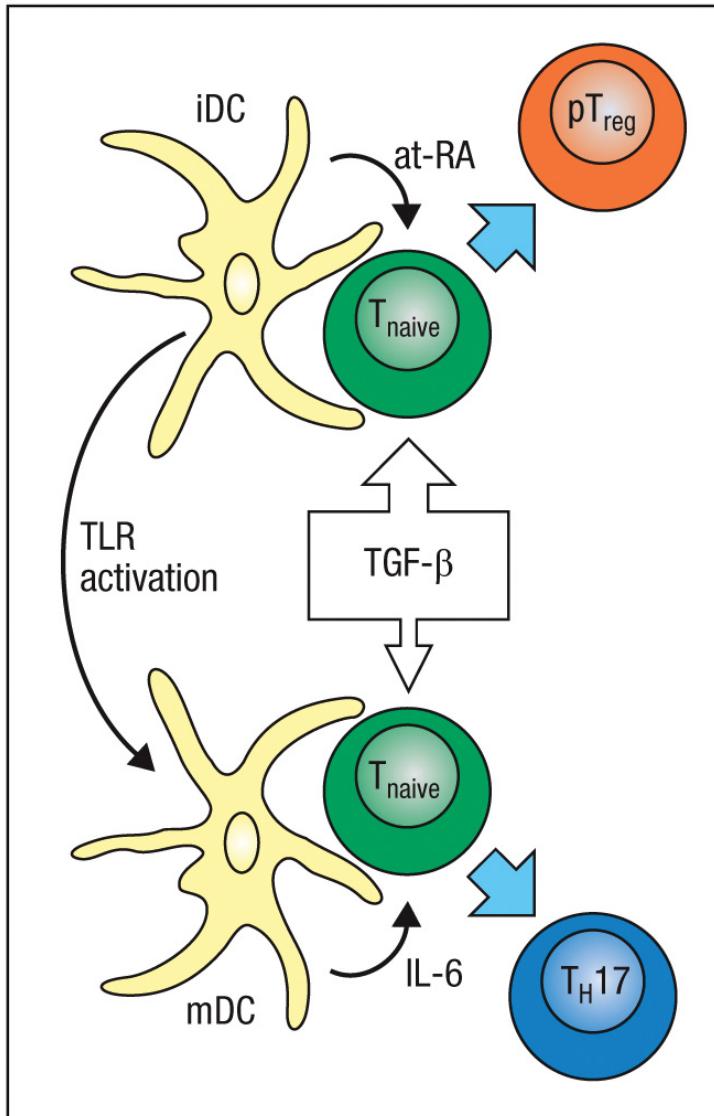




Strength of TCR Signalling



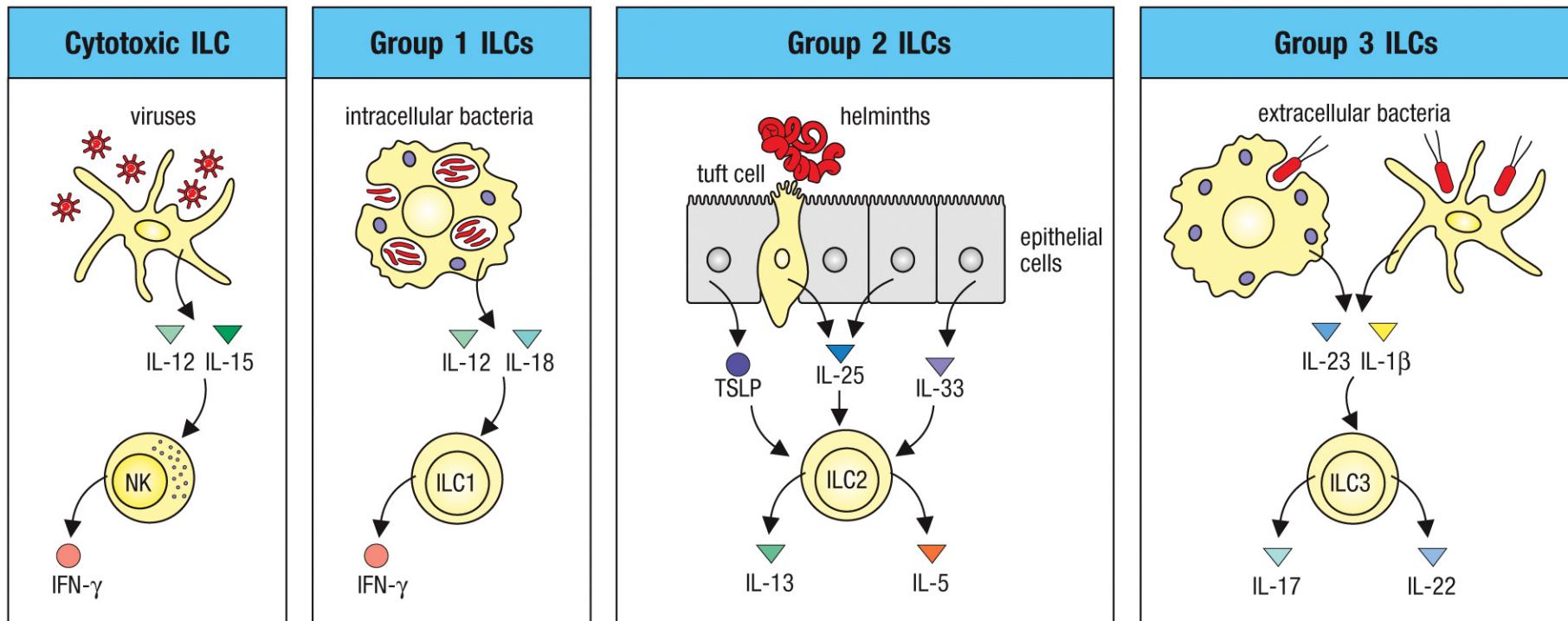
Infection Status Determines the Fate of T Cells



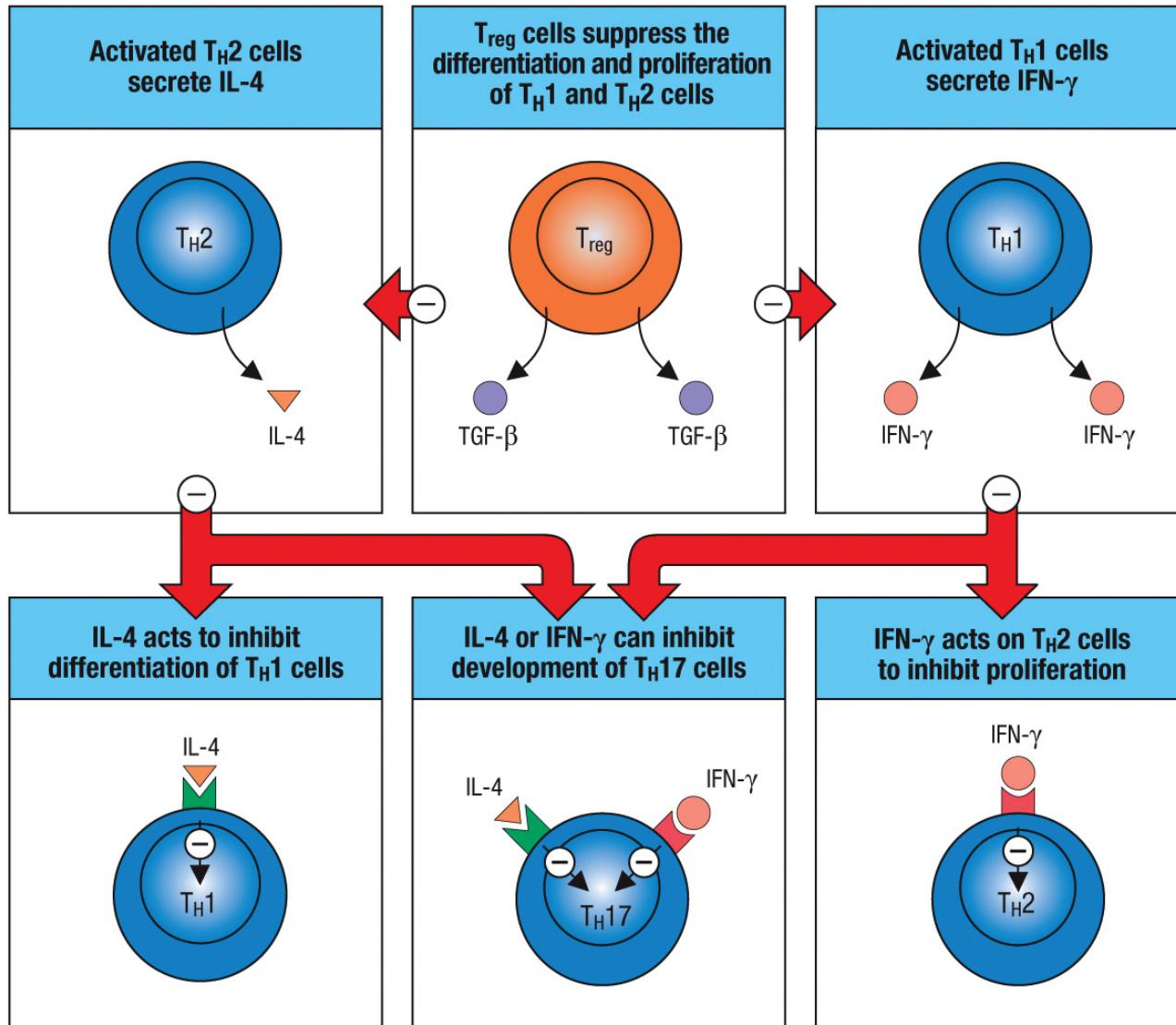
Induced regulatory T cells

All-trans 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		T _H 1 cells		T _H 2 cells		CD4 T cells: peptide + MHC class II		T _{FH} cells	
Cytotoxic (killer) T cells		Macrophage-activating effector molecules		Barrier immunity-activating effector molecules		T _H 17 cells		B-cell help	
Cytotoxic effector molecules	Others	Others		Others		Others		Others	
Perforin Granzymes Granulysin Fas ligand	IFN- γ GM-CSF TNF- α CD40 ligand Fas ligand	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_{H1} , some CD8	Stimulates growth and J-chain synthesis	Growth and differentiation	–	–	–	↓ T-cell responses IBD
Interferon- γ (IFN- γ)	T_{H1} , T_{FH} , CTL	Differentiation IgG2a synthesis (mouse)	Inhibits T_{H2} and T_{H17} cell differentiation	Activation, ↑MHC class I and class II	Activates NK cells	Antiviral ↑MHC class I and class II	Susceptible to mycobacteria, some viruses
Lymphotxin- α (LT- α , TNF- β)	T_{H1} , 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_{H2} , T_{FH}	Activation, growth IgG1, IgE ↑MHC class II induction	Growth, survival	Promotes marginal zone macrophage activation	↑Growth of mast cells	–	No T_{H2}
Interleukin-5 (IL-5)	T_{H2}	Mouse: Differentiation IgA synthesis	–	–	↑Eosinophil growth and differentiation	–	Reduced eosinophilia
Interleukin-13 (IL-13)	T_{H2}	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_{H17}, 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_{H17}	–	–	–	–	Stimulates mucosal epithelium and skin to produce antimicrobial peptides	Impaired antibacterial defense
Interleukin-21 (IL-21)	T_{FH} , some T_{H1} , T_{H17} , 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_{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	↑MHC class II	Inhibits T_{H1}	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 _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
Interleukin-3 (IL-3)	T _H 1, T _H 2, T _H 17, some CTL	—	—	—	Growth factor for progenitor hematopoietic cells (multi-CSF)	—	—
Tumor necrosis factor-α (TNF-α)	T _H 1, T _H 17, some T _H 2, some CTL	—	—	Activates, induces NO production	—	Activates microvascular endothelium	Susceptibility to Gram + sepsis
Granulocyte–macrophage colony-stimulating factor (GM-CSF)	T _H 1, T _H 17, some T _H 2, some CTL	Differentiation	Inhibits growth?	Activation Differentiation to dendritic cells	↑Production of granulocytes and macrophages (myelopoiesis) and dendritic cells	—	—

Question

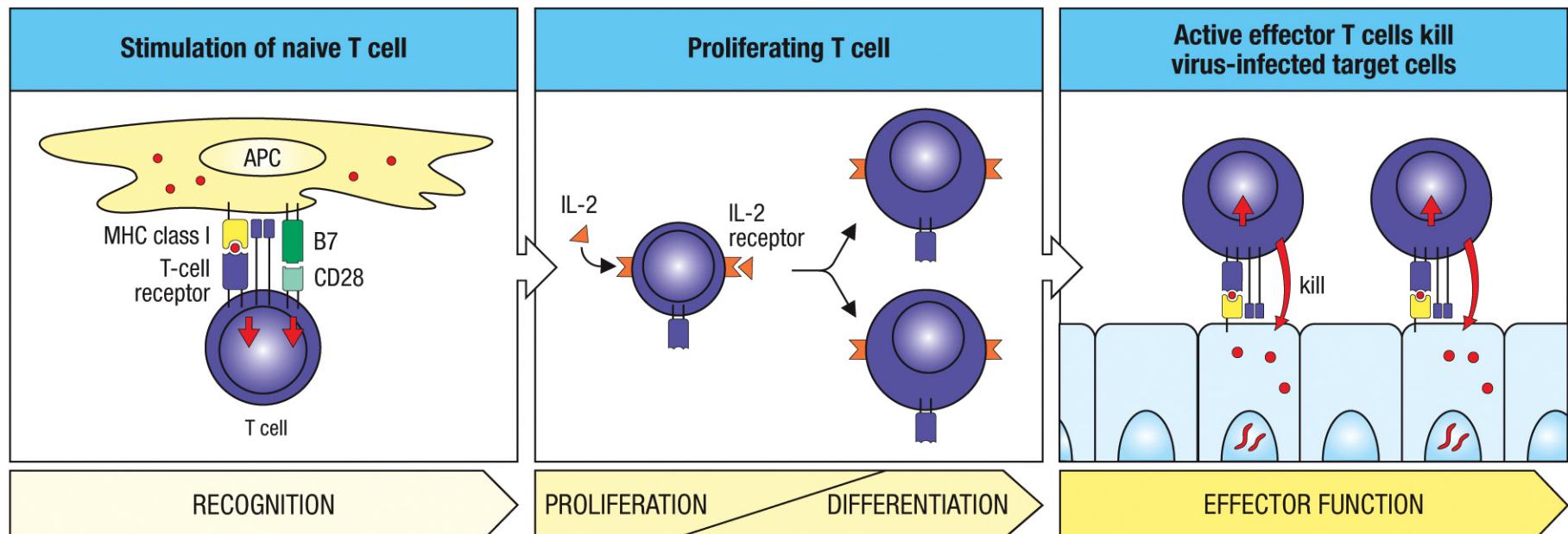
- What are the major subtypes of CD4+ T cells? And their function?
- Which cytokines are required to promote their differentiation, respectively?

Outline

T cell mediated immunity

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

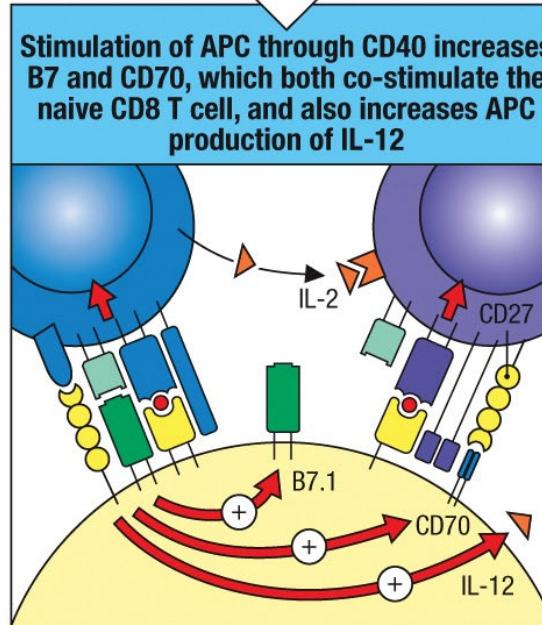
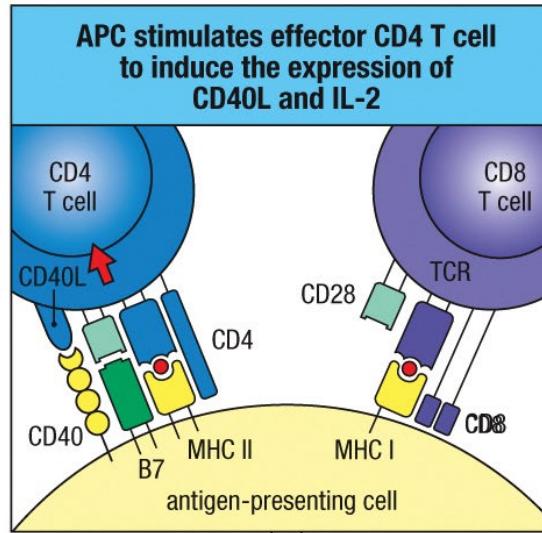
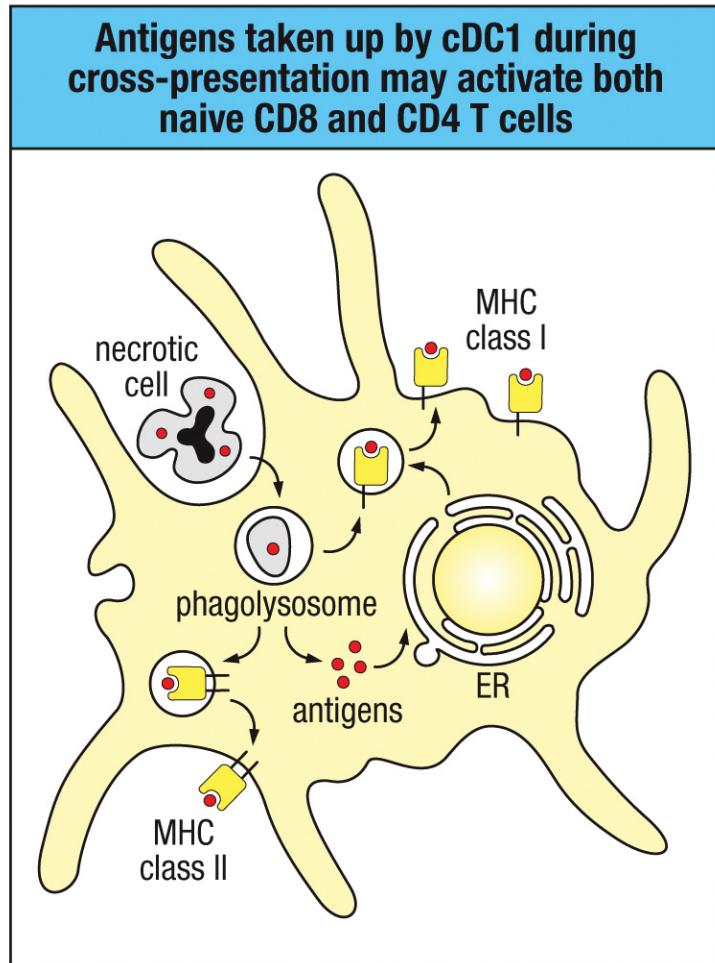
CD8 T Cells



Priming
In lymph nodes

At infection site

Most CD8 T-Cell Responses Require CD4 T-Cells



CD8 T-Cell Memory Requires CD4 T-Cells

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

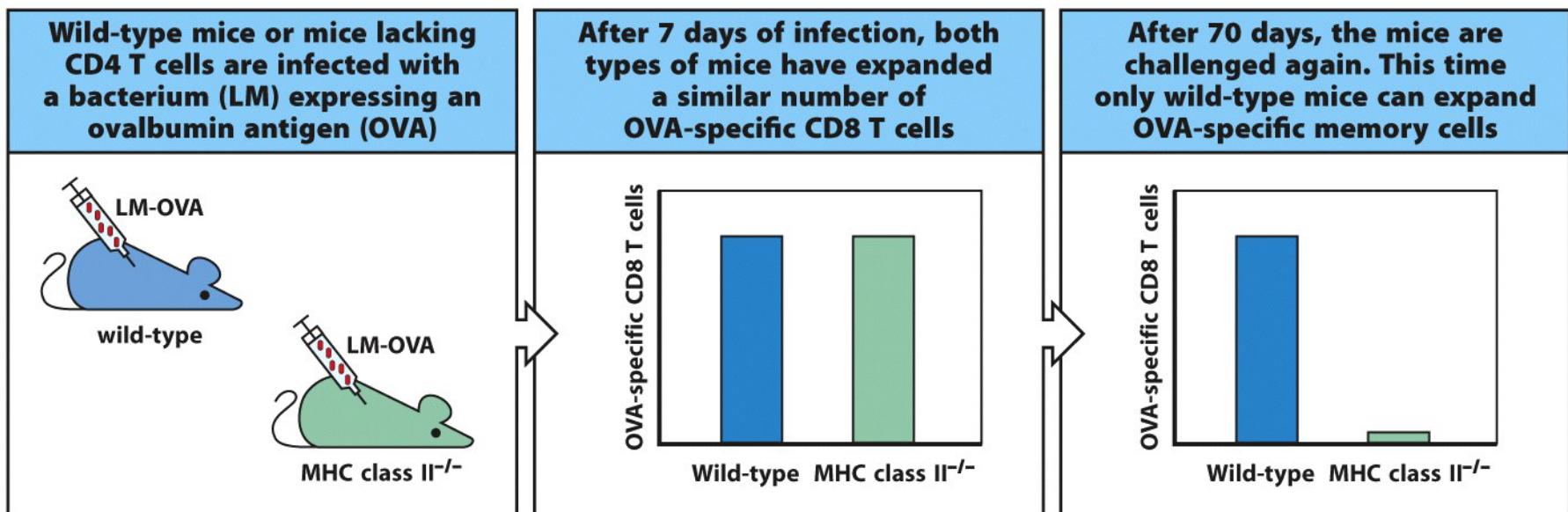
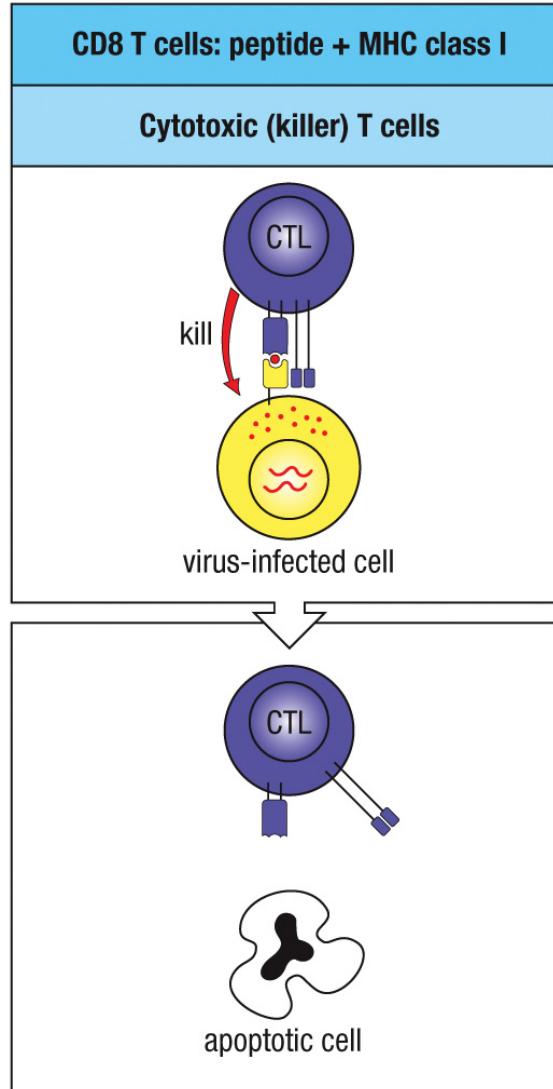


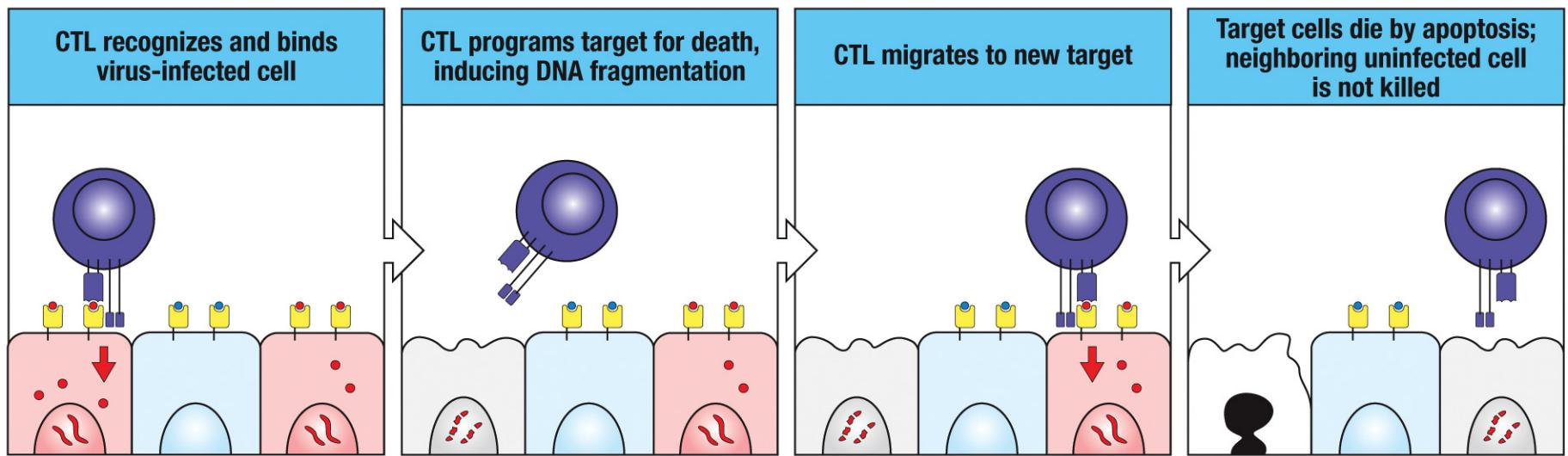
Figure 11.26 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

CD8 T Cells

Target killing does not require co-stimulation

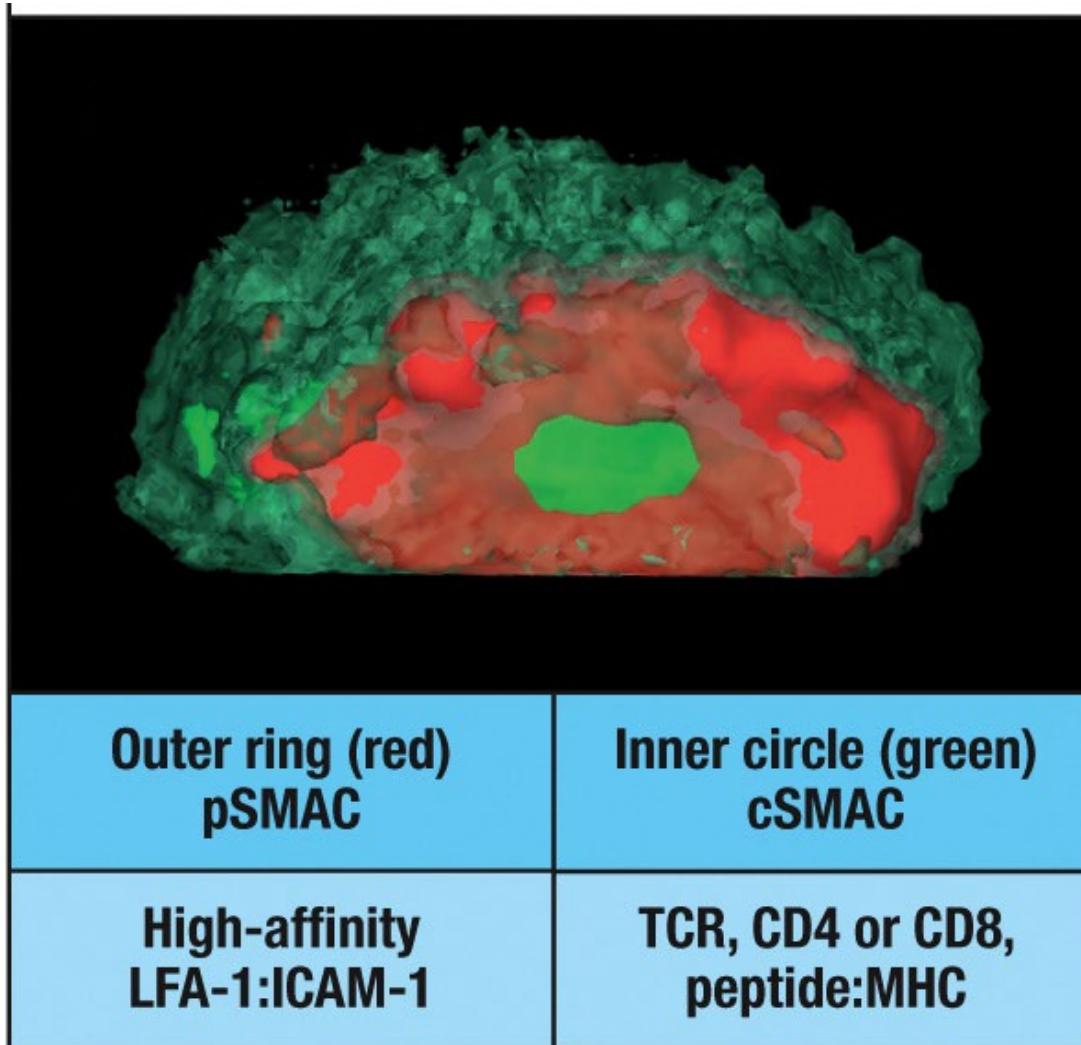


Cytotoxic T Cells are Serial Killers



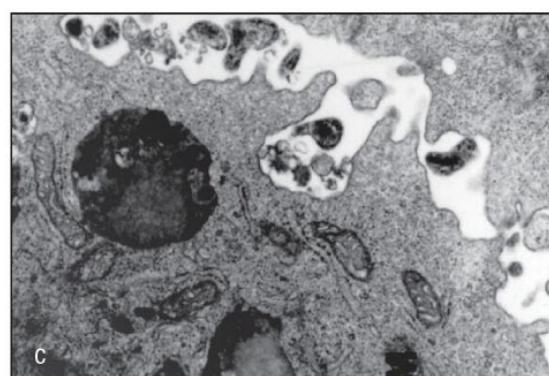
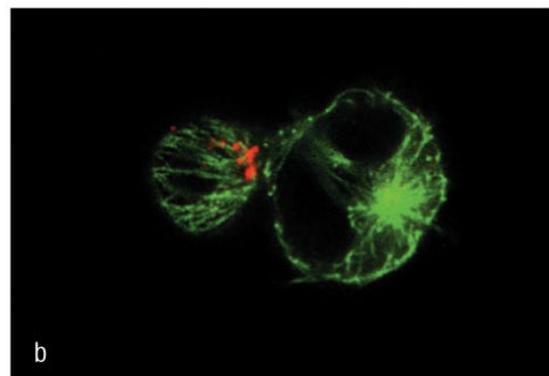
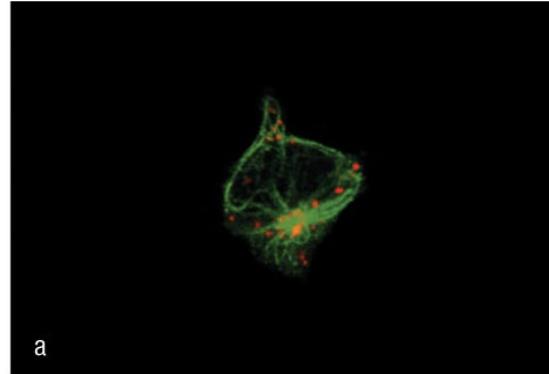
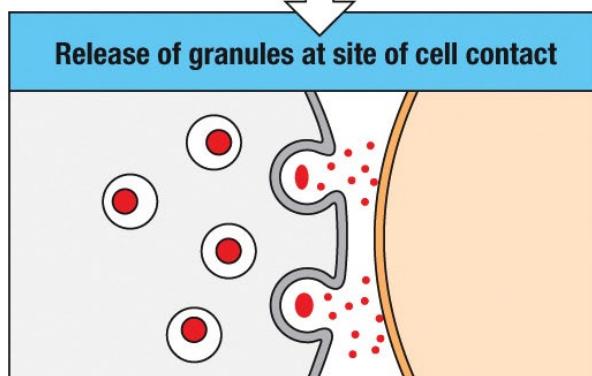
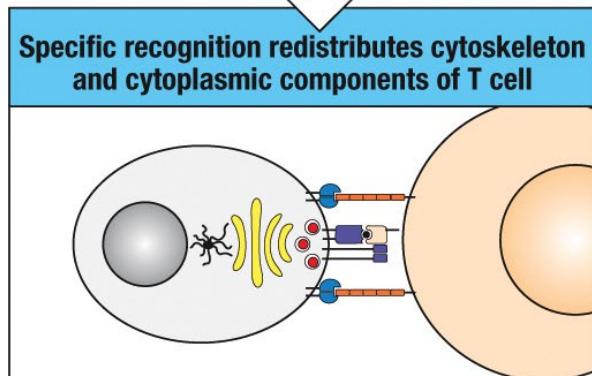
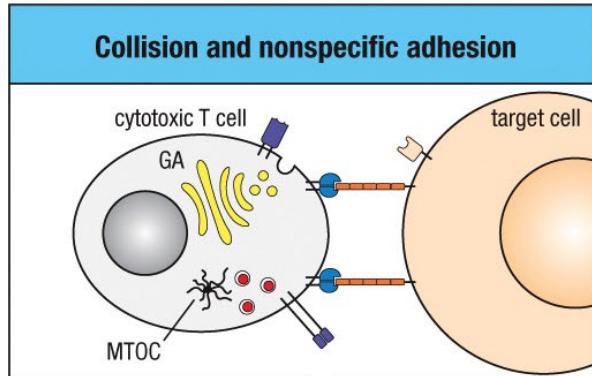
Immunological Synapse

supramolecular adhesion complex



Photograph courtesy of Avi Kupfer

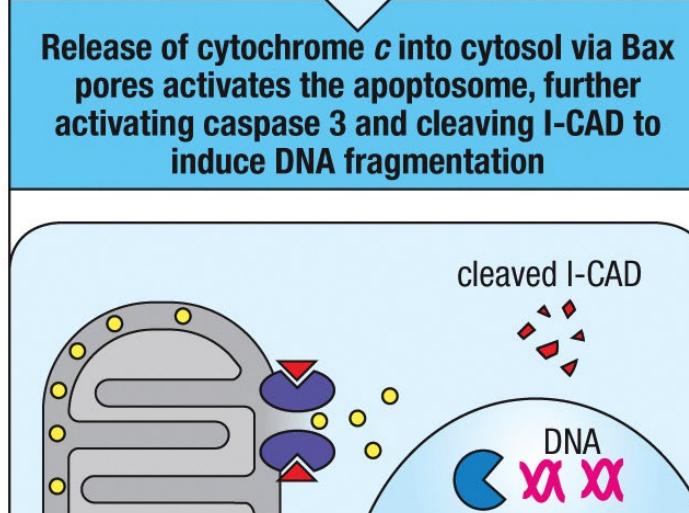
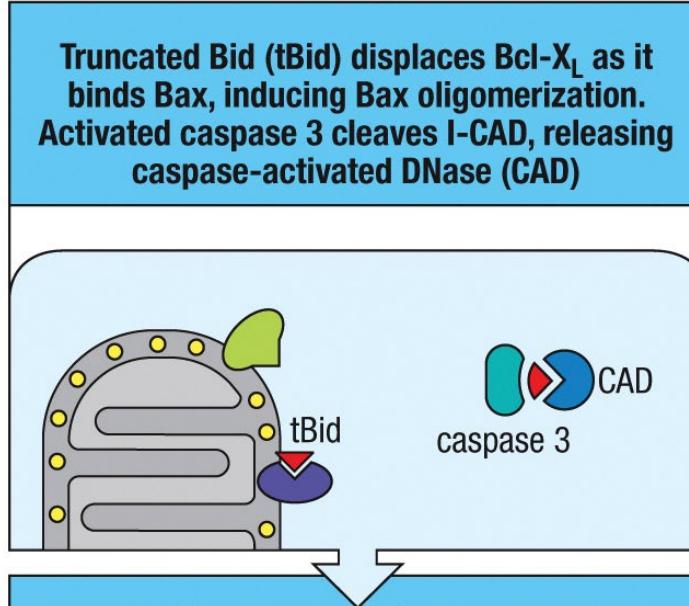
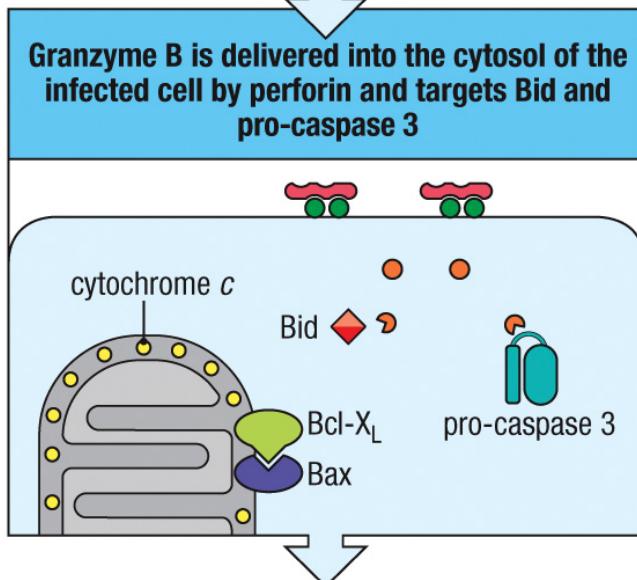
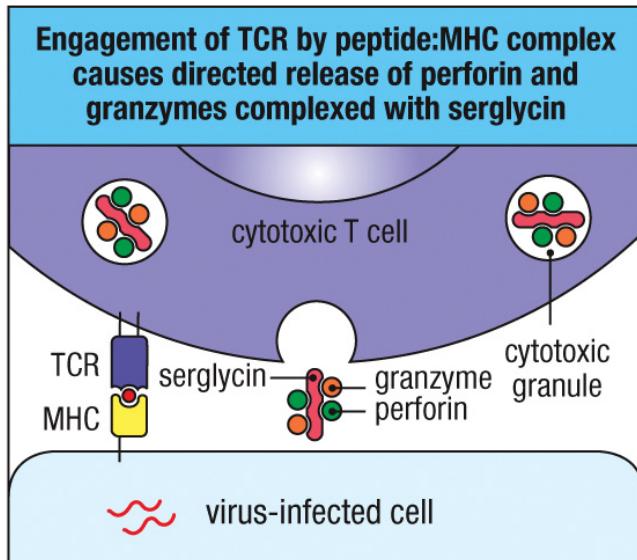
Polarization of T-Cells During Antigen Recognition



Cytotoxic granules
Microtubules

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

Granzyme Induced Apoptosis



Question

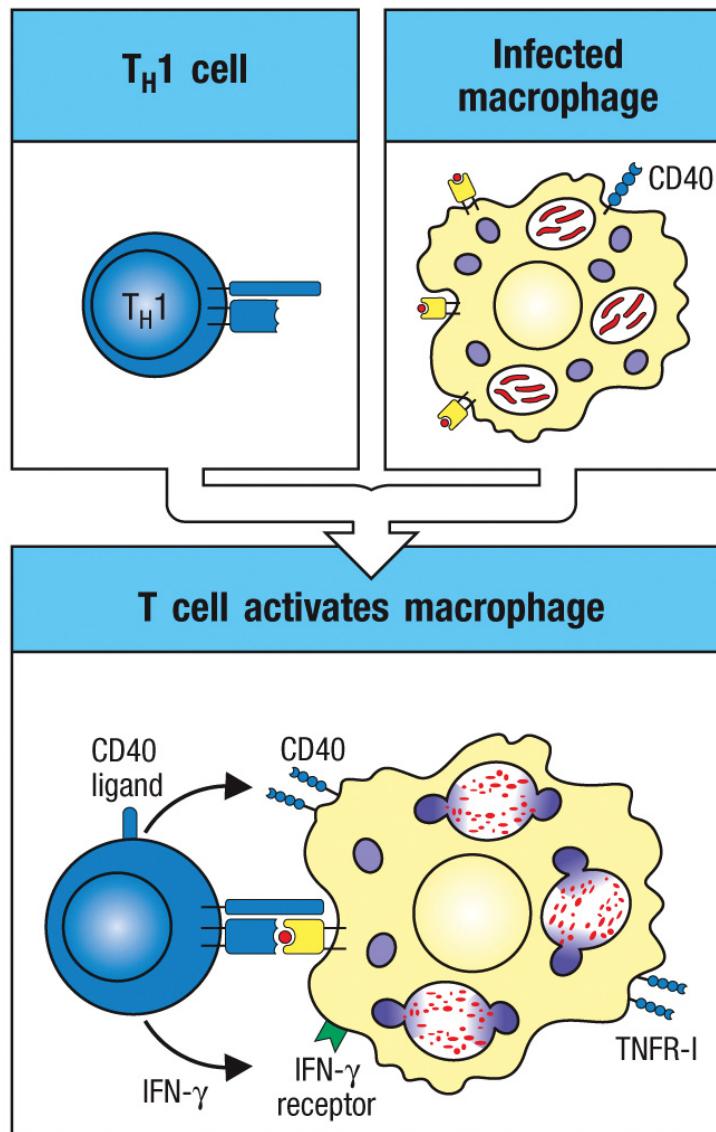
- How does CD4 T cells help CD8 T cells to become activated in the lymph node?

Outline

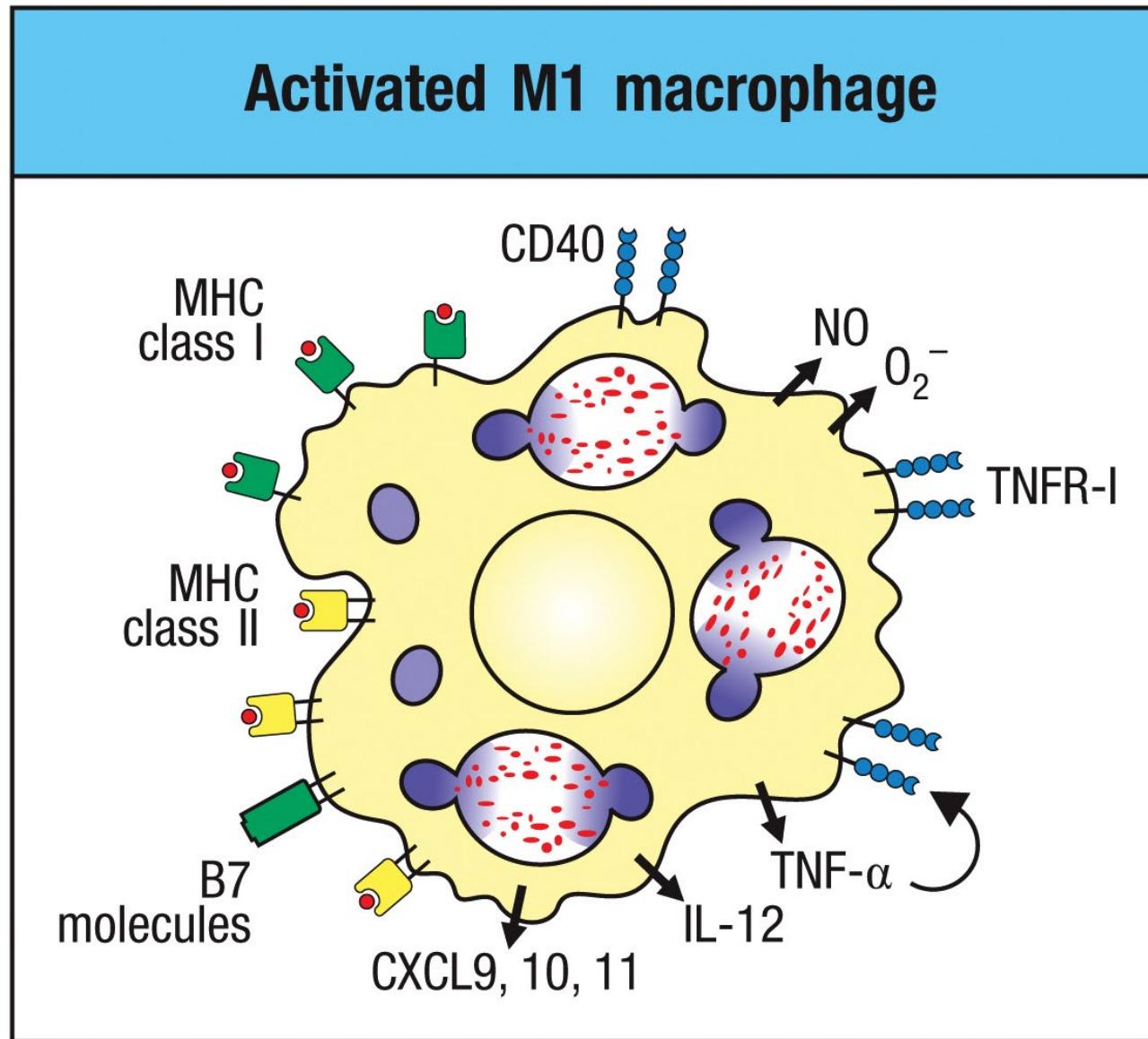
T cell mediated immunity

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

T_{H1} Cells Activate Infected Macrophages



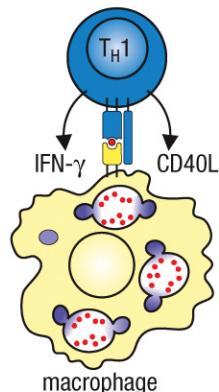
Macrophages Activated by T_H1 Cells Are Highly Microbicidal



Responses to Intravascular Pathogens Are T_H1 Dependent

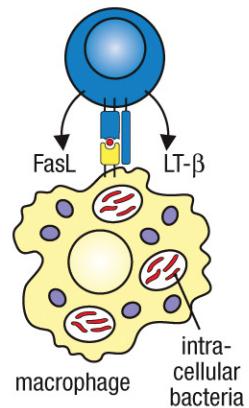
T_H1 effector functions in infections by intracellular bacteria

T_H1 cells produce IFN- γ and CD40L, which induce and activate M1 macrophages



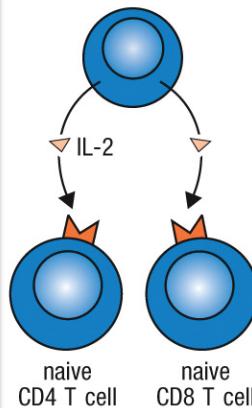
Enhances macrophage killing of engulfed bacteria

Fas ligand and LT- β produced by T_H1 cells induce apoptosis of bacteria-laden macrophages



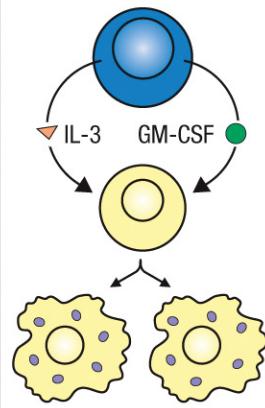
Kills chronically infected cells, releasing bacteria to be destroyed by fresh macrophages

IL-2 produced by T_H1 cells acts on activated naive CD4 and CD8



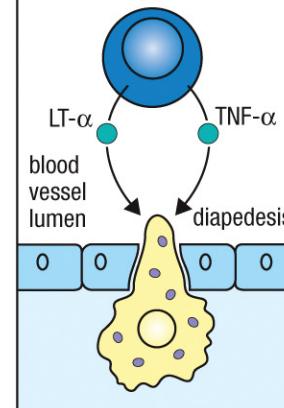
Alters balance of T_H1 versus T_{FH} differentiation to favor T_H1 ; influences differentiation of CD8 CTLs and memory CD8 T cells

IL-3 and GM-CSF produced by T_H1 cells stimulate production of monocytes by bone marrow



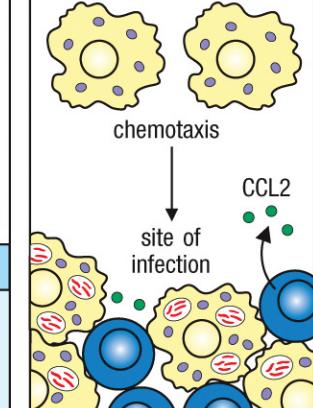
Induces monocyte differentiation in the bone marrow

T_H1 cells produce TNF- α and LT- α , which act on local blood vessels



Activates endothelium to induce monocyte binding and exit from blood vessel at site of infection

CCL2 produced by T_H1 cells is a chemoattractant for monocytes

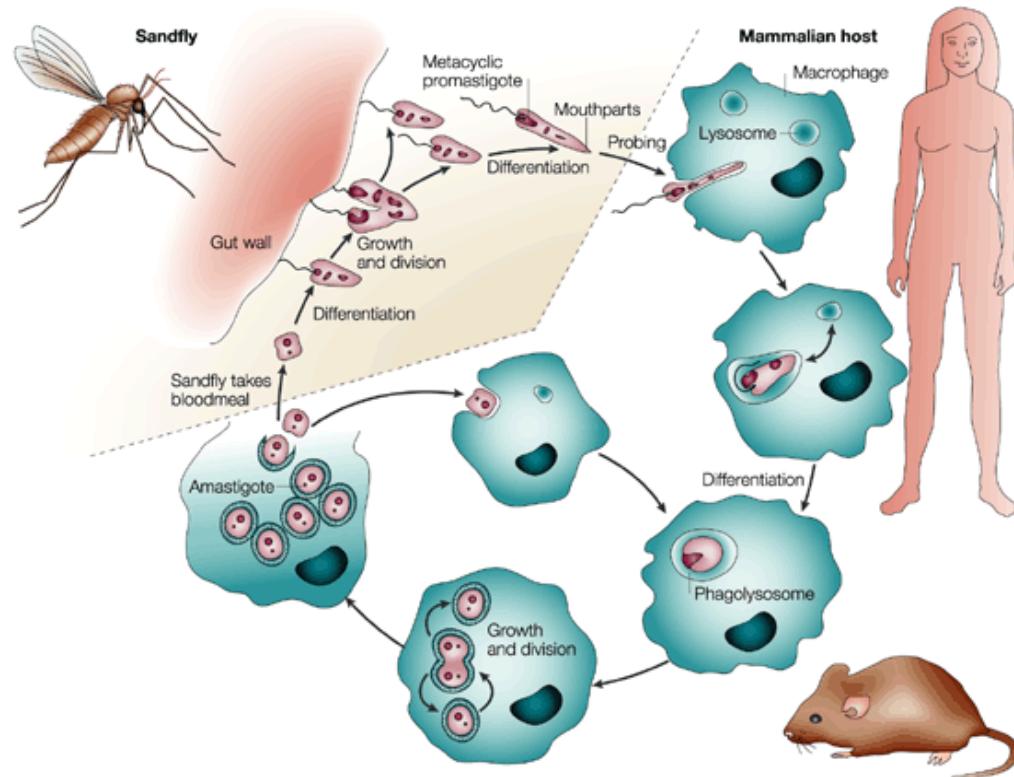


Causes macrophages to accumulate at site of infection

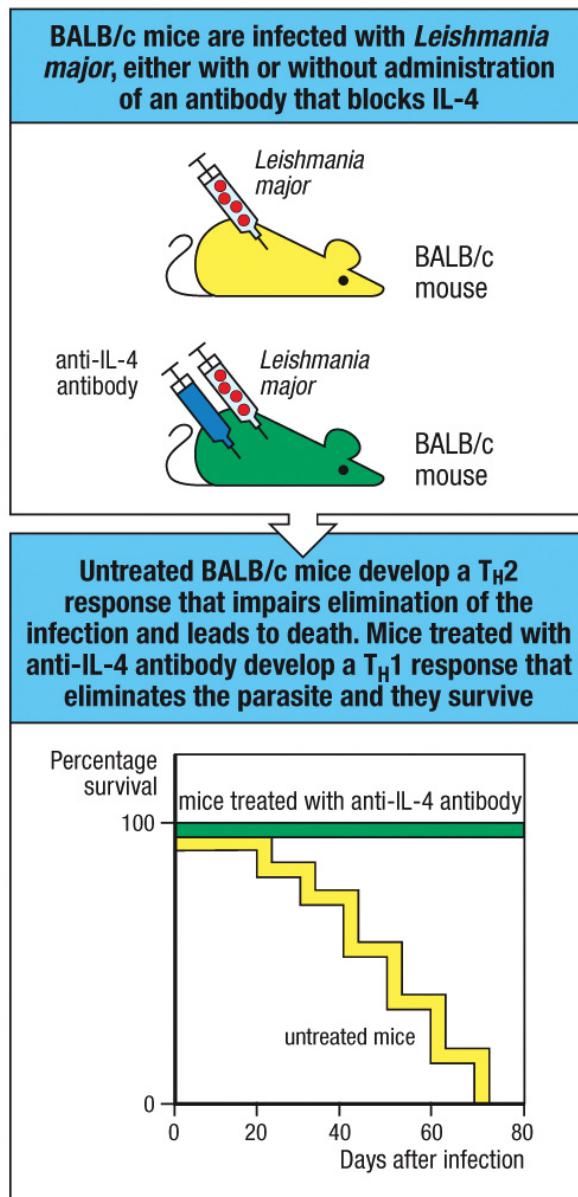
Increase the number of effector cells at infection site
Proinflammatory

Leishmania major

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



Responses to Intravascular Pathogens Are T_H1 Dependent

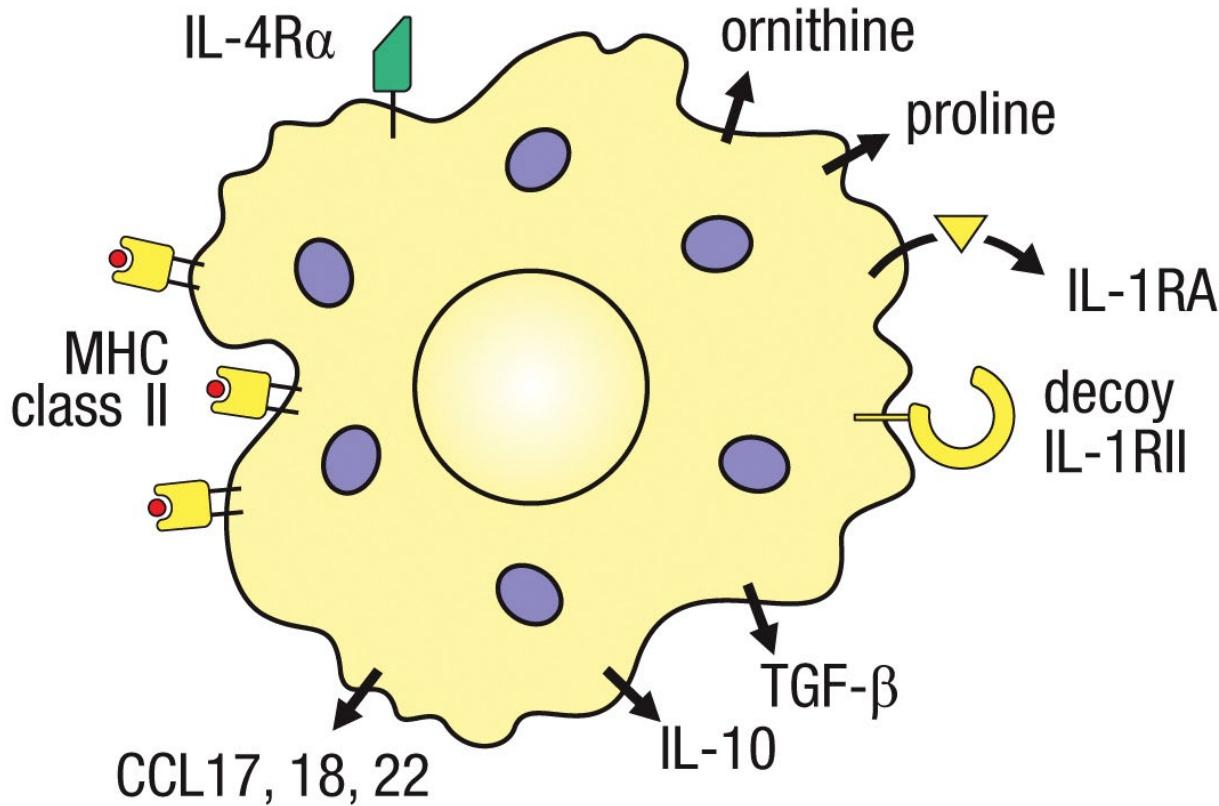


T_{H2} Cells in Helminth Infection

T_{H2} cell effector functions in helminth infections				
T_{H2} cells produce IL-13, which induces epithelial cell repair and mucus	IL-13 produced by T_{H2} cells increases smooth muscle contractility that enhances worm expulsion	T_{H2} cells recruit and activate M2 macrophages via IL-4 and IL-13	IL-5 produced by T_{H2} cells recruits and activates eosinophils	T_{H2} cells drive mast cell recruitment via IL-3, IL-9. Specific IgE arms mast cells against helminths
<p>T_{H2} cell produces IL-13, which acts on goblet cell to induce epithelial cell repair and mucus production. This leads to increased cell turnover and movement, helping to shed parasitized epithelial cells. Mucus prevents adherence and accelerates loss of parasite.</p>	<p>T_{H2} cell produces IL-13, which acts on smooth muscle cells to increase contractility and enhance worm expulsion.</p>	<p>T_{H2} cell produces IL-4 and IL-13, which act on M2 macrophage to recruit and activate it.</p>	<p>T_{H2} cell produces IL-5, which acts on eosinophil to recruit and activate it.</p>	<p>T_{H2} cell produces IL-9 and IL-3, which act on mast cell to recruit and activate it. Specific IgE arms mast cells against helminths.</p>
Increased cell turnover and movement helps shedding of parasitized epithelial cells. Mucus prevents adherence and accelerates loss of parasite	Increased contractility of mucosal smooth muscle enhances worm expulsion	Products of arginase-1 expressed by M2 macrophages increase smooth muscle contraction and enhance tissue remodeling and repair	Eosinophils produce MBP, which kills parasites. They can also mediate ADCC using parasite-specific Ig	Mast cells produce mediators such as histamine, TNF- α , and MMCP. These recruit inflammatory cells and remodel the mucosa

M2 Macrophages

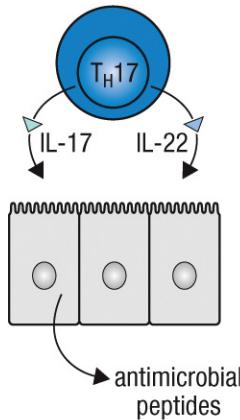
Alternatively activated, M2 macrophage



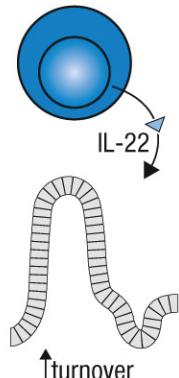
$T_{H}17$ Cells in Extracellular Bacterial Infection

$T_{H}17$ effector functions in infections by extracellular bacteria

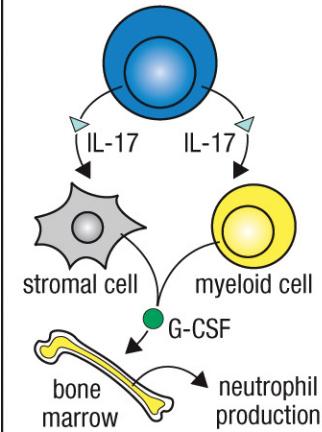
IL-17 and IL-22 produced by $T_{H}17$ cells induce the production of antimicrobial peptides by epithelial cells



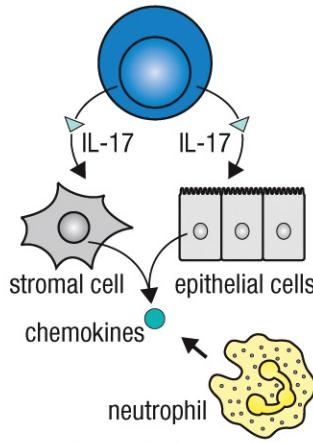
IL-22 produced by $T_{H}17$ cells increases epithelial cell turnover



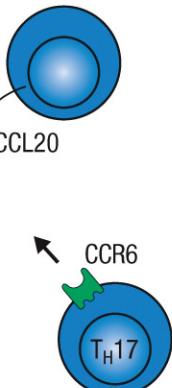
IL-17 produced by $T_{H}17$ cells activates stromal cells and myeloid cells to produce G-CSF, which stimulates neutrophil production in bone marrow



IL-17 produced by $T_{H}17$ cells activates stromal cells and epithelial cells to produce chemokines that recruit neutrophils



CCL20 produced by $T_{H}17$ cells is a chemoattractant for other $T_{H}17$ cells



Direct killing or growth inhibition of bacteria attached to the epithelium

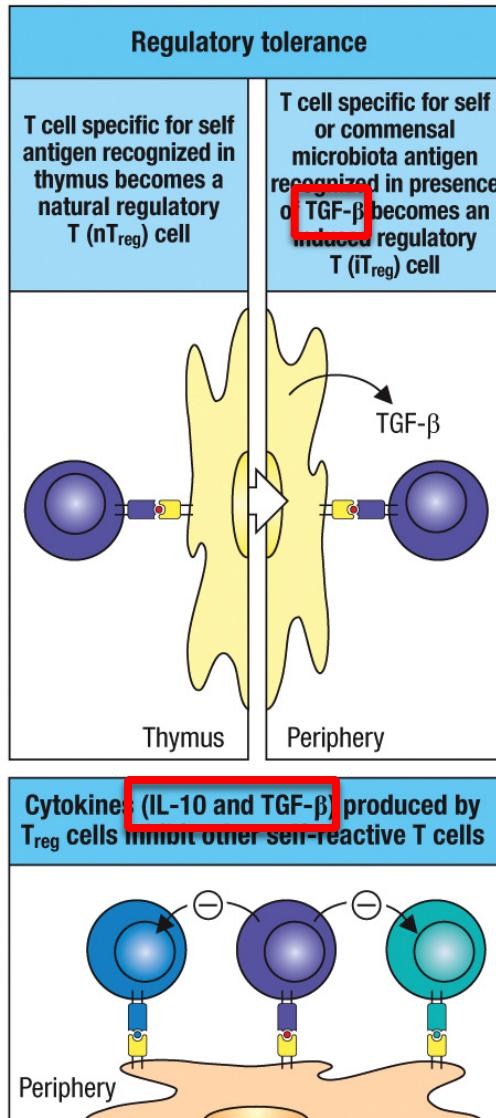
Increased epithelial cell division and shedding impairs bacterial colonization

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

Recruitment of neutrophils to the site of infection

Increased recruitment of $T_{H}17$ 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

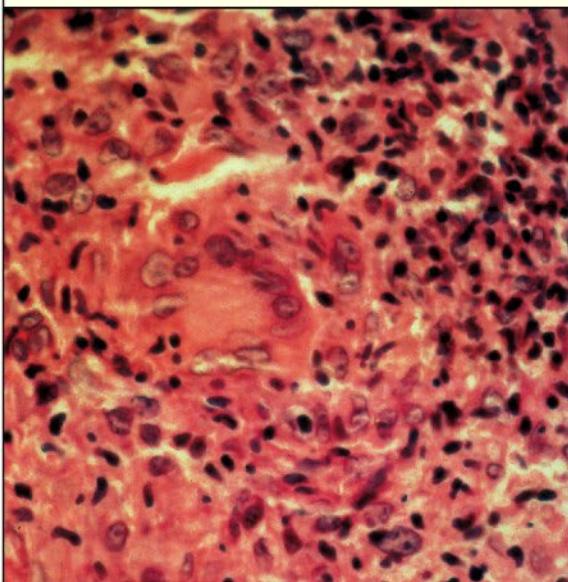


Figure 48.3 Case Studies in Immunology, 6ed. (© Garland Science 2012)

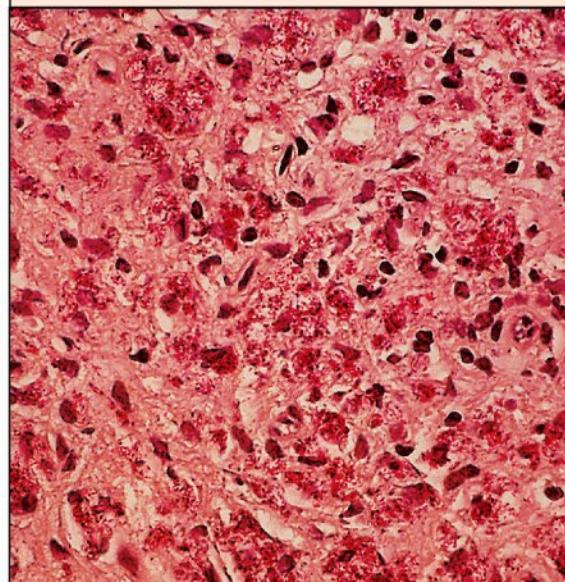
Infection with *Mycobacterium leprae* can result in different clinical forms of leprosy

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

Tuberculoid leprosy



Lepromatous 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

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

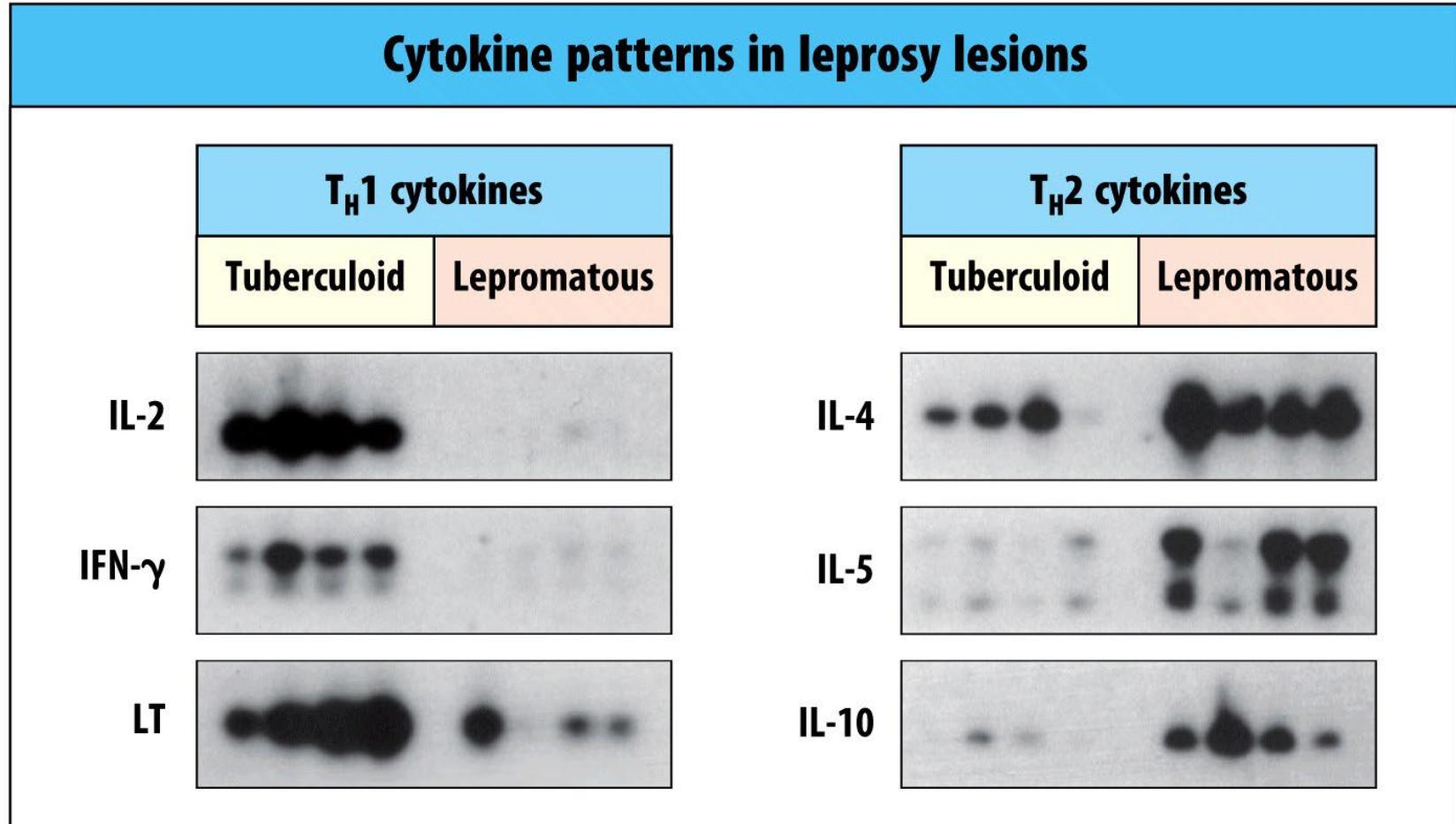


Figure 48.5 Case Studies in Immunology, 6ed. (© Garland Science 2012)

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?