Biology of T-cells, TCR, and antigen presentation

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- T cells involved in defense against intracellular and extracellular pathogens (Tc in cell mediated immunity and Th help in humoral immunity)
- Tumor immune response
- allograft rejection

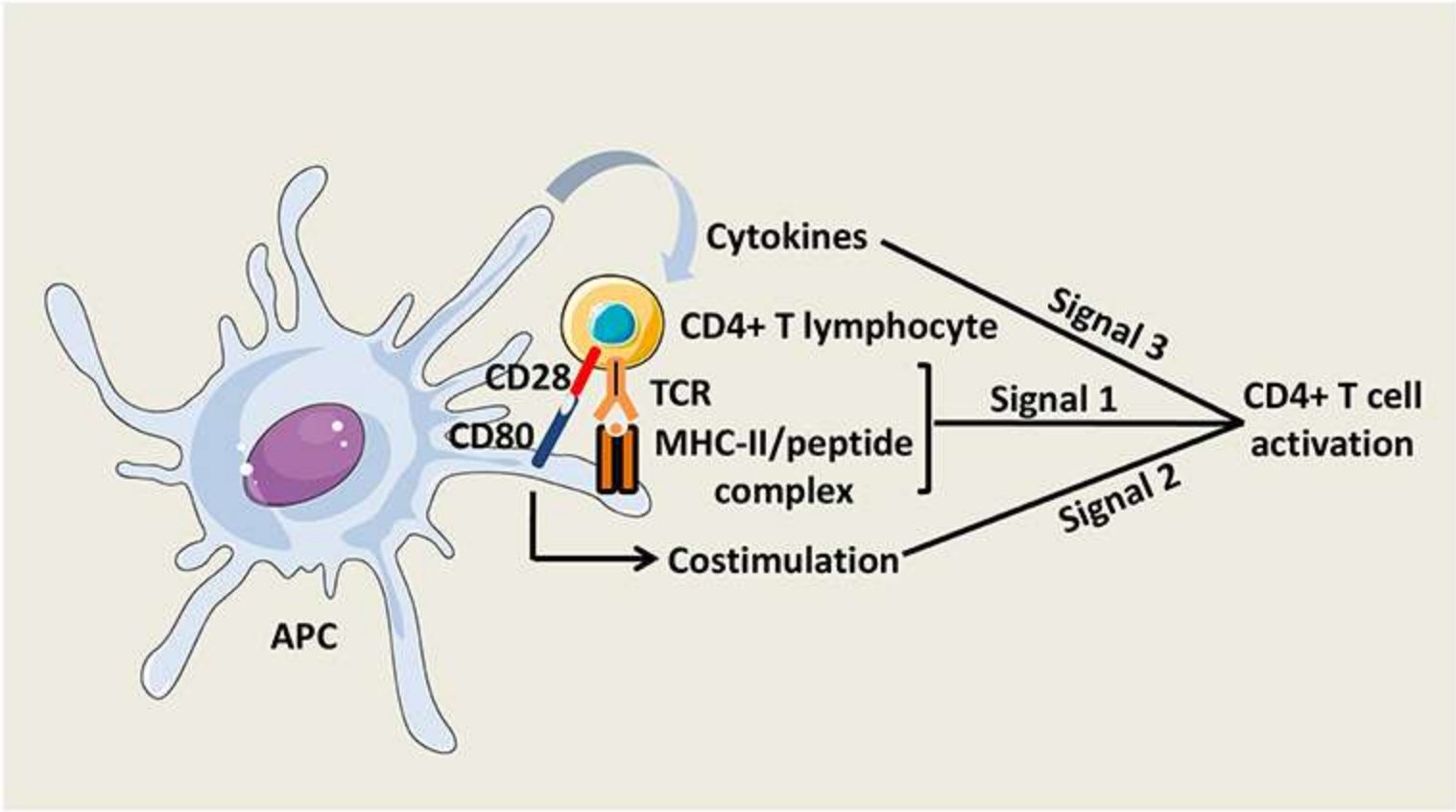
αß T cells

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

- Immunoglobulin superfamily includes the antigen receptors of T and B cells, CD3, the co-receptors CD4, CD8, most Fc receptors, CD28 and B7 adhesion molecules, cytokine receptors and the MHC molecules.

Requirement for T cell activation

- Specific antigen on the appropriate MHC molecule on APC bind TCR on T cell(signal1)
- Co stimulatory molecules (signal 2) mainly CD28
- Signal 3, cytokine effect; T cells proliferation by the effect of IL-2 growth factor from T cell to act on itself and on B cells
- If one of these is absent-----T cell anergy and tolerance
- If all present-------T cell proliferation and differentiation to effecter and memory cells
  - Effecter cell in CD8 cells is always cytotoxic T lymphocyte (CTL).
  - Where as effecter CD4 T cells might be TH1, TH17 or TH2 cells.


Cytokines
CD4+ T lymphocyte
CD28
TCR
CD80
MHC-II/peptide complex
Costimulation
APC
Signal 3
Signal 1
Signal 2
CD4+ T cell activation

T cell costimulatory molecules for binding

- Enough Naïve CD4&8 cell activation need 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

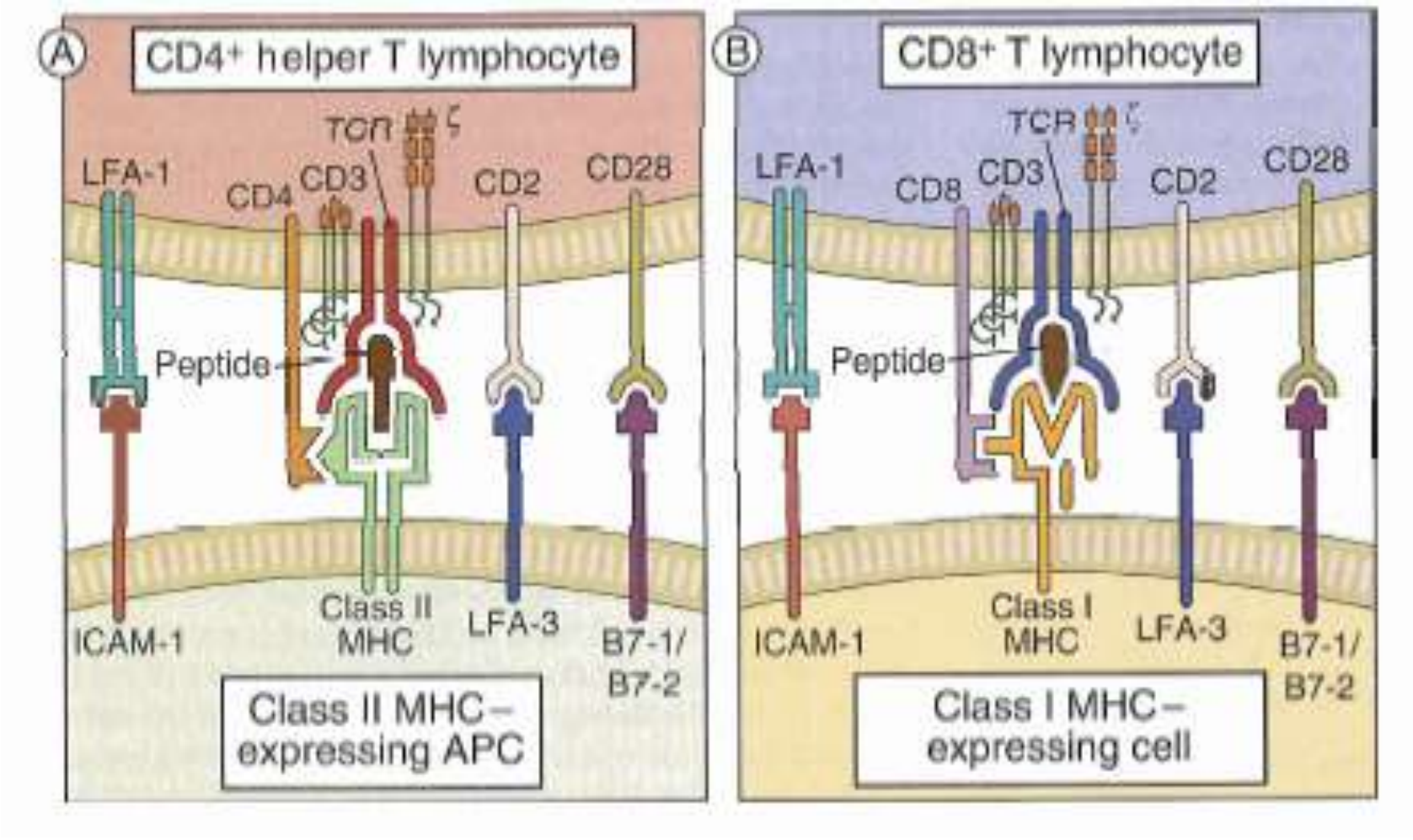
And accessory or costimulatory molecules

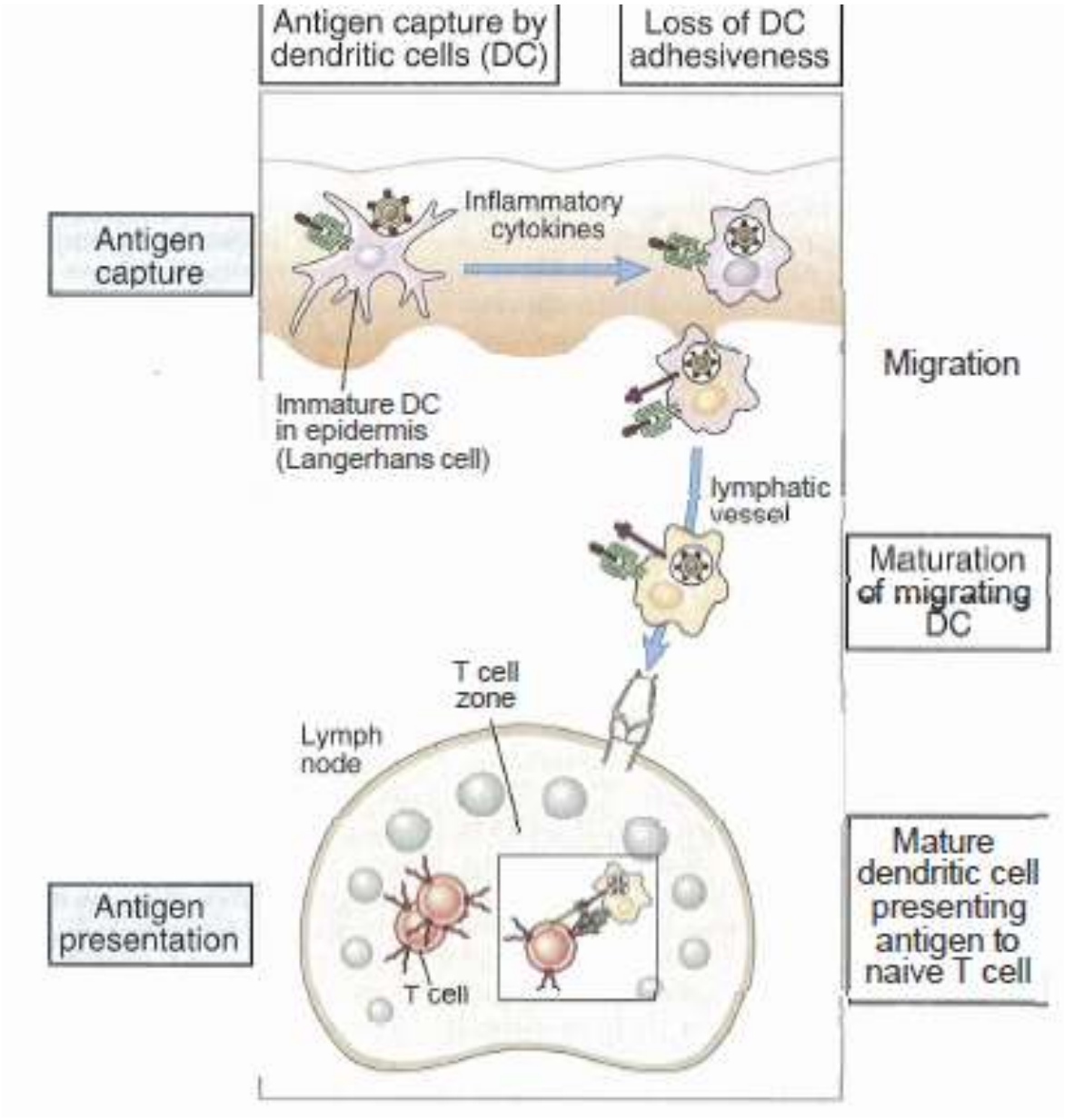
1- CD28---B7 (CD80/86)(immunoglobulin super family, signal for co-stimulation and production of IL2 for T cell survival and proliferation,)

2- CD2---LFA3

3- CD40L---CD40 (important for activation and isotype switch of B cells,)

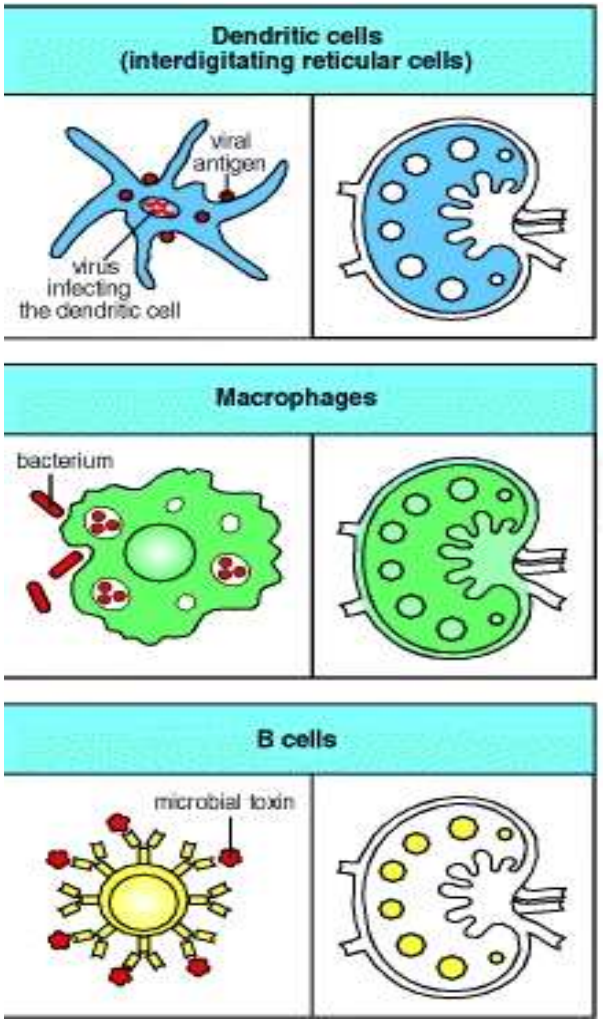
costimulatory molecules on T cells

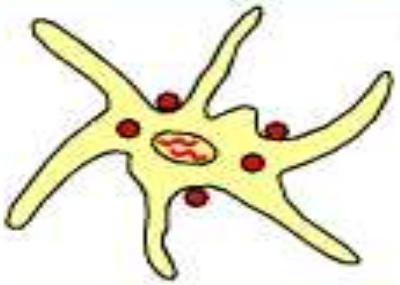
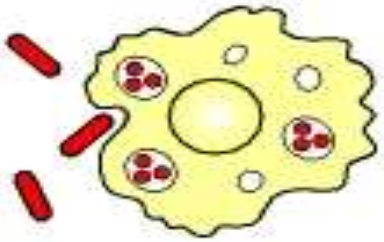
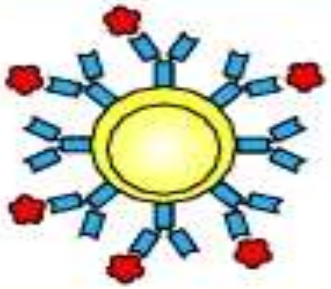


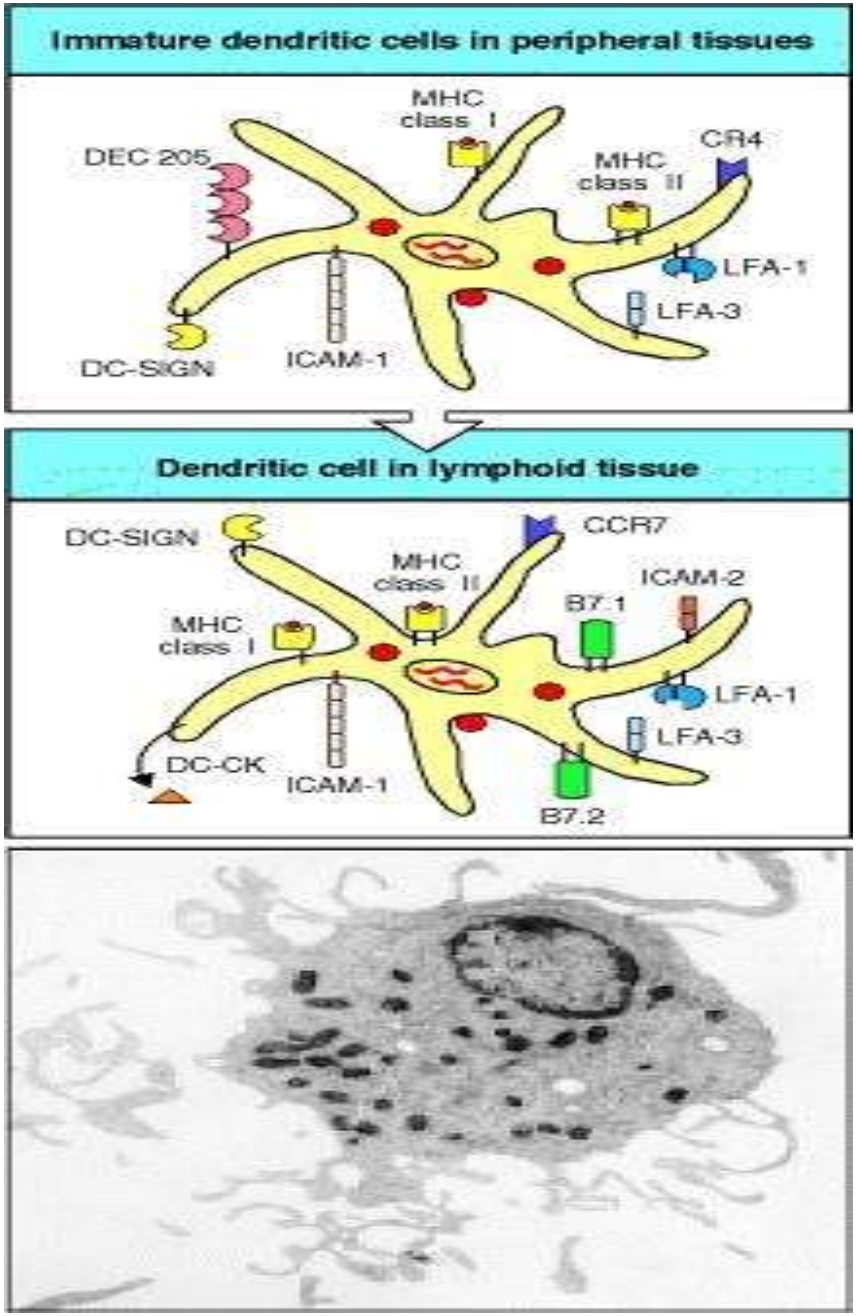

Antigen capture by dendritic cells (DC)
Loss of DC adhesiveness
Antigen capture
Inflammatory cytokines
Immature DC in epidermis (Langerhans cell)
Migration
lymphatic vessel
Maturation of migrating DC
T cell zone
Lymph node
Antigen presentation
T cell
Mature dendritic cell presenting antigen to naive T cell

APCs

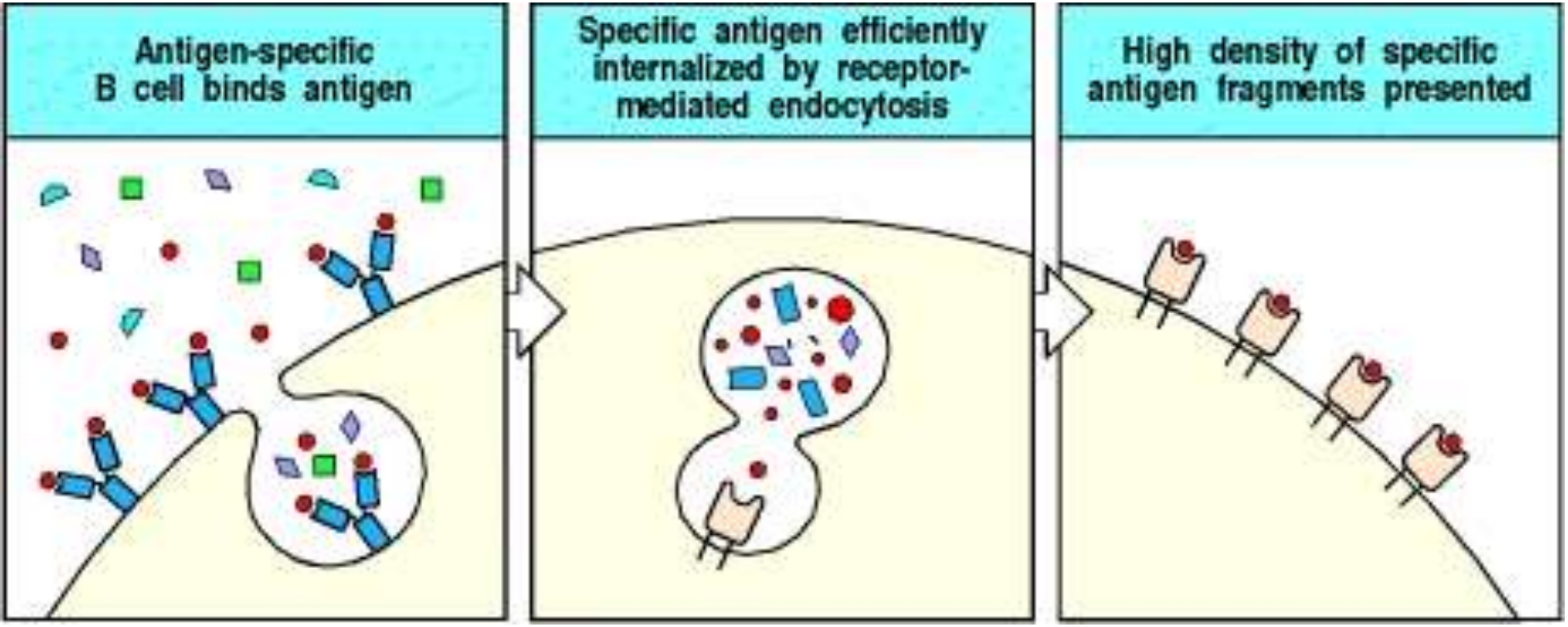
- **Antigen-presenting cells are distributed in tissues, blood and in the lymph node**
- Dendritic cells, Macrophages and B cells
- Mature dendritic cells are by far the most important activators of naive T cells and activated by wide range of antigens (viral. Bacterial and allergens)
- B cell bind soluble intact antigen and present it to TH by MHC2



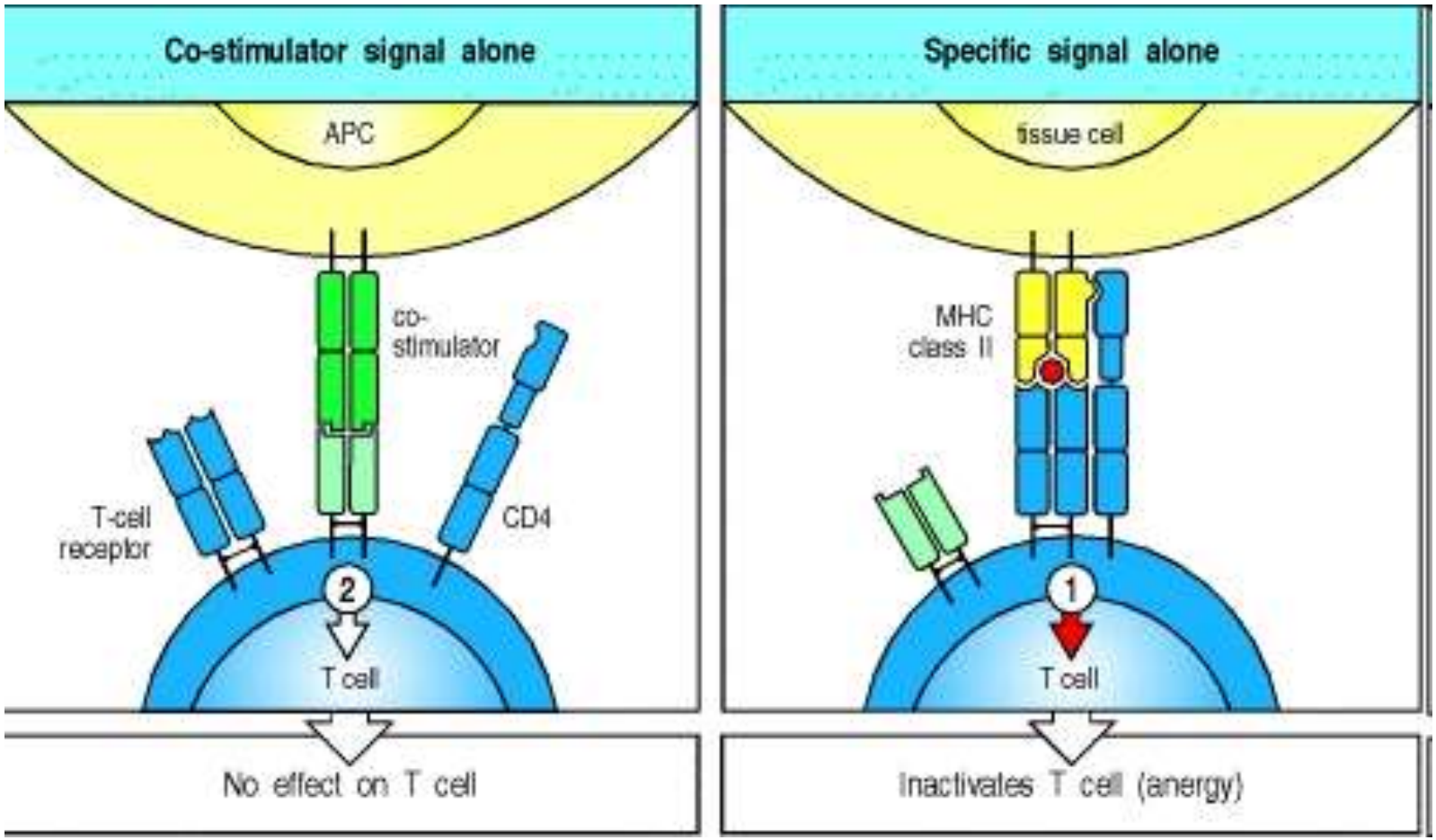
	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and 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	Lymphoid tissue Connective tissue Epithelia	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood



- Immature dentritic cells, exist at tissues and sites of infection, they express low levels of MHC1 & 2 and phagocytic receptor PRR, but low adhesion molecules.
- Internalization occur as a result of binding the Ag with PRR or by macropinocytosis.
- After engulfing the pathogen they become mature DC; migrate to peripheral L.N.
  - lose their phagocytic activity
  - and express more adhesion molecules, MHC and co-stimulatory molecules,
  - secret chemotactic factors to attract naïve T cells to the LN.

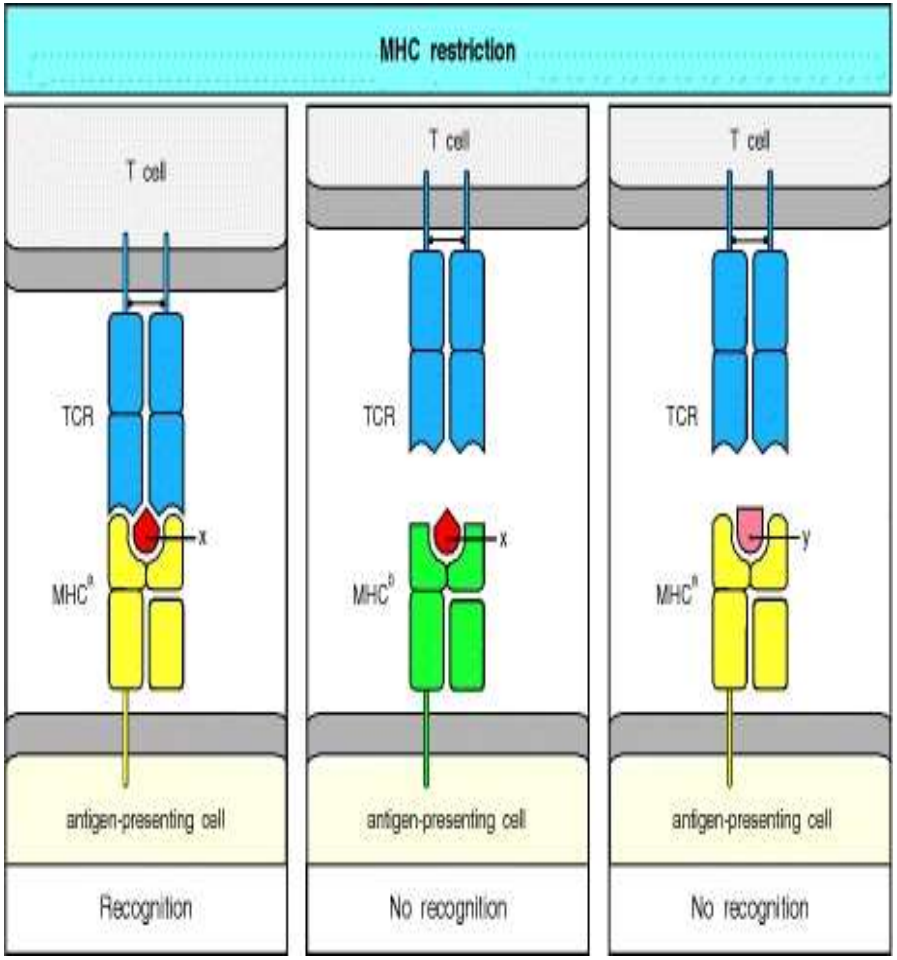


- Surface immunoglobulin (IGM or IGD) allows B cells to bind and internalize specific soluble intact antigen very efficiently. The internalized antigen is processed in intracellular vesicles where it binds to MHC class II molecules. These vesicles are then transported to the cell surface where the MHC class II:antigen complex can be recognized by Th2 cells. Because of high specificity, it is perfect when Ag concentration is low.


Co-stimulator signal alone
APC
co-
stimulator
T-cell
receptor
CD4
2
T cell
No effect on T cell
Specific signal alone
tissue cell
MHC
class II
1
T cell
Inactivates T cell (anergy)

Inappropriate Ag or MHC

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



CD4 cells

- Activated CD4+ helper T lymphocytes proliferate and differentiate into effector cells

  -Th2 differentiations are mediated largely by

  – binding B cells or APC that engulf allergen or small extracellular microbe or worm
  – and the presence of IL-4,
  – Th secrete cytokine to induce antibody production; IL-4 and IL-6 which activate B cell

  -Th1 differentiations are mediated by

  binding Th to DC that secret IL12 and IFN gamma,

  intracellular pathogen multiplying within the macrophage's phagosomes,

  -Th17

CD8 cells

- Activated CD8+ lymphocytes result from infected DC or infected cell (antigen multiply in cytosol) presentation and the presence of IL12 and IFN gamma proliferate and differentiate into CTLs that kill cells harboring microbes as viruses or intracellular pathogen in the cytoplasm or cancer cells. By destroying the infected cells, CTLs eliminate the reservoirs of infection

CD4+ Th cells

- T cells with CD4 marker (glycoprotein) represent 70% of T cells in the periphery

- Play central role in modulating immunity via secretion of cytokines that modulate:
  - B cell activation (Th2)
  - Immunoglobulin secretion (Th2)
  - Macrophage and dendritic cell activation (Th1)
  - Cellular chemotaxis and inflammation (Th17)

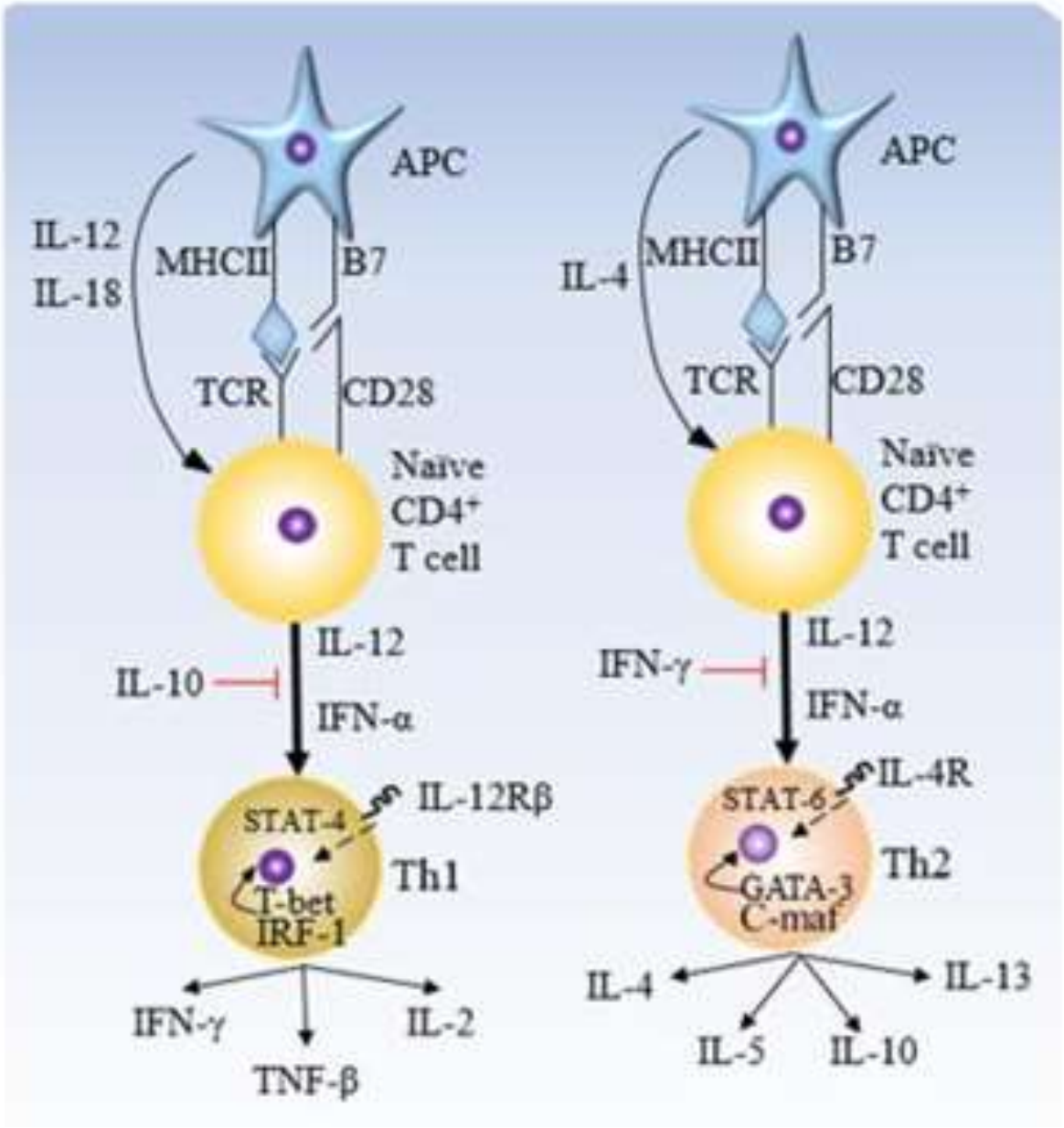
Th1 or Th2 or TH17 cells

- **CD4+ T helper cells can be classified into 3 based on their cytokine profiles at time of activation of CD4 and type of antigen: T helper cell type 1 (Th1) and T helper cell type 2 (Th2). And TH17**

Cytokine effect in priming TH1 TH2 or TH17

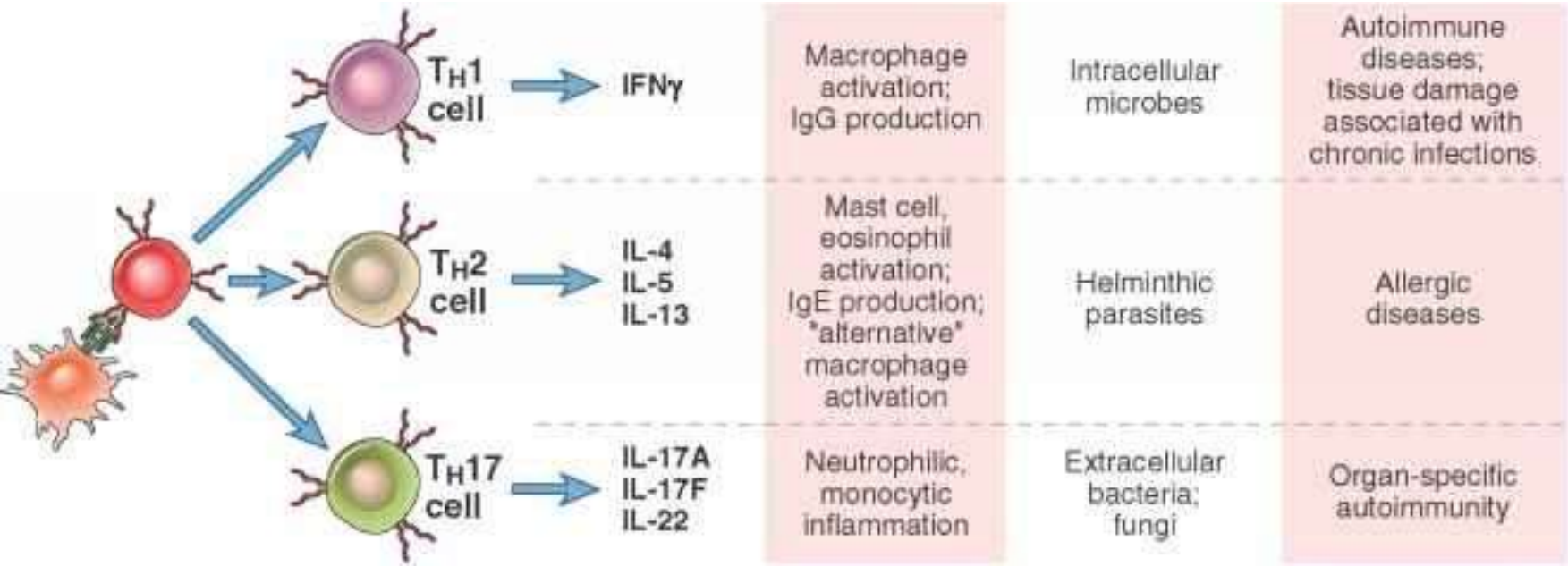
- **The differentiation of naive CD4 T cells into different subclasses of armed effector T cells is influenced by cytokines elicited by the pathogen.**
- Many pathogens, especially intracellular bacteria and viral infected cells, engulfed by dendritic cells to produce IL-12 and IFN-γ, which cause proliferating CD4 T cells to differentiate into T_H1 cells.
- IL-4, produced by DC cell or B cells engulfing parasitic worms or allergens and small microbes, and by Th2 cells. acts on proliferating CD4 T cells to cause them to become T_H2 cells.. IL-4 can inhibit IFN-gamma responses and inhibit TH1.
- In TH17 the antigen is extracellular fungi or bacterial, DC secret L-6, TGF-beta,

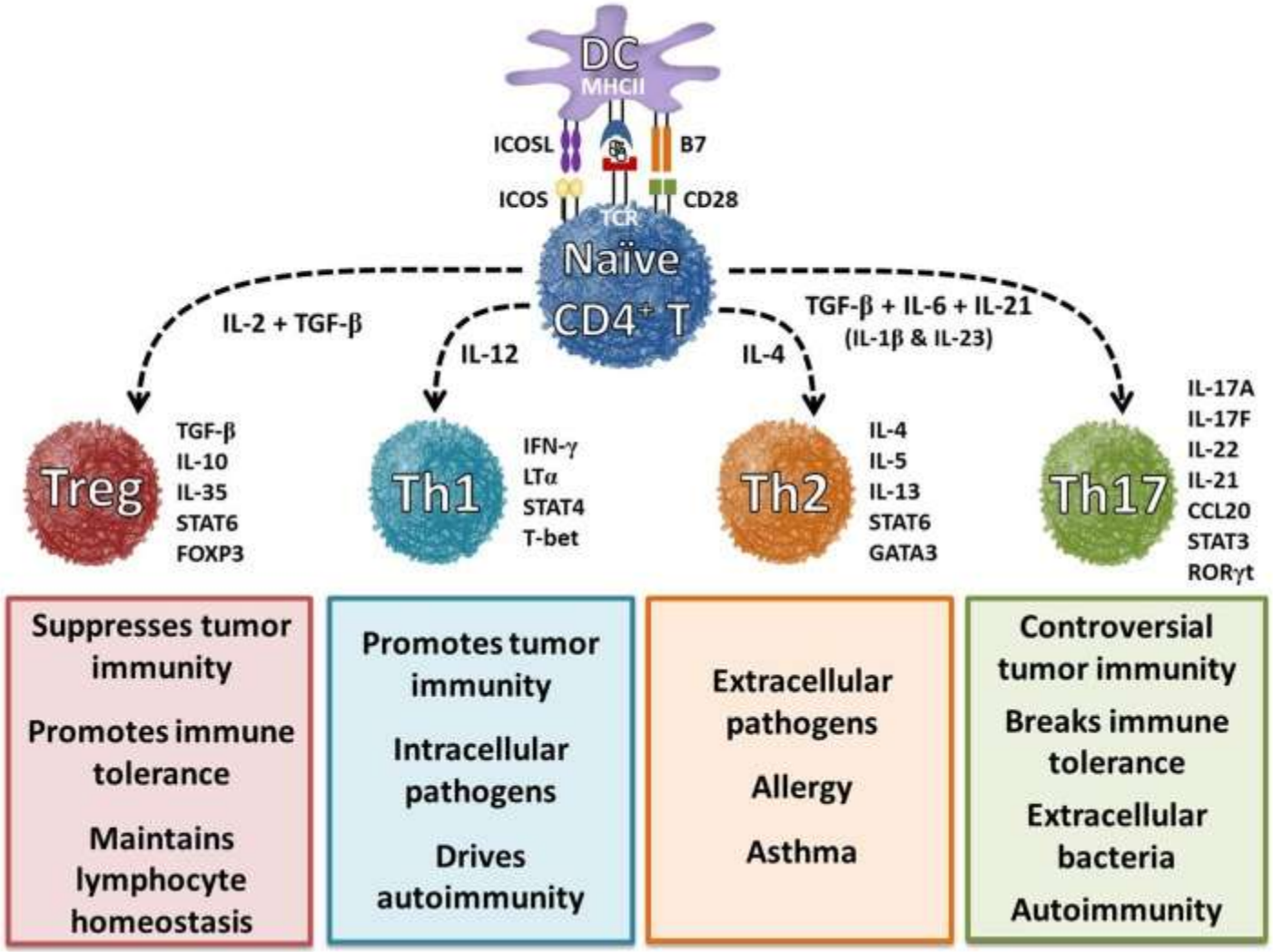
- Each subset of differentiated effector cells produces cytokines that promote its own development and may suppress the development of the other subsets
- IFN-γ secreted by TH1 cells promotes further TH1 differentiation and inhibits the generation of TH2 and TH17 cells.
- Similarly, IL-4 produced by TH2 cells promotes TH2 differentiation and inhibit TH1,
- and IL-17 produced by TH17 cells enhances TH17 differentiation.


APC
IL-12
IL-18
MHCII
B7
TCR
CD28
Naive
CD4+
T cell
IL-12
IL-10
IFN-α
STAT-4
IL-12Rβ
T-bet
IRF-1
Th1
IFN-γ
IL-2
TNF-β
APC
IL-4
MHCII
B7
TCR
CD28
Naive
CD4+
T cell
IL-12
IFN-γ
IFN-α
STAT-6
IL-4R
GATA-3
C-maf
Th2
IL-4
IL-13
IL-5
IL-10

Antigen effect in priming TH1 or TH17 or TH2

- The nature and amount of ligand presented to a CD4 T cell during primary stimulation can determine its functional phenotype.
- CD4 T cells presented by B cell with low levels of a small antigen or toxins or worms that bind the T-cell receptor less tightly, differentiate preferentially into TH2 cells making IL-4 and IL-5. Such T cells are most active in stimulating naive B cells to make antibody. Or activate eosinophils. the antigen is extracellular helminth or allergen
- T cells presented with a high density of a ligand that binds the T- cell receptor strongly differentiate into TH1 cells that secrete and IFN-gamma, and are most effective in activating macrophages. intracellular pathogen multiplying within the macrophage's phagosomes,


T_H1 cell
IFNγ
Macrophage activation; IgG production
Intracellular microbes
Autoimmune diseases; tissue damage associated with chronic infections
T_H2 cell
IL-4
IL-5
IL-13
Mast cell, eosinophil activation; IgE production; "alternative" macrophage activation
Helminthic parasites
Allergic diseases
T_H17 cell
IL-17A
IL-17F
IL-22
Neutrophilic, monocytic inflammation
Extracellular bacteria; fungi
Organ-specific autoimmunity


DC
MHCII
ICOSL
B7
ICOS
CD28
TCR
Naïve
CD4+ T
IL-2 + TGF-β
IL-12
IL-4
TGF-β + IL-6 + IL-21
(IL-1β & IL-23)
Treg
TGF-β
IL-10
IL-35
STAT6
FOXP3
Th1
IFN-γ
LTα
STAT4
T-bet
Th2
IL-4
IL-5
IL-13
STAT6
GATA3
Th17
IL-17A
IL-17F
IL-22
IL-21
CCL20
STAT3
RORγt
Suppresses tumor immunity
Promotes immune tolerance
Maintains lymphocyte homeostasis
Promotes tumor immunity
Intracellular pathogens
Drives autoimmunity
Extracellular pathogens
Allergy
Asthma
Controversial tumor immunity
Breaks immune tolerance
Extracellular bacteria
Autoimmunity

Effector T cells

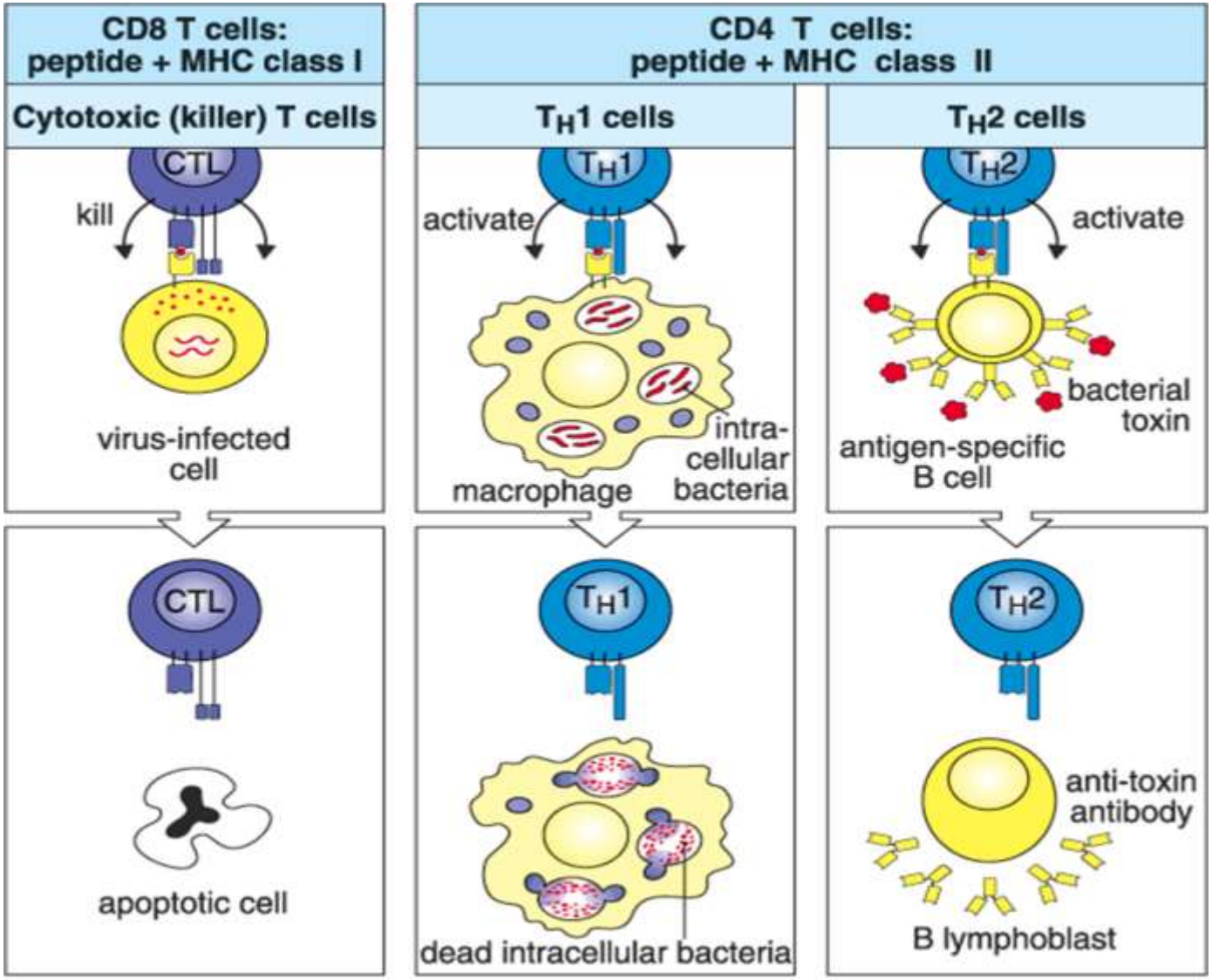
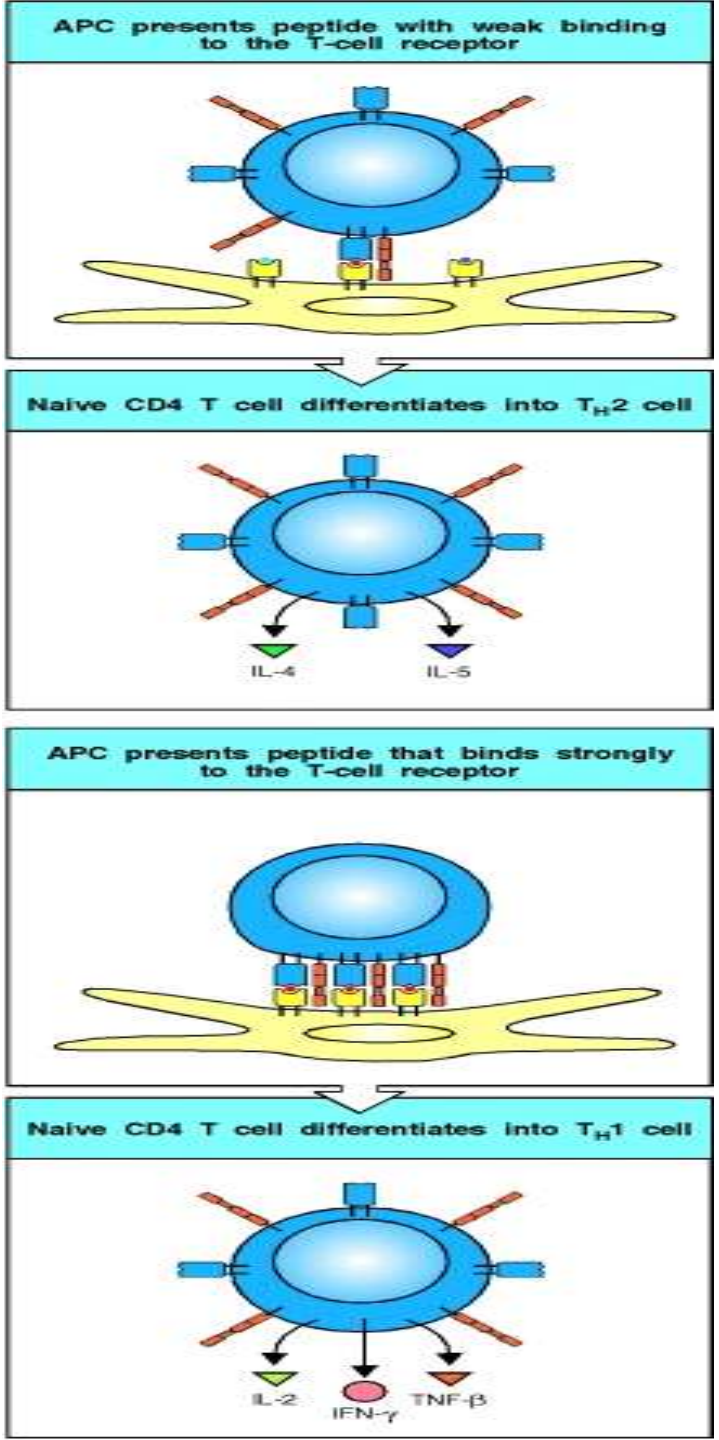
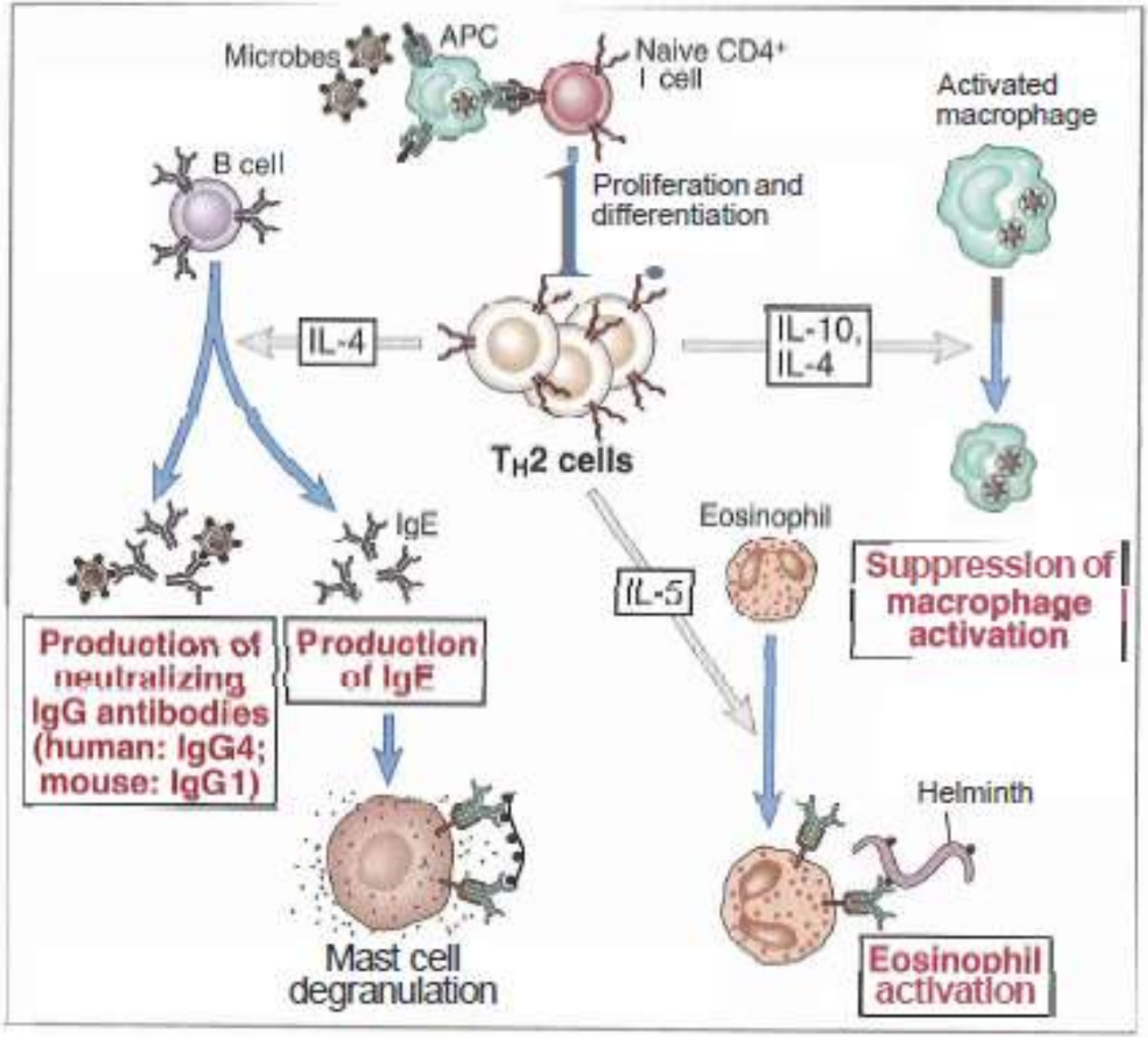


Fig 8.27 © 2001 Garland Science


APC presents peptide with weak binding to the T-cell receptor
Naive CD4 T cell differentiates into T_H2 cell
IL-4
IL-5
APC presents peptide that binds strongly to the T-cell receptor
Naive CD4 T cell differentiates into T_H1 cell
IL-2
IFN-γ
TNF-β

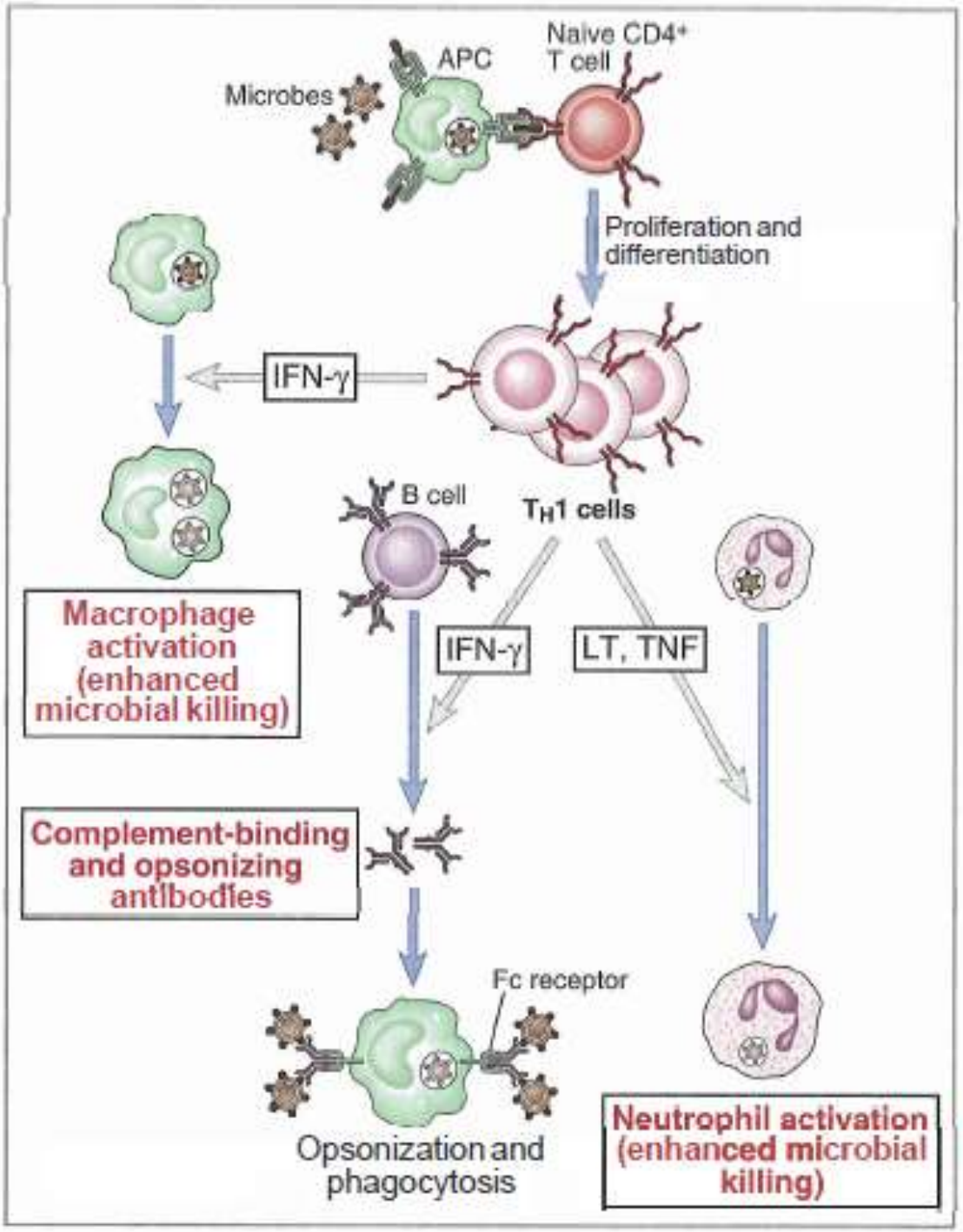
Th2

– 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


Microbes
APC
Naive CD4+
T cell
Activated
macrophage
B cell
Proliferation and
differentiation
IL-4
IL-10,
IL-4
TH2 cells
IgE
Eosinophil
IL-5
Suppression of
macrophage
activation
Production of
neutralizing
IgG antibodies
(human: IgG4;
mouse: IgG1)
Production
of IgE
Helminth
Mast cell
degranulation
Eosinophil
activation

Th1

- TH1 function
  - Activate CD8, macrophages and NK to do direct killing of infected cell (by secreting IFN gamma and IL-2)
  - do neutrophil activation
  - Activate B cell to secret opsonizing antibodies belonging to certain IgG subclasses (IgG1 and IgG3 in humans that increase phagocytosis
  - Help in cell mediated immunity


Naive CD4+
T cell
APC
Microbes
Proliferation and
differentiation
IFN-γ
B cell
TH1 cells
Macrophage
activation
(enhanced
microbial killing)
IFN-γ
LT, TNF
Complement-binding
and opsonizing
antibodies
Fc receptor
Opsonization and
phagocytosis
Neutrophil activation
(enhanced microbial
killing)