

Chapter 7:

The Development of T Lymphocytes

Development of T cells in the thymus

- Immature T cells that enter the thymus are called **thymocytes**
- The thymus is a **primary lymphoid organ** (production of T lymphocytes with re-arranged receptors)
- Epithelial cells of the thymus form a network of "caves" (**thymic stroma**) surrounding the lymphocytes

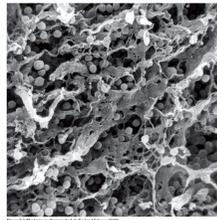


Figure 7.7 The Immune System, 3rd ed. © Garland Science 2003

Some differences between T and B cells

1) B cells re-arrange their receptors in the **bone marrow** whereas T cells do that in the **thymus**

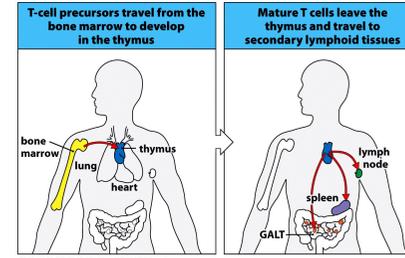


Figure 7.1 The Immune System, 3rd ed. © Garland Science 2003

2) The receptors of B cells recognize **naïve antigen** but T cells see **degraded antigen segments** in the context of MHC molecules

Involution of the thymus

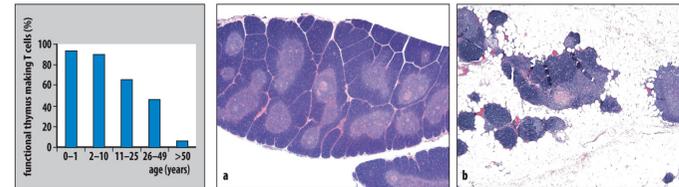


Figure 7.4 The Immune System, 4th ed. © Garland Science 2015

The proportion of the thymus that produces T cells decreases with age

Is the thymus important?

DiGeorge syndrome will result in **Severe Combined Immunodeficiency Disease (SCID)** whereas **thymectomy** in adults does not have a gross impact on the T cell repertoire

Why: T cells are long-lived

The cellular organization of the thymus

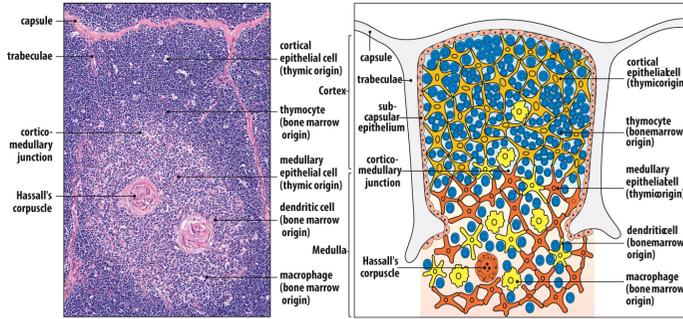


Figure 7.3 The Immune System, 4th ed. (© Garland Science 2015)

A detailed picture of a lobule, note the density difference between cortex and medulla

Hassall's corpuscle thought to be sites of destruction but latest literature claims production of cytokine Thymic stromal lymphoprotein (TSLP) that directs maturation of dendritic cells that are specialized in production of CD4⁺ regulatory cells

Commitment to the T cell lineage involves changes in gene expression and in cell surface differentiation (CD) markers

		Uncommitted progenitor cell	Double-negative thymocyte committed to the T-cell lineage
CD34	stem-cell surface marker	+	-
CD44	adhesion	+	-
CD2	adhesion and signaling	-	+
CD5	adhesion and signaling	-	+
IL-7 receptor (CD127)	cytokine receptor	-	+
CD1A	MHC class-I-like molecule	-	+
CD4	co-receptor	-	-
CD8	co-receptor	-	-
TCR genes	antigen receptor	germline	beginning to rearrange

Figure 7.5 The Immune System, 3ed. (© Garland Science 2009)

DN= CD4/8 negative

IL-7: a cytokine produced by thymic stromal cells

Thymocytes commit to the T-cell lineage before rearranging their T cell receptor genes: a process driven by Notch-1

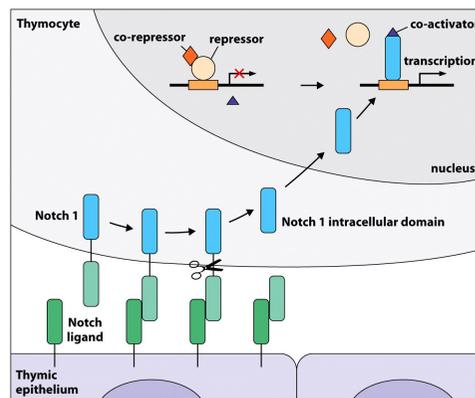


Figure 7.6 The Immune System, 3ed. (© Garland Science 2009)

Two lineages of T cells arise from a common thymocyte progenitor

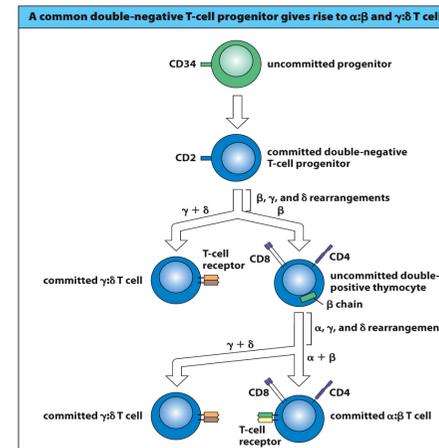
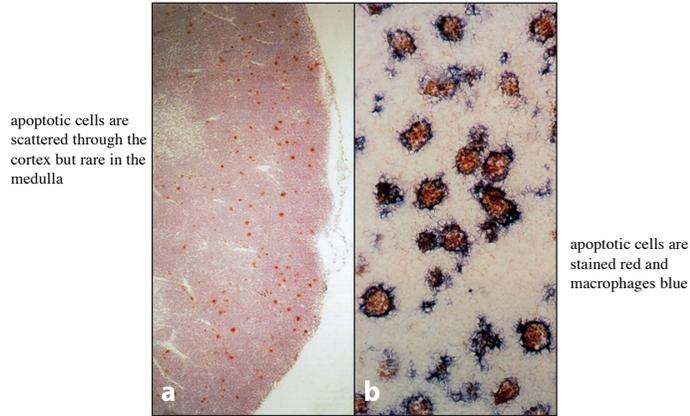


Figure 7.7 The Immune System, 4th ed. (© Garland Science 2015)

DP=Double Positive

Immature T cells that fail to make productive T cell rearrangements (98%) undergo apoptosis and are ingested by macrophages in the thymic cortex



The T cell receptor is a heterodimer

TCRA and D locus are positioned on chromosome 14 whereas the TCRB and G locus are found on #7

The TCR beta and delta chains are generated by a VDJ recombination

The TCR alpha and gamma chains are generated by a VJ recombination

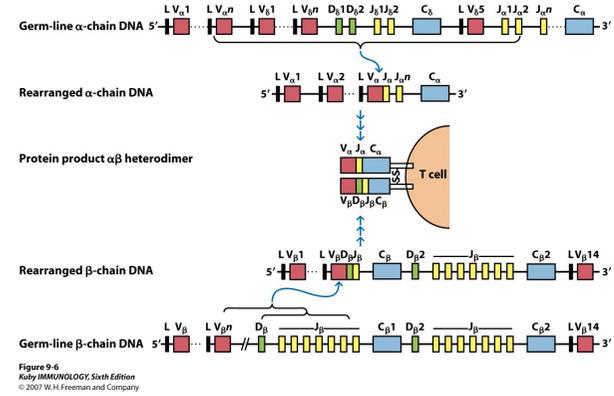
Unlike B cells, T cells do not undergo somatic hypermutation and do not express Activation-induced (Cytidine) Deaminase (AID) but they have a terminal Deoxynucleotidyl Transferase adding nucleotides to the V, D and J exons to generate junctional diversity

Number of gene segments (simplified scheme)

- TCRB: 30 V, 2 D, 7 J, 2 C
- TCRA: 41 V, 61 J, 1 C
- TCRD: 3 V, 3 D, 4 J, 1 C
- TCRG: 11 V, 3 J, 2 C

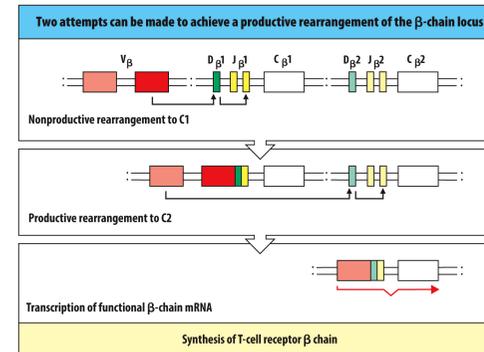
Rearrangement is facilitated by the RAG genes

Tcr and Ig rearrangement is very similar

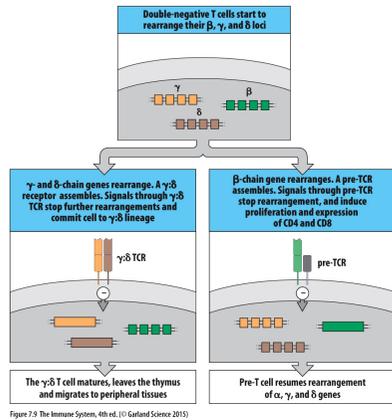


TCR B locus has two D-J clusters

Allows a 2nd rearrangement if 1st is nonproductive, in total 4 attempts can be made due to heterozygosity



Gene rearrangement in double-negative thymocytes leads to assembly of either a $\gamma\delta$ or a pre-T-cell receptor



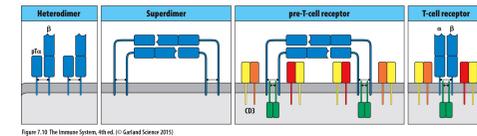
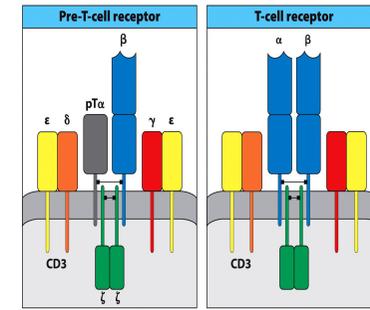
The pre-T-cell receptor and T-cell receptor/CD3 complex

after formation of pre-T cell receptor, RAG genes are temporarily inactivated and pre-T cell is induced to proliferate creating a clonal expansion of cells expressing the same chain

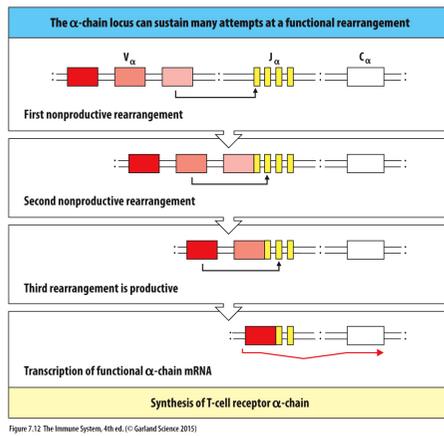
Subsequent rearrangement of the α chain gene happens only in pre T cells

Pre T cell receptor signals the induction of CD4/8 expression

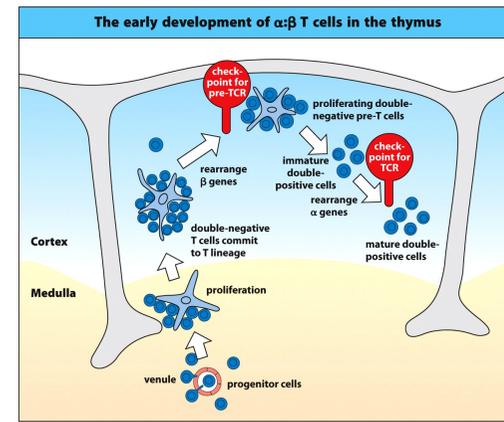
Pre-T cell receptor is a superdimer.



TCRA locus-replacement rearrangement in pre-T-cells



Thymal development of double positive T cells in a nut shell



T cells that recognize self-MHC molecules are positively selected in the thymus

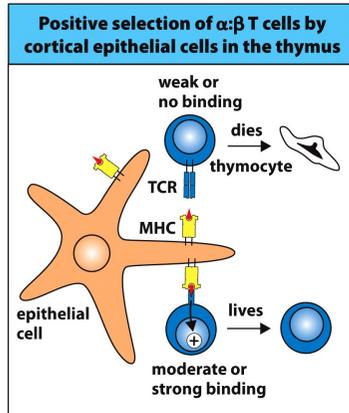


Figure 7.16 The Immune System, 3ed. (© Garland Science 2009)

Receptor editing to match self MHC

- If first gene rearrangement of Tcr α -chain is productive, subsequent positive selection (MHC) will shut off RAG gene transcription.
- Continuing α -chain gene rearrangement increases the chance for positive selection
- no allelic exclusion at the α -chain locus, a small proportion of T cells (1 to 2%) has two receptors, of which **only one** is functional.

Positive selection determines expression of either the CD4 or the CD8 co-receptor

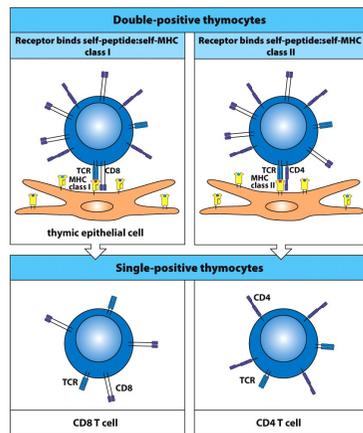


Figure 7.17 The Immune System, 3ed. (© Garland Science 2009)

No MHC class I or II expression is called Bare Lymphocyte syndrome

High affinity T cells specific for self antigens are removed in the thymus by negative selection

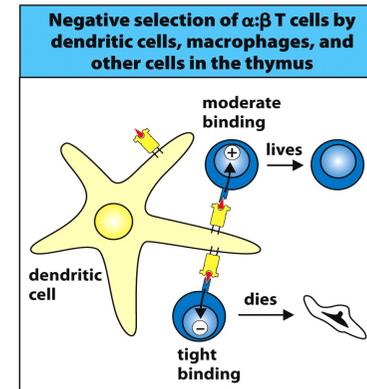


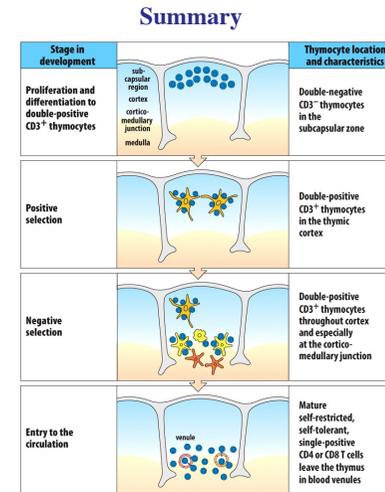
Figure 7.18 The Immune System, 3ed. (© Garland Science 2009)

The T-cell repertoire is shaped by AIRE

- Tissue-specific proteins are expressed in the thymus and participate in **negative selection** (AIRE=autoimmune regulator)

Aire deficient patients suffer from autoimmune polyglandular syndrome type 1 (broad spectrum autoimmune disease)

- Negative selection (removal of T cells specific for self antigens) by thymus produces **central tolerance**



Chapter 8:

T Cell-Mediated Immunity

Activation of naive T cells on encounter with antigen

- Immature dendritic cells capture antigen and migrate to secondary lymphoid tissue (for instance, T cell regions of the cortex of lymph nodes) during their travel they become mature/activated dendritic cells
- Macrophages (role in defense and repair of damaged tissue) are resident in tissues
- The T cell rich areas of secondary lymphoid tissues provide specialized sites where naive T cells are activated by their specific antigens.

Dendritic cells carry antigens from sites of infection to secondary lymphoid tissues

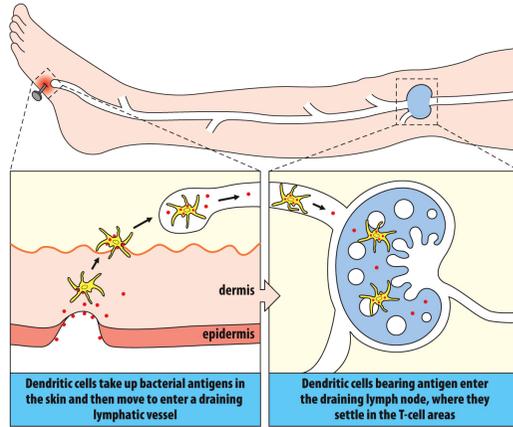
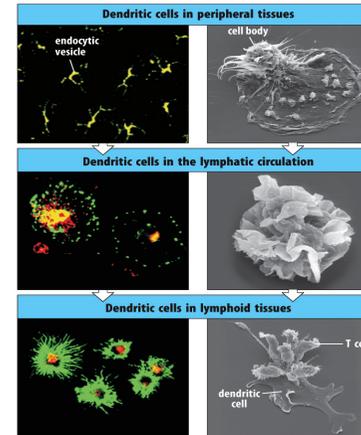


Figure 8.1 The Immune System, 4th ed. (© Garland Science 2015)

Maturation of dendritic cells



yellow = endocytic vesicles
red = lysosomal protein
green = MHC class II

activation induces CCR7, the receptor for CCL21, which chemokine is made in secondary lymphoid tissues (results in migration to lymph node and stops further processing as a consequence dendritic cell focusses on T cell activation)

Figure 8.2 The Immune System, 4th ed. (© Garland Science 2015)

Dendritic cells (are adapt and versatile) = use various pathways to process and present degraded protein antigen segments

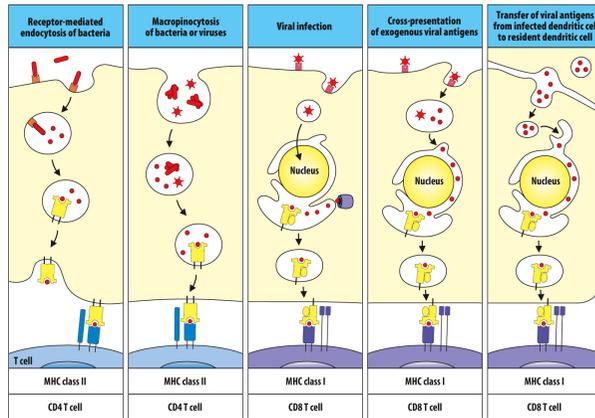


Figure 8.3 The Immune System, 4th ed. (© Garland Science 2015)

How the lymph network works

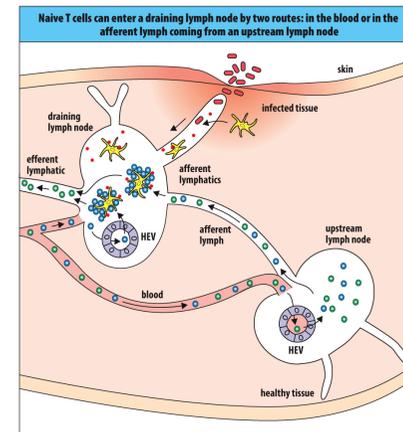


Figure 8.5 The Immune System, 4th ed. (© Garland Science 2015)

In any given infection only 1 in 10^4 to 10^6 of the total pool of circulating T cells is activated.

Homing of naive T cells to secondary lymphoid tissues is determined by chemokines and cell adhesion molecules

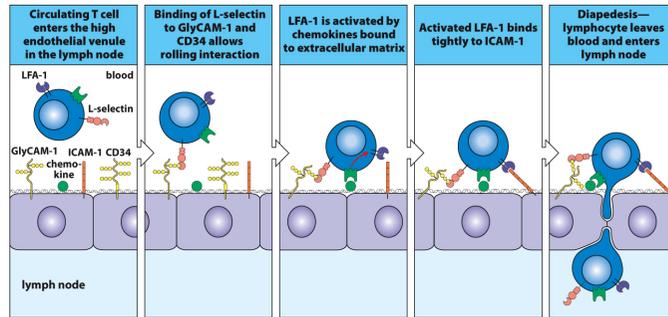


Figure 8.6 The Immune System, 4th ed. (© Garland Science 2015)

chemokine = CCL21 and 19 which binds to CCR7 receptor (green) on Naive T cell

Transitory interactions; lymphocyte adhesion to dendritic cells

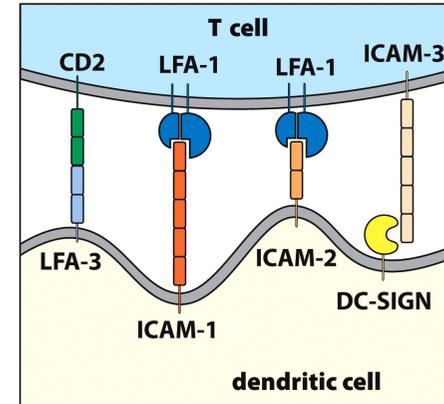


Figure 8.8 The Immune System, 3ed. (© Garland Science 2009)

DC-SIGN a lectin unique to activated DC

Transient adhesive interactions between T cell and DC are stabilized by recognition of antigen in the context of MHC (cognate pair)

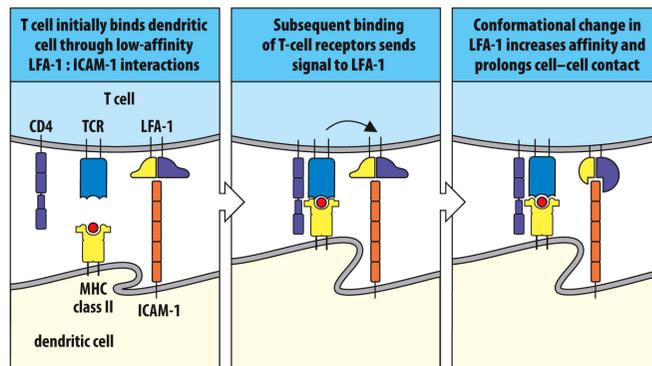
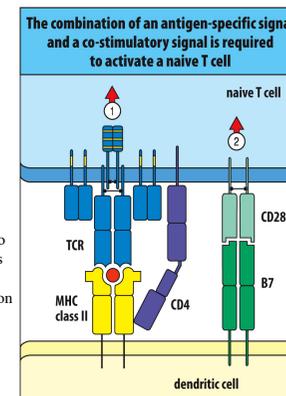


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Activation of naive T cells requires signals from the TCR complex (1) and a co-stimulatory receptor (2)



CTLA4 is expressed only on activated T cells, is similar to CD28 but binds much stronger to its ligand B7 and works as an antagonist and inhibits activation and proliferation

signal 1 induces clonal expansion but only when signal 2 is delivered

B7.1 and 7.2 are known as costimulatory molecules

Figure 8.8 The Immune System, 4th ed. (© Garland Science 2015)

Secondary lymphoid tissues contain **three** kinds of professional antigen-presenting cells which populate distinct areas

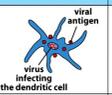
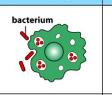
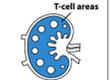
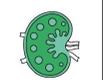
	Professional antigen-presenting cells		
	Dendritic cell	Macrophage	B cell
Cell type	 viral antigen virus infecting the dendritic cell	 bacterium	 microbial toxin
Location in lymph node	 T-cell areas		 follicle
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines - to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible - to +++	Inducible - to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellular and extracellular pathogens	Soluble antigens Toxins Viruses
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

Figure 8.11 The Immune System, 3ed. (© Garland Science 2009)

What drives Effector T cells to leave the lymph node

- There is a concentration gradient of sphingosine 1-phosphate (S1P) from the lymph/blood to the secondary lymphoid tissues
- T cells activated by Ag suppress the expression of S1P receptors for several days (makes them stay in the lymph node while they differentiate into effector cells). Later they are drawn away by the gradient of S1P

Proliferation and differentiation of activated T cells is driven by Interleukin 2 (IL2)

Activated T cells secrete and respond to IL-2

Production of IL2 requires Signal 1 (TCR) and 2 (CD28)

Signal 2 increases IL2 Production a 100 fold

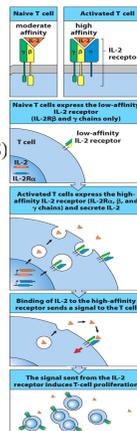


Figure 8.12 The Immune System, 4th ed. (© Garland Science 2015)

cyclosporine-A, tacrolimus (FK506), and rapamycin are immunosuppressive drugs that inhibit IL-2 production or signalling by the IL-2 receptor

Antigen recognition in the absence of co-stimulation (signal 2) leads to T cell anergy

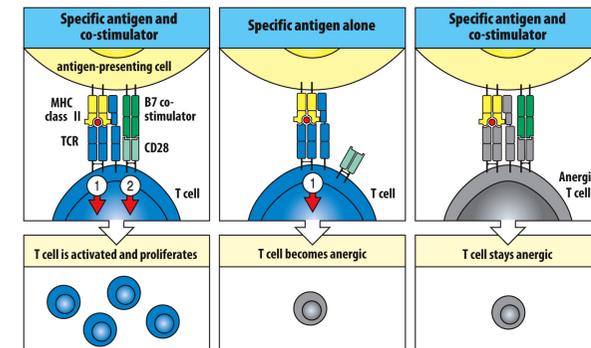


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No IL2 production

Anergy: peripheral tolerance of self-reactive T cells that “escaped” from the thymus

Activation of naive CD4 T cells give rise to effector T cells with distinctive helper functions

	T _H 1 cells	T _H 17 cells	T _H 2 cells	T _{FH} cells	T regulatory cells (T _{reg})
Effector CD4 T cell					
Cytokines that induce differentiation	IL-12 IFN-γ	IL-6 IL-21	IL-4	IL-16 TGF-β IL-23	TGF-β
Defining transcription factor	T-bet	ROR-γT	GATA3	Bcl6	FoxP3
Characteristic cytokines	IL-12 IFN-γ	IL-17 IL-6	IL-4 IL-5	IL-21	TGF-β IL-10
Function	Activate macrophages	Enhance neutrophil response	Activate cellular and antibody response to parasites	Activate B cells and antibody response	Suppress other effector T cells

Figure 8.14 The Immune System, 4th ed. (© Garland Science 2015)

T_{FH} = follicular helper cells
Cytokine environment determines which differentiation pathway a naive T cell takes

Polarization of immune responses in different clinical forms of leprosy

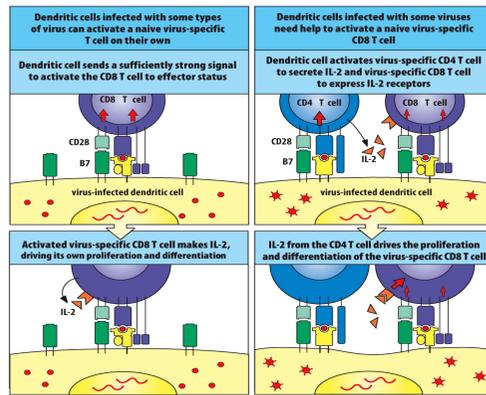
Infection with <i>Mycobacterium leprae</i> can result in different clinical forms of leprosy	
There are two polar forms, tuberculoid and lepromatous leprosy, but several intermediate forms also exist	
Tuberculoid leprosy	Lepromatous leprosy
Organisms present at low to undetectable levels	Organisms show florid growth in macrophages
Low infectivity	High infectivity
Granulomas and local inflammation. Peripheral nerve damage	Disseminated infection. Bone, cartilage, and diffuse nerve damage
Normal serum immunoglobulin levels	Hypergammaglobulinemia
Normal T-cell responsiveness. Specific response to <i>M. leprae</i> antigens	Low or absent T-cell responsiveness. No response to <i>M. leprae</i> antigens

T_H1
Cytokines:
IL-2
γ-IFN
LT

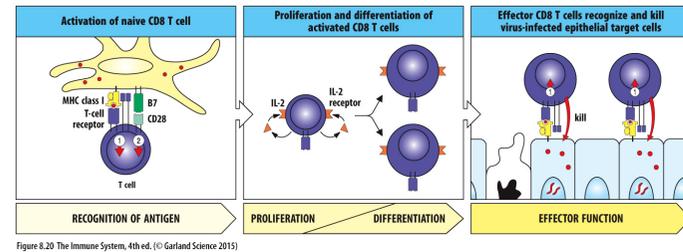
T_H2
Cytokines:
IL-4
IL-5
IL-10

Figure 8.21 The Immune System, 3ed. (© Garland Science 2009)

Two ways to activate naive CD8 T cells by infected DC



Co-stimulatory signals are required for the activation of naive T cells but not for effector CD8 T cells



Cytotoxic CD8⁺ T cells are selective and serial killers of target cells at sites of infection

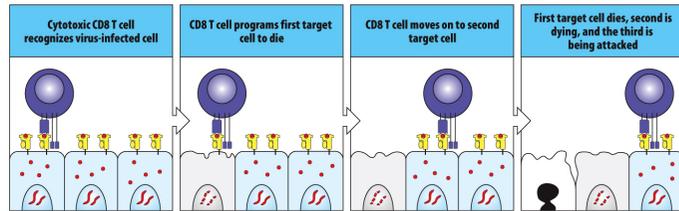


Figure 8.24 The Immune System, 4th ed. (© Garland Science 2015)

Naive CD8 T cells require stronger activation signals than naive CD 4 T cells

Effector T-cell functions are mediated by cytokines and cytotoxins

CD8 T cells		CD4 T cells				
Cytotoxic T cells		T _H 1 cells	T _H 2 cells	T _H 17 cells	T _H 17 cells	T regulatory cells (T _{reg})
Cytotoxins	Cytokines	Cytokines	Cytokines	Cytokines	Cytokines	Cytokines
perforin granzymes granulysin serglycin	IFN- γ IL-2	IFN- γ GM-CSF TNF- α IL-2	IL-4 IL-5 IL-10 IL-13 TGF- β	IL-21 IL-4 IFN- γ	IL-17 IL-21 IL-22 IL-26	TGF- β IL-10 IL-35
Kill virus-infected cells		Help macrophages to suppress intracellular infections	Help basophils, mast cells, eosinophils, and B cells respond to parasite infections	Help B cells become activated, switch isotype, and increase antibody affinity	Enhance the neutrophil response to fungal and extracellular bacterial infections	Suppress the activities of other effector T-cell populations

Figure 8.21 The Immune System, 4th ed. (© Garland Science 2015)

Cytotoxic T cells kill their target cells by inducing apoptosis

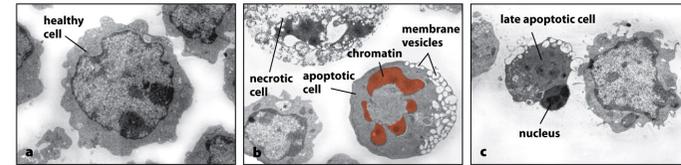


Figure 8.31 The Immune System, 3ed. (© Garland Science 2009)

Two pathways; 1 by granzymes, perforin and granulysin
2 Fas ligand

T_H1 CD4 cells activate macrophages to become highly microbicidal

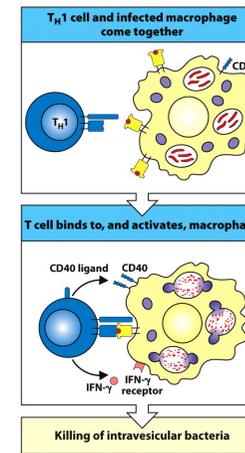


Figure 8.34 The Immune System, 3ed. (© Garland Science 2009)

conjugate pair, activation requires two signals

T_{FH} cells, and the naive B cell that they help, recognize different epitopes of the same antigen

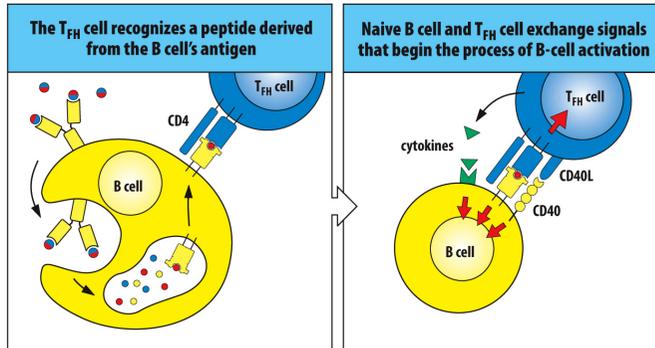


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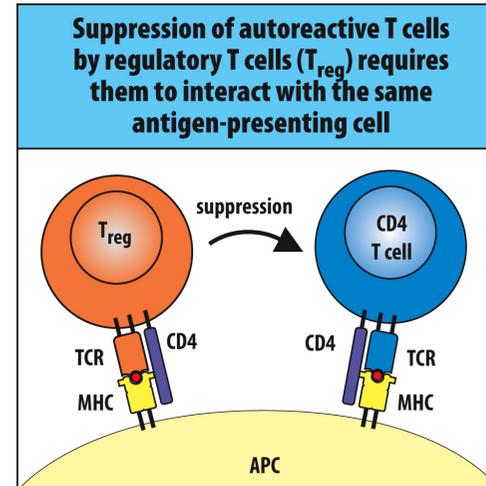


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