Adaptive Immunity

Adaptive immunity:

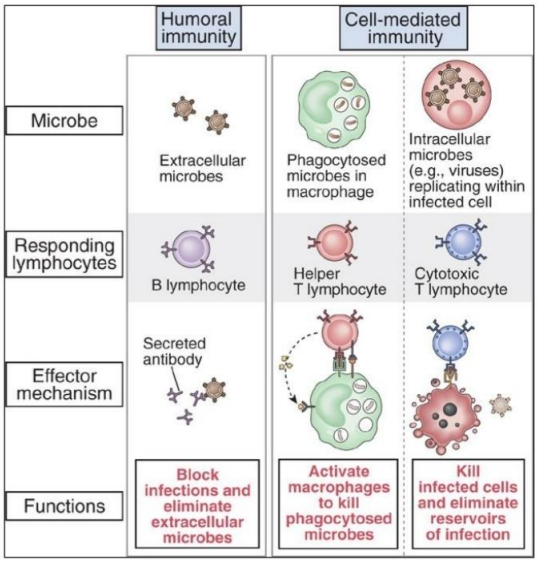
Induced resistance to a specific pathogen(Learnt by experience)

• Enhanced by second exposure (Has memory)

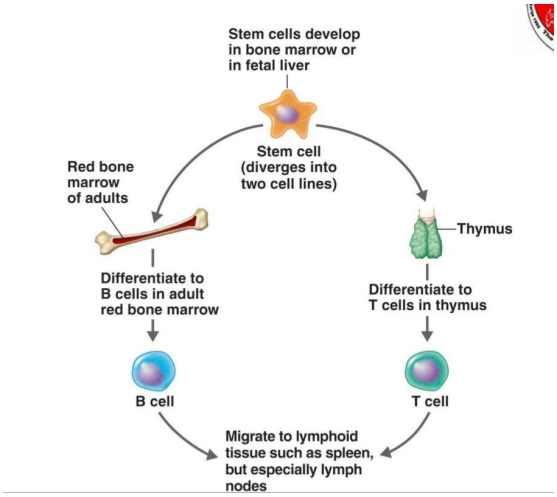
Is poorly effective without innate immunity

1. Humoral immunity: B cells and antibodies
2. Cellular immunity: Due to T cells and cytokines

Types of Adaptive Immunity



Dual Nature of Adaptive Immunity



Cellular Immunity (T Cells)

• This type of immunity is performed by T cells to combat infection by intracellular microbes

• Intracellular infections include:
– Microbes ingested by macrophage that resist microbicidal activity of macrophage
– Viruses that binds to cells receptors and replicate in the cytoplasm of these cells
• T cells help B cells to produce antibodies
• T cells interact with other cells of the immune system
• Types of T cells:
1. Helper T cells
2. Cytotoxic T cells
3. Regulatory T cells

Stages of Cellular Immunity

1. Antigen processing and presentations (APC and MHC)
2. T cells recognize and bind to Ag by T-cell receptors (TCRs)
3. Activation and signaling
4. Clonal expansion and differentiation of T cells
5. Effector functions
6. Shut down of immune response and formation of T memory

1. Antigen Processing and Presentation

• Naïve T cells can not recognize antigens directly before processing
• The antigens need to be processed and displayed by MHC molecules on professional antigen presenting cells

2&3. Recognition and Binding & Signaling and Activation

αß T cells
• About 90-95% of the blood T cells
• The receptor has two polypeptide chains α and ß
• Complete TCR is the αß receptor plus CD3 and zeta chain
• Besides TCR is CD coreceptor bind MHC
– CD4+ = (Th) bind MHC 2
– CD8+ = (Tc) bind MHC 1

• Clusters of differentiation (CD) are proteins expressed on T cells (CD4 or CD8), also called co-receptors, have a role in binding the MHC and used to differentiate T cells by binding to monoclonal antibodies.
CD8 T cells are Tc, CD4 T cell is Th1 or Th2

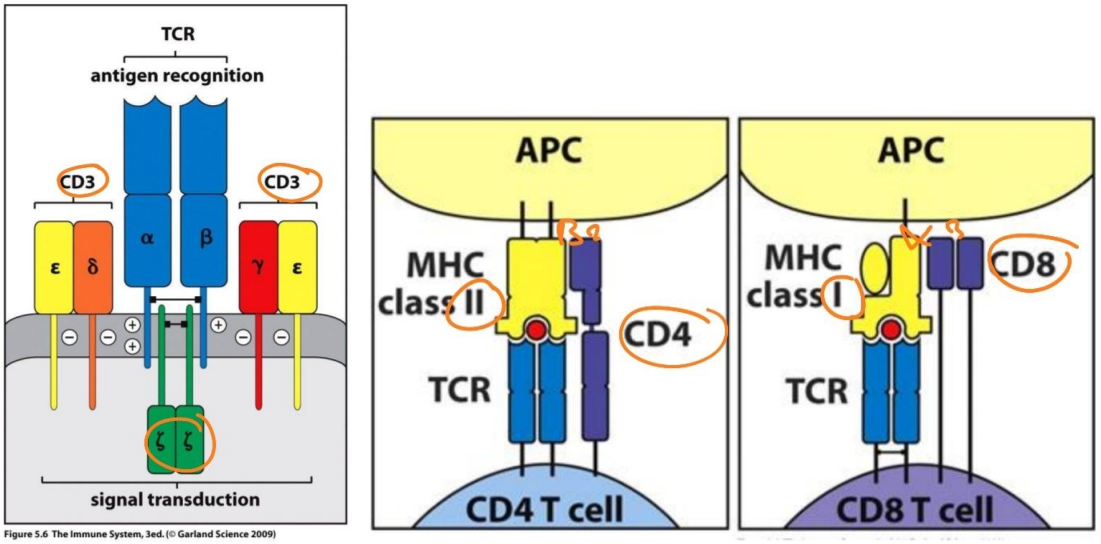


Figure 5.6 The Immune System, 3ed. (© Garland Science 2009)

Requirement for T cell activation
• Signal 1: Specific antigen on the appropriate MHC molecule on APC bind TCR on T cell.

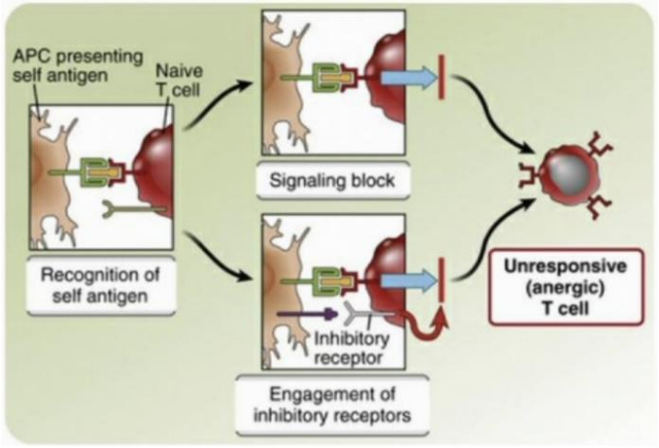
• Signal 2: Binding of co-stimulatory molecules mainly CD28

• Signal 3: cytokine effect; T cells proliferation by the effect of IL-2 (influx of calcium into the cell Calcium activates calcineurin Calcineurin activates gene for IL-2) growth factor from DC to act on T cell, and from T cell to act on itself

• If one of the first 2 is absent → T cell anergy and tolerance
• If both present →T cell proliferation and differentiation to effector and memory cells
– Effector cells in CD8 cells are always cytotoxic T lymphocytes (CTL).
– Where as effector CD4 T cells might be Th1 or Th2 cells,Th17,Thf

Inappropriate Ag or MHC
• CD4 bind MHC2 and CD8 bind MHC1
• TCR bind both the Ag and part of MHC
• Self Ag results in immature DC and macrophages (no co-stimulatory molecules) → T cell anergy.

Anergy, or immune intolerance, occurs when the there is a failure to mount a complete immune response to an antigen. Anergy can occur in both T and B lymphocytes.



T cell costimulatory molecules for binding

A sufficient activation of Naïve CD4&8 cell needs binding of T cell with APC by:

CD4/8 cell == APC

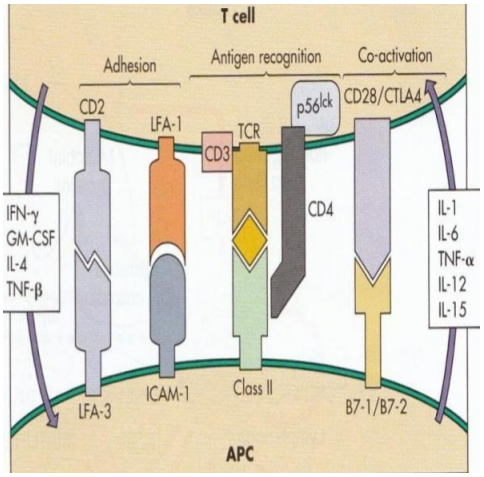
1- TCR/CD3 == antigen +MHC (CD3 signal for TCR aggregation)

2- CD4/8 == MHC2/1

3- And accessory or costimulatory molecules

a. CD28 == B7-1 (CD80) (immunoglobulin superfamily, signal for co-stimulation and production of IL2 for T cell survival and proliferation,)

b. LFA-1== ICAM-1&2 Other accessory molecules including CD45 and CD2 participate in Adhesion



Cross presentations?

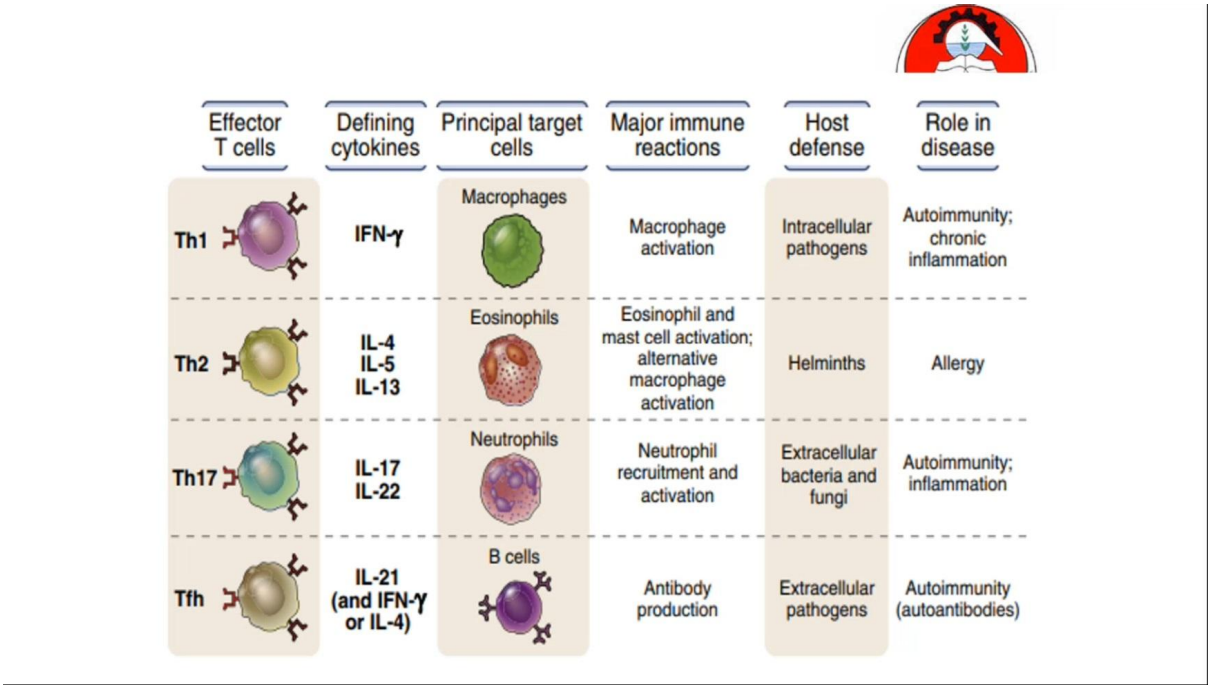
4. Proliferation and Differentiation

• As a result of T cells activation and Interleukin Secretion T cells start to proliferate resulting in expansion of antigen specific cells or clones (1-2 days)
• after 4-5 days T cells differentiate and expand to yield enough numbers of functional T cells (effectors cells)
• These cells leave the peripheral lymphoid tissue and migrate to site of infection
• A small subset of T cells will differentiate into memory T cells

5-Effector Mechanisms

Cytokine effect in priming Th1, Th2 or Th17

• The differentiation of naive CD4 T cells into different subclasses of armed effector T cells are influenced by cytokines elicited by the pathogen.
• Each subset of differentiated effector cells produces cytokines that promote its own development and may suppress the development of the others



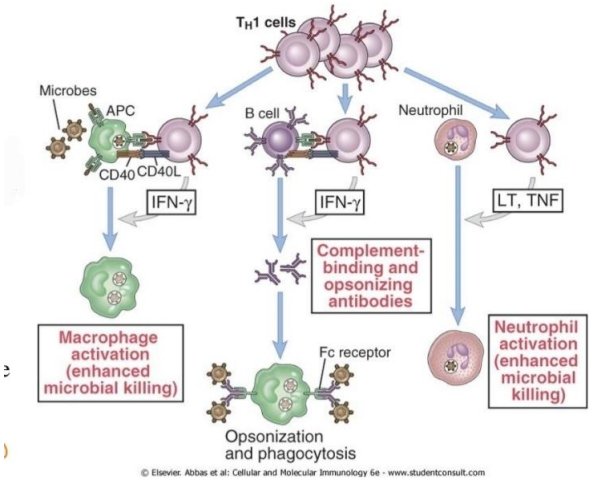
Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1	IFN-γ	Macrophages	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2	IL-4 IL-5 IL-13	Eosinophils	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
Th17	IL-17 IL-22	Neutrophils	Neutrophil recruitment and activation	Extracellular bacteria and fungi	Autoimmunity; inflammation
Tfh	IL-21 (and IFN-γ or IL-4)	B cells	Antibody production	Extracellular pathogens	Autoimmunity (autoantibodies)

Th1 cells

Th1 functions

• Activate CD8, macrophages and NK to do direct killing of infected cell (by secreting IFN gamma and IL-2)

• do neutrophil activation



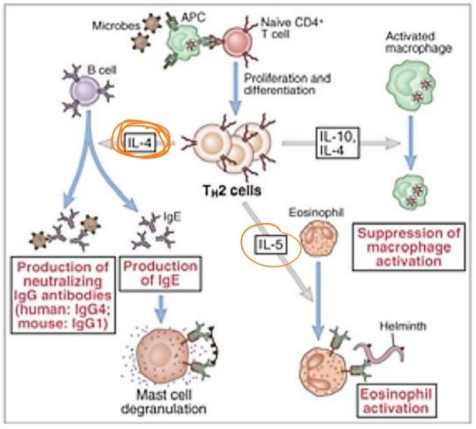
Th2 cells

Th2 functions

• Bind B cell and secret IL-4 that lead to B cell activation and antibody secretion

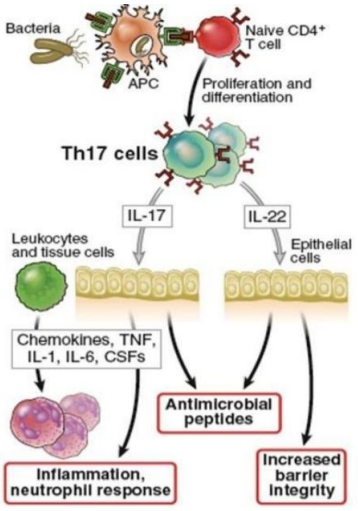
• Secret IL-5 to Activate eosinophils to react against worms

• Secret IL-10 that suppress macrophages



Th17 cells

The TH17 subset primarily produces IL-17 that is involved in:
– Recruiting neutrophils and macrophages to site of infection,
– Inducing inflammation
– Cause some autoimmune diseases.

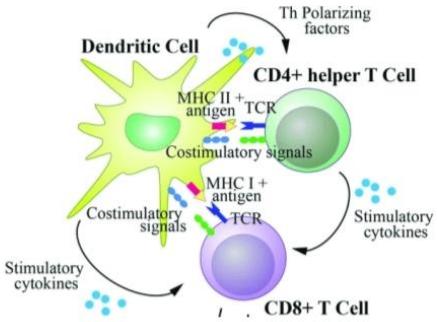


Cytotoxic T cells

• Function: killing tumor cells and virally infected cells (tissue and APC)
• CD8 activation needs cytokines as IL-2 from CD8, IL-12 and IFN gamma from TH1 and DC
• Class I MHC molecules (infected nucleated body cells) expose foreign proteins
• Tc cell releases perforin and granzymes, proteins that form pores in the target cell membrane; causing cell lysis and/or apoptosis
• A membrane-bound effector molecule expressed on CD8 T cells is Fas ligand. When this binds to Fas on a target cell it activates apoptosis in the Fas-bearing cell.

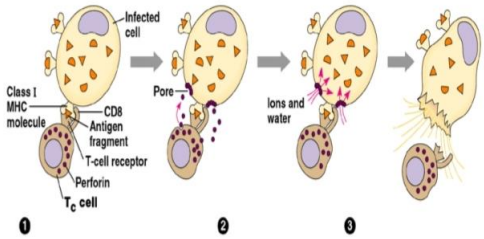
Naïve CD8 activation

2 ways for activation
1- Directly, endogenous Ag processing inside any infected cell in the presence of MHC1 plus expression of high amounts of co-stimulatory molecules
2- Indirectly by TH1 cells that secret IFN gamma to stimulate CD8



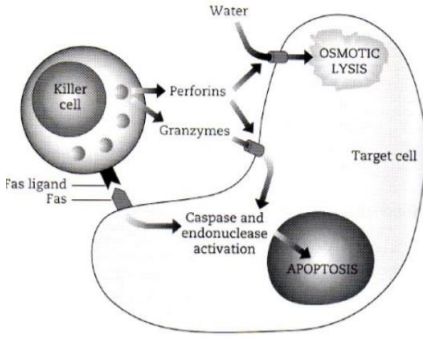
Killing by CD8 cells

1- Production of perforins & Secretion of granzymes(ADCC)
2- Induction of apoptosis by activation fasL-fas pathway



Fas-FasL

• Most important death receptor. When bound, the caspases are activated in target cell and apoptosis is induced
• Help in NK and CD8 killing of target cells.
• Help in T cell regulation:
– Killing of T cells by NK after activation (activation induced cell death (AICD))



6. Shut down of Immune Response and Formation of T Memory Cells

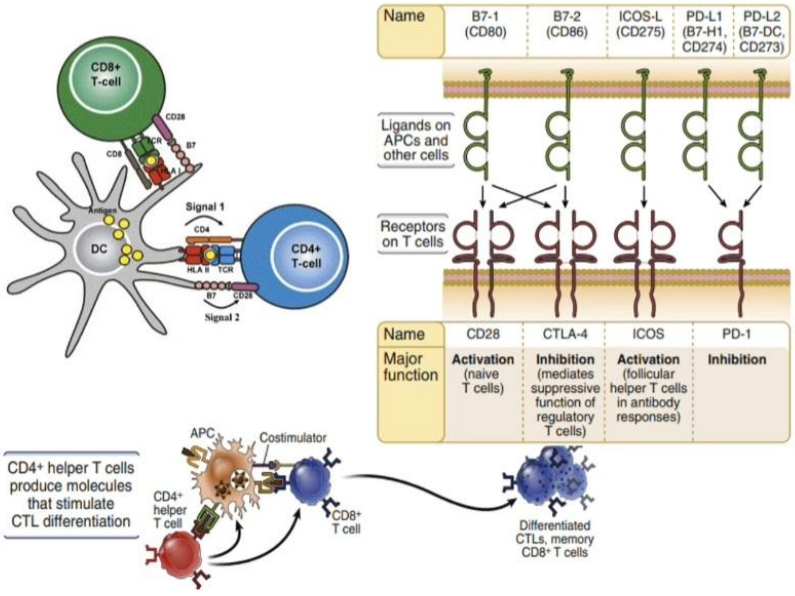
• Treg cells (have CD4 and CD25 on surface): Suppress T cells against self and shut down the T cells immune response after the microbe is eradicated
• As the infection is cleared proliferated immune cells are deprived of survival factors and the cells die by programmed cells death (apoptosis)
• A fraction of antigen-activated T cells differentiate into long lived memory T cells(IL7+15)
• Memory T cells do not produce any cytokines and they do not kill microorganism, they recognize the same antigen if it enters the body again and activate the immune response faster in the second attack of microorganism

Regulation of T lymphocyte responses
Why? To prevent tissue damage as a result of over stimulation and prevent auto-immunity

How?After clearing the Ag, CTLA-4 is expressed instead of CD28 on T cells, which binds B7 on APC and inhibits T cell activity.

- Persistent activation of T cells lead to activation induced cell death (AICD) by surface interactions of fas-fasL on Tc cells and killer cells with the target T cell.
- Elimination of Ag results in passive cell death.
- CD4 reg in the presence of IL-10 and TGF beta

PD-1 pathway
PD-1 on T cells; programmed cell death
1, PD-1 recognizes two ligands, called PD-L1 and PD-L2; PD-L1 is expressed on APCs and many other tissue cells, and PD-L2 is expressed mainly on APCs. Engagement of PD-1 by either ligand leads to inactivation of the T cells.



Biologic actions of selected T cell cytokines

Cytokine	Principal action	Cellular source(s)
IL-2	T cell proliferation; regulatory T cell survival	Activated T cells
Interferon-γ (IFN-γ)	Activation of macrophages (classical pathway)	$CD4^+$ Th1 and $CD8^+$ T cells, natural killer (NK) cells
IL-4	B cell switching to IgE; alternative macrophage activation	$CD4^+$ Th2 T cells, mast cells
IL-5	Activation of eosinophils	$CD4^+$ Th2 T cells, mast cells, innate lymphoid cells
IL-13	B cell switching to IgE; alternative macrophage activation	$CD4^+$ Th2 T cells, mast cells, innate lymphoid cells
IL-17	Stimulation of acute inflammation	$CD4^+$ Th17 T cells, other cells
IL-21	B cell activation; Tfh differentiation	$CD4^+$ Tfh T cells
IL-22	Maintenance of epithelial barrier function	$CD4^+$ Th17 T cells, NK cells, innate lymphoid cells

Surface molecules of T lymphocytes	Function	Ligand	
		Name	Expressed on
TCR	Antigen recognition	Peptide-MHC	All T cells
CD3		None	
ζ	Signal transduction by TCR complex	None	
CD4	Signal transduction	Class II MHC	Antigen-presenting cells
CD8	Signal transduction	Class I MHC	All nucleated cells
CD28	Signal transduction (costimulation)	B7-1/ B7-2	Antigen-presenting cells
CTLA-4	Negative regulation	B7-1/ B7-2	Antigen-presenting cells
PD-1	Negative regulation	PD-L1/ PD-L2	Antigen-presenting cells, tissue cells, tumor cells
LFA-1	Adhesion	ICAM-1	Antigen-presenting cells, endothelium

Superantigens

• They activate multiple clones of T-lymphocytes
• They are active at very low concentration causing release of large amounts of cytokines
• The massive T-cell activation and release of large amounts of cytokines cause systemic toxicity
• It does not lead to acquired immunity i.e no memory
• Example: Bacterial toxins:
– Staph. aureus toxic shock syndrome toxin (TSST) and enterotoxins
– Strpt. pyogenes pyrogenic toxin A

Done by:Dr.mohammed farhoud

Which of the following receptor - ligand interaction is correct?

A. CD2 - LFA-1.

B. LFA 3- ICAM-1.

C. TCR- CD4.

D. LFA-1- ICAM-1.

E. CD28- CTLA-4.

Which of the following receptor expression on T cells is expected to occur late after T cells activation:

A. CD69.

B. CD25.

C. CD4OL.

D. Adhesion and chemokine receptors.

E. CTLA-4.

Which of the following T cell types are more likely to remain in tissue?

A. Naive T cell.

B. Effector T cell.

C. Memory T cells.

D. Cytotoxic T cell. E. Helper T cell.

Mechanisms of action of regulatory T cells include all of the following EXCEPT:

A. Production of IL 10.

B. Production of TGF-beta.

C. Production of IL-2.

D. Reduced ability of APCs to stimulate T cells.

E. Inhibition of NK cells.

Which of the following cytokines and its function is correct?

A. IL5 - LPS activated monocytes.

B. IL3 - RBCs formation.

C. IL7 - Innate immune response.

D. IL5 - Eosinophilia.

E. IL35 - Activating cytokine.

Ans:D/D/C/C/D