Biology of T-cells, TCR, and antigen presentation

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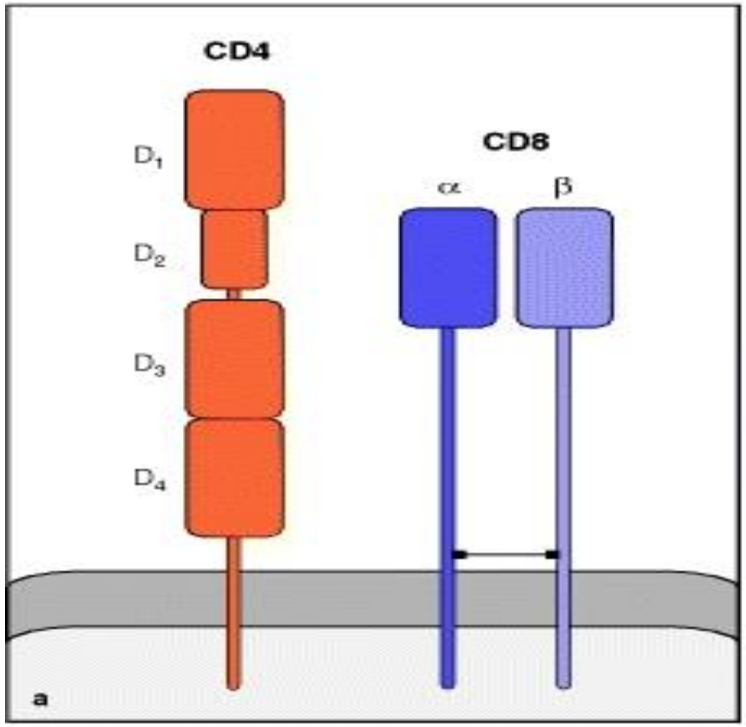
Factors influencing the Strength binding of the TCR to antigen

- Antigen binding increase by
- (TCR CD4/8 binding to MHC and antigen provides the first signal).
- Coreceptors binding;
  - **T cells coreceptors** are the CD4 and CD8 proteins (Th or Tc respectively). CD8 and CD4 interact with class I and class II MHC molecules, respectively.
  - These besides co-receptors CD3 and zeta chain do signal transduction to inside T cells

CD4 and CD8



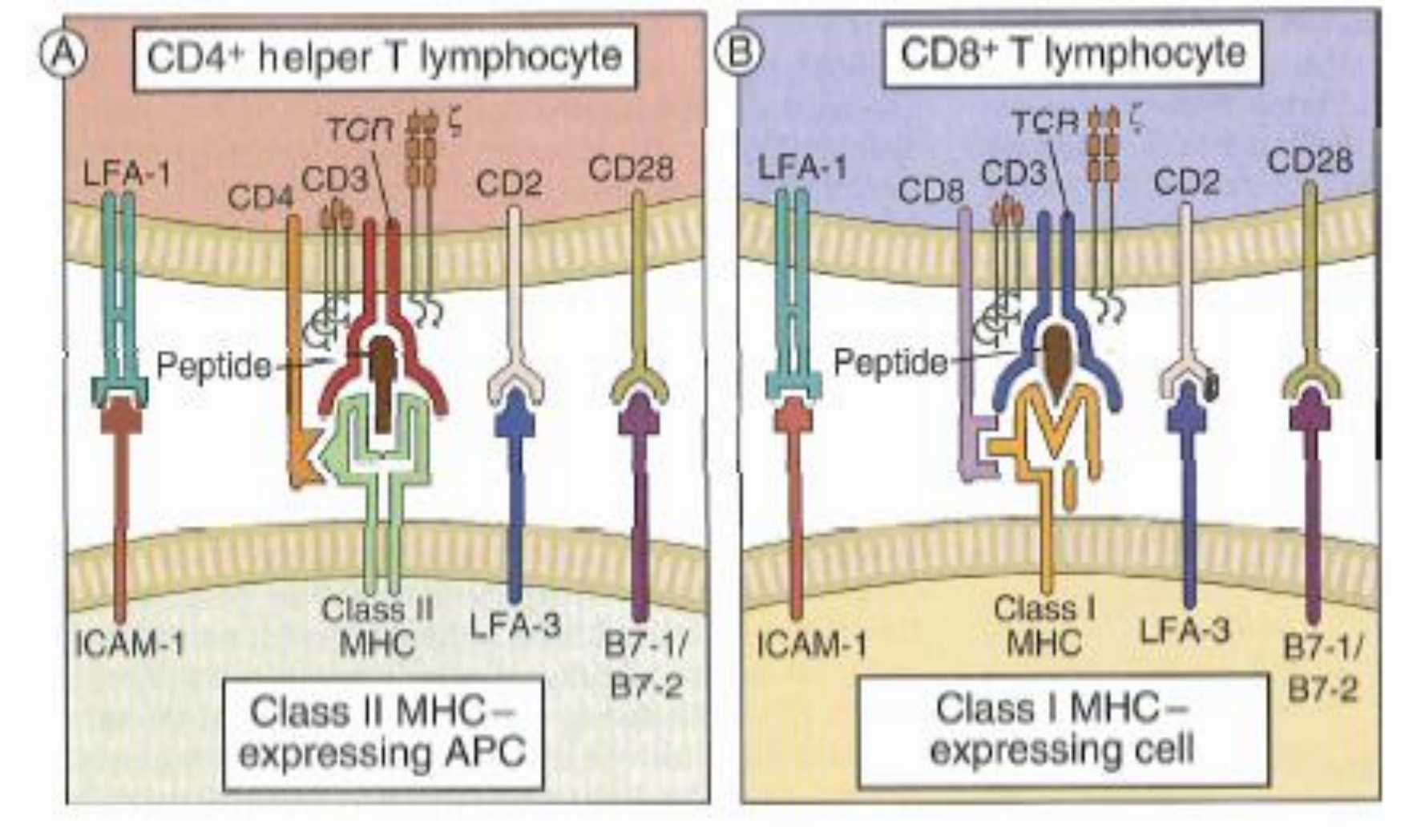
- Cluster of differentiation (CD) are proteins expressed on T cells (CD4 or CD8) have a role in binding the MHC and used to differentiate the cells by binding to monoclonal antibodies. CD8 T cells are Tc, CD4 T cell is Th1 or Th2

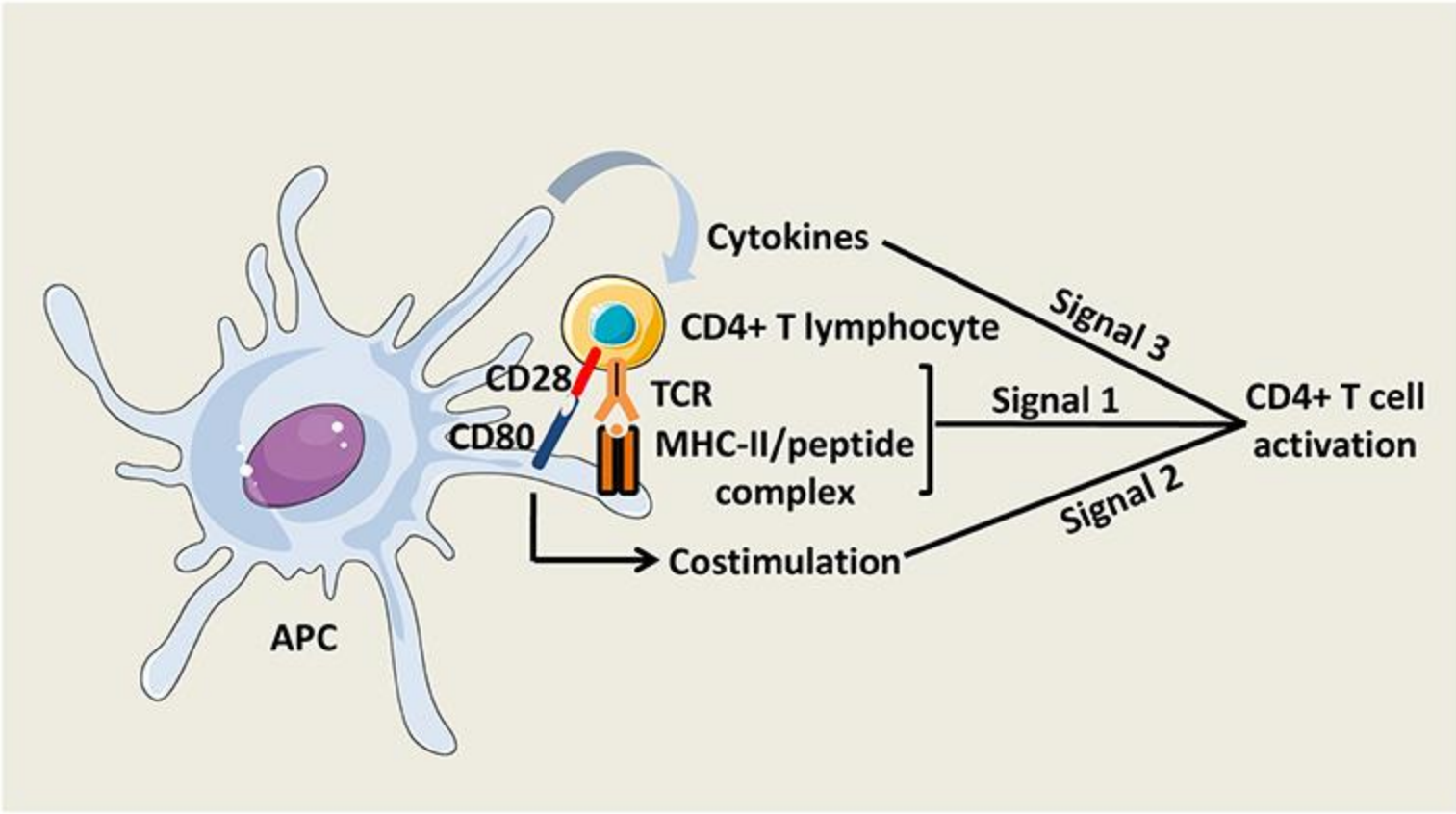
Costimulatory receptors on T cells

- Provide so-called second signals for lymphocytes
  - CD28, the earliest accessory molecules induce signaling. when it bind B7 on APC, it initiate T cell proliferation by expression of IL-2 cytokine and its receptor. it binds CTLA-4 on T cell when the antigen is cleared So that T cell is regulated, lead to T cell death.
  - CD2 is a glycoprotein present on more than 90% of mature T cells, and on NK cells. The principal ligand for CD2 in humans is a molecule called leukocyte function associated antigen 3 (LFA-3, or CD58), CD2 functions as a signal transducer
  - CD40L---CD40 on B cells (important for activation and isotype switch of B cells,)

- Signal 3, cytokine effect; T cells proliferation by the effect of IL-2 growth factor from Th and Tc 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 CD4 cells is T h1 , Th2 or Th17 lymphocyte
  - Effecter cell in CD8 cells is always cytotoxic T lymphocyte (CTL).

Costimulatory receptors on T cells



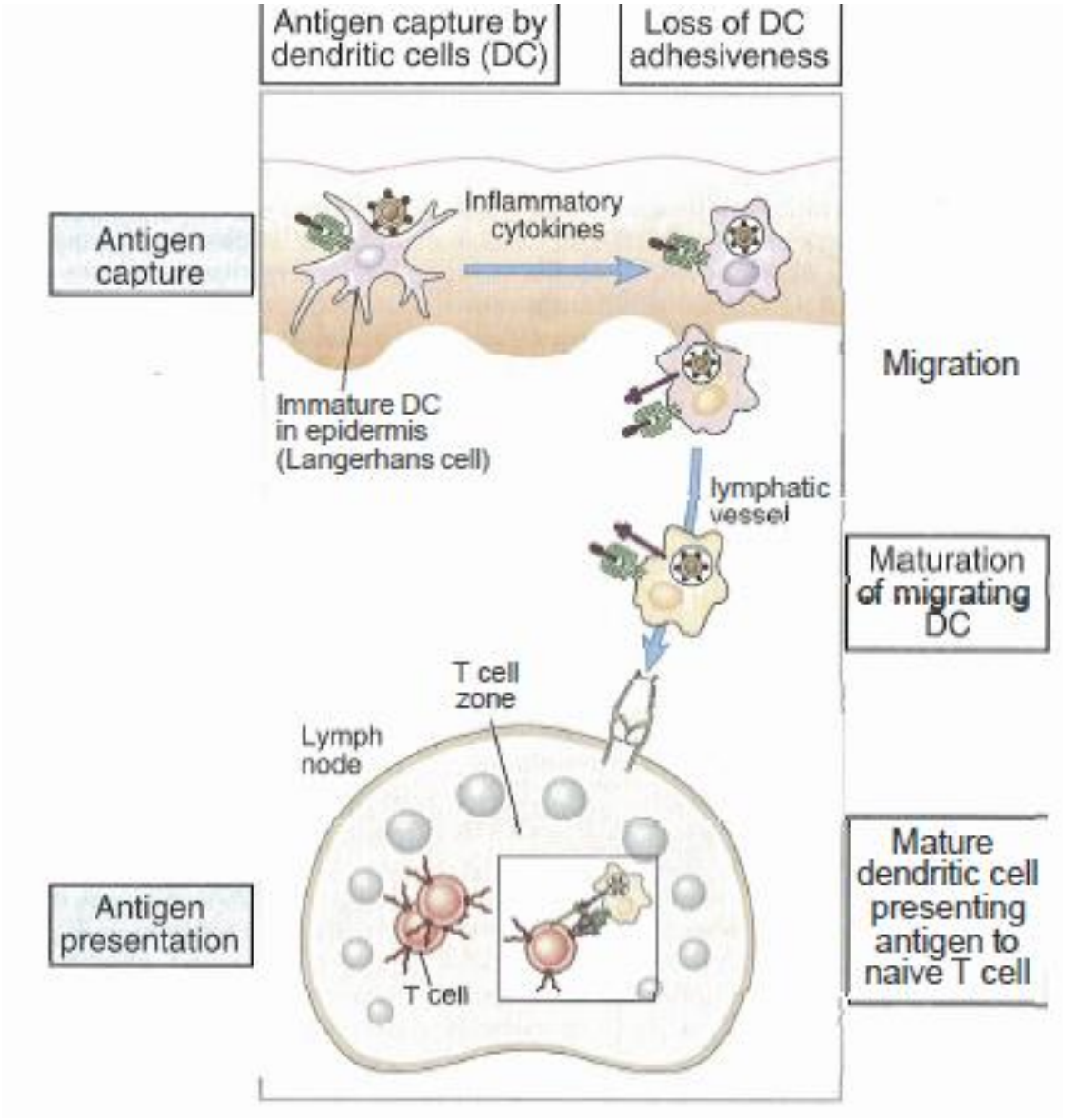

Cytokines
CD4+ T lymphocyte
CD28
TCR
CD80
MHC-II/peptide complex
Costimulation
APC
Signal 3
Signal 1
Signal 2
CD4+ T cell activation

The immunologic synapse.

- When the TCR complex recognizes MHC-associated peptides on an APC, several T cell surface proteins and intracellular signaling molecules are rapidly mobilized to the site of T cell–APC contact
- This region of physical contact between the T cell and the APC is called an immunologic synapse or a supramolecular activation cluster (SMAC).
- The T cell molecules that are rapidly mobilized to the center of the synapse include the TCR complex (the TCR, CD3, and ζ chains), CD4 or CD8 coreceptors, receptors for costimulators (such as CD28), enzymes, and adaptor proteins that associate with the cytoplasmic tails of the transmembrane receptors.

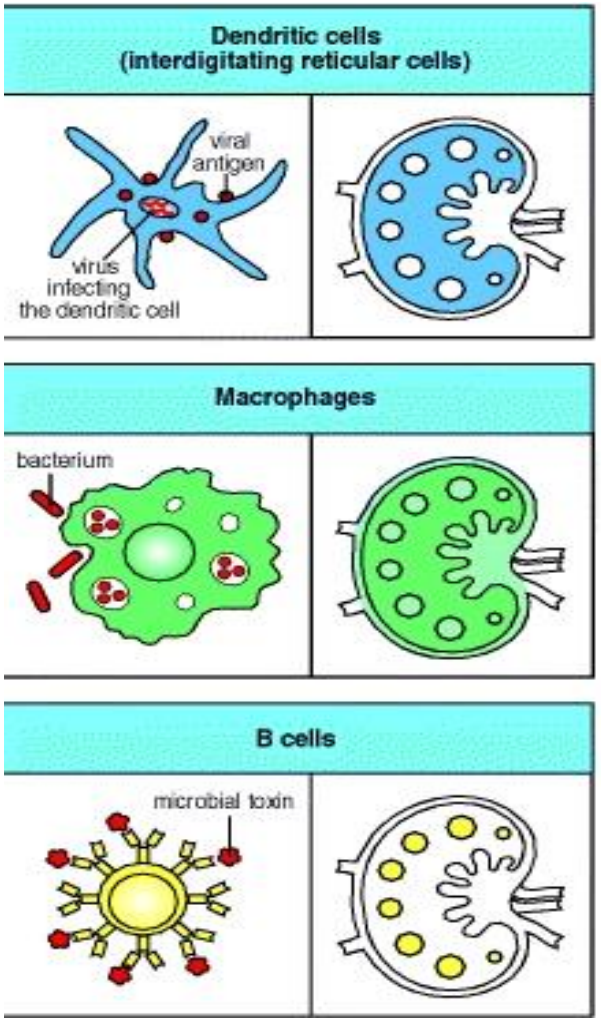
- T cells involved in
  - Defense against intracellular and extracellular pathogens (Tc in cell mediated immunity and Th help in humoral immunity)
  - Tumor immune response
  - Graft rejection
  - Autoimmune diseases

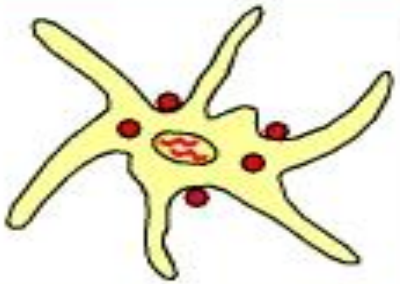
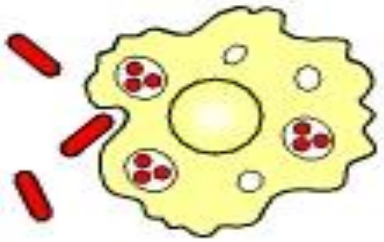
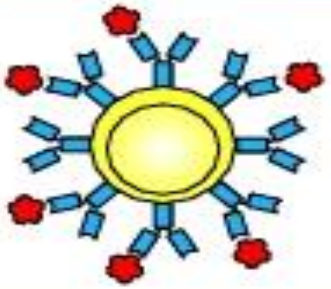
- Immunoglobulin superfamily includes the antigen receptors of T and B cells, CD3, the co-receptors CD4, CD8, most Fc receptors, CD28 and B7 adhesion molecules, cytokine receptors and the MHC molecules.

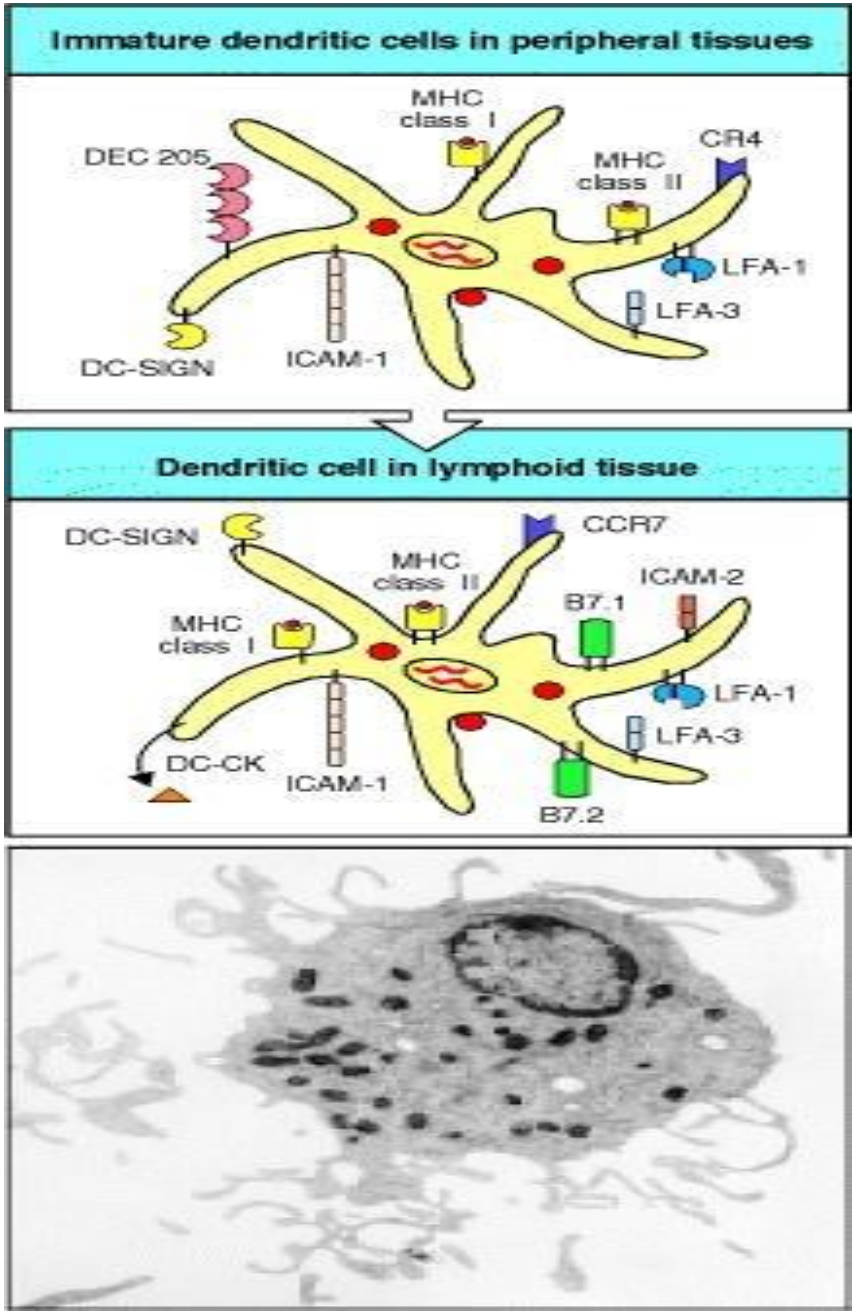

Antigen capture by dendritic cells (DC)
Loss of DC adhesiveness
Antigen capture
Inflammatory cytokines
Immature DC in epidermis (Langerhans cell)
Migration
lymphatic vessel
Maturation of migrating DC
T cell zone
Lymph node
Antigen presentation
T cell
Mature dendritic cell presenting antigen to naive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

APCs

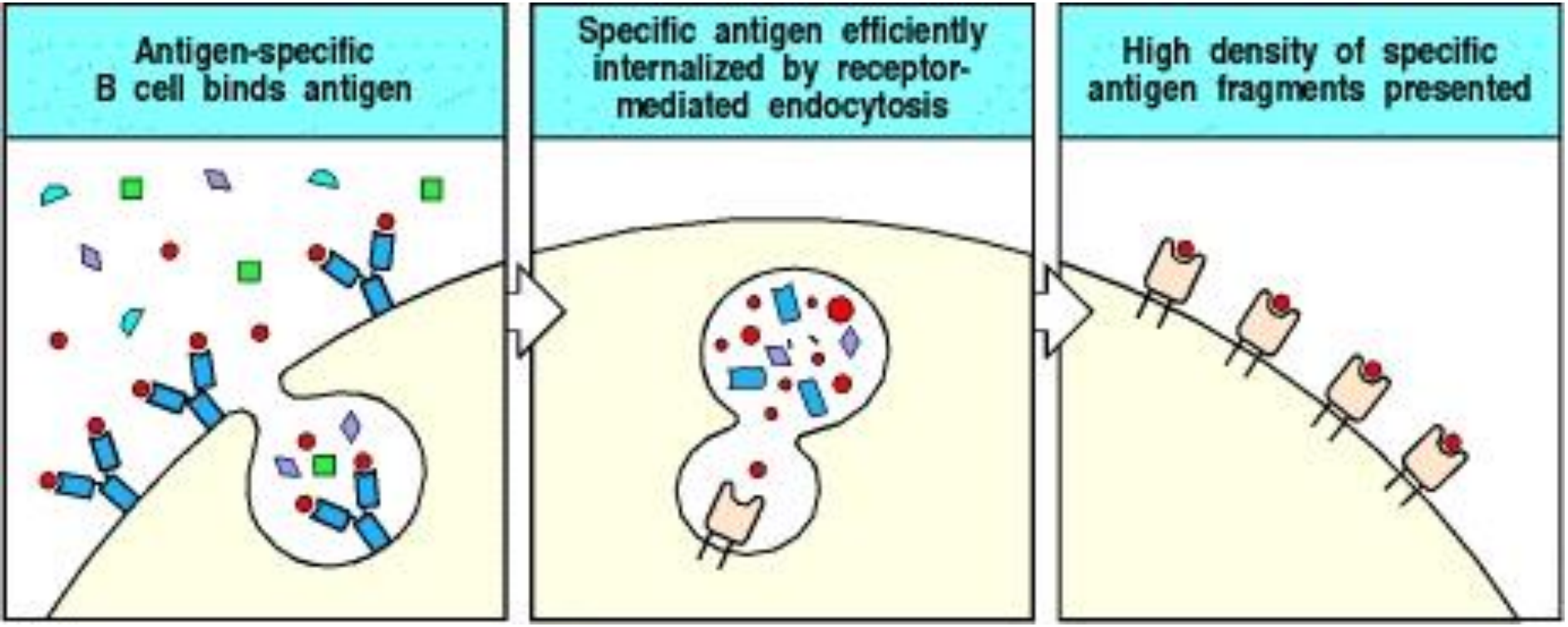
- **Antigen-presenting cells are distributed in tissues, blood and in the lymph node**
- Dendritic cells, Macrophages and B cells
- Mature dendritic cells are by far the most important activators of naive T cells and activated by wide range of antigens (viral. Bacterial and allergens)
- B cell bind soluble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



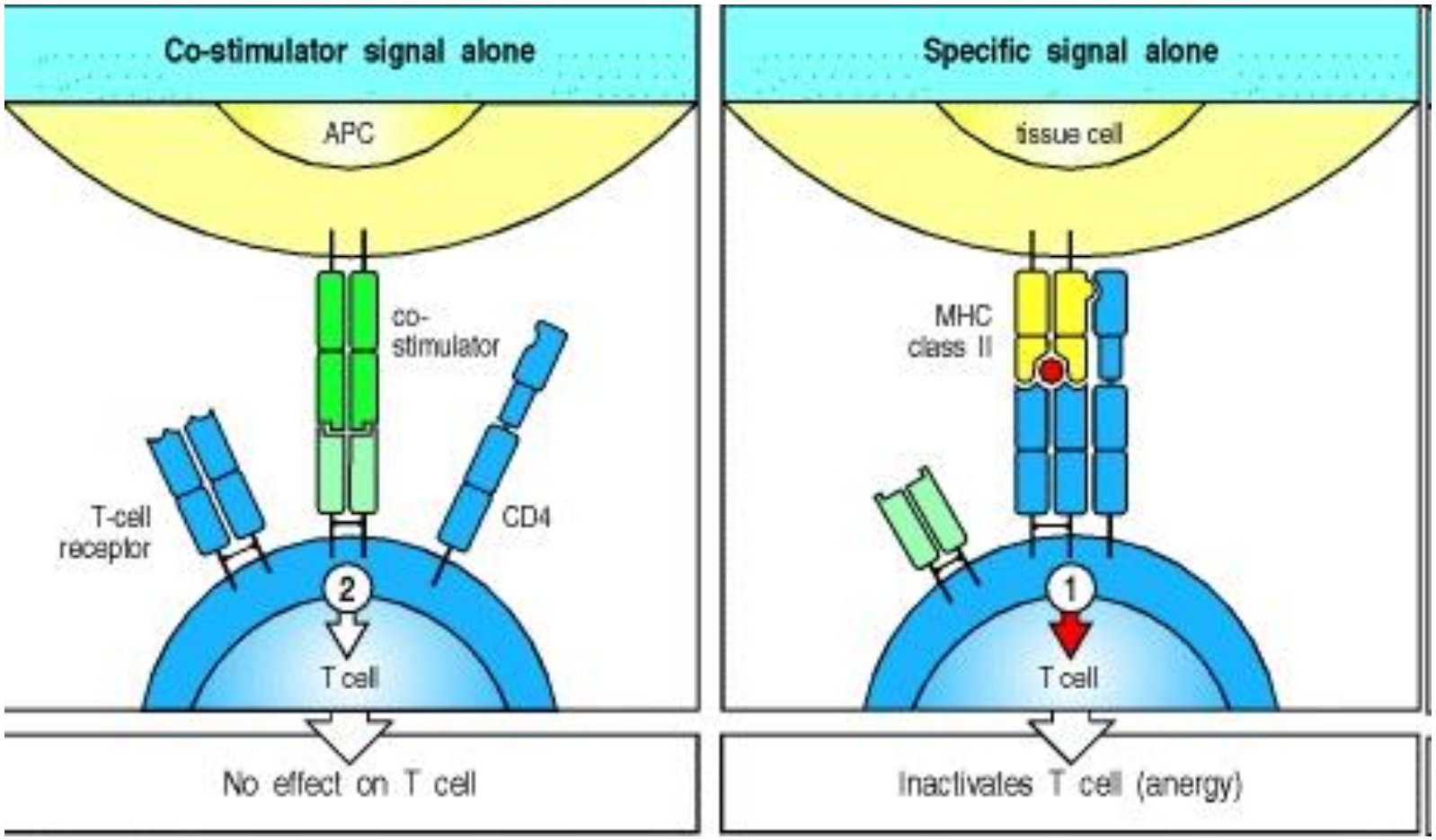
	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and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

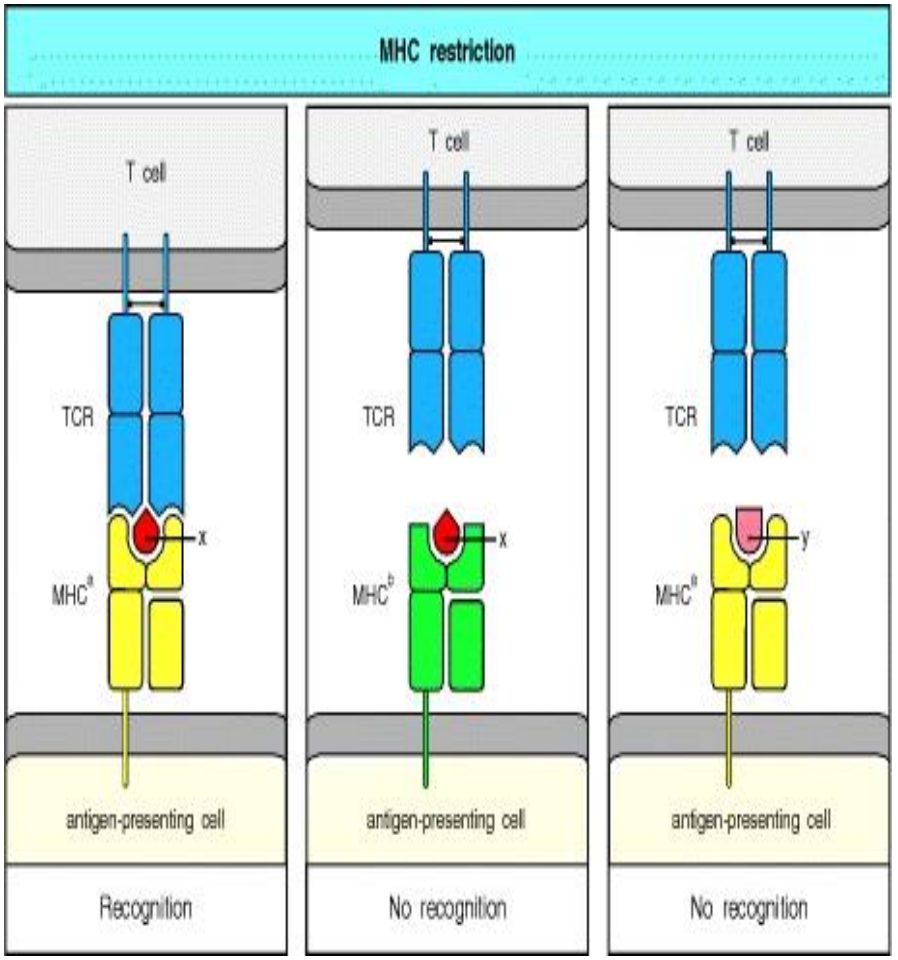


- Surface immunoglobulin (IGM or IGD) allows B cells to bind and internalize specific soluble intact antigen very efficiently. The internalized antigen is processed in intracellular vesicles where it binds to MHC class II molecules. These vesicles are then transported to the cell surface where the MHC 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.



Effector CD4 cells

- Activated CD4+ helper T lymphocytes differentiate into

-Th2 differentiations are mediated largely by

  - binding B cells that engulf allergen or small extracellular microbe, soluble toxins, virus or worm
  - and the presence of IL-4 from DC,
  - 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 vesicle after engulf infected cells,

  -Th1 produces IFN gamma

-Th17; DC secret IL-6, TGF-beta in response to extracellular bacteria and fungi,

CD4+ Th cells

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

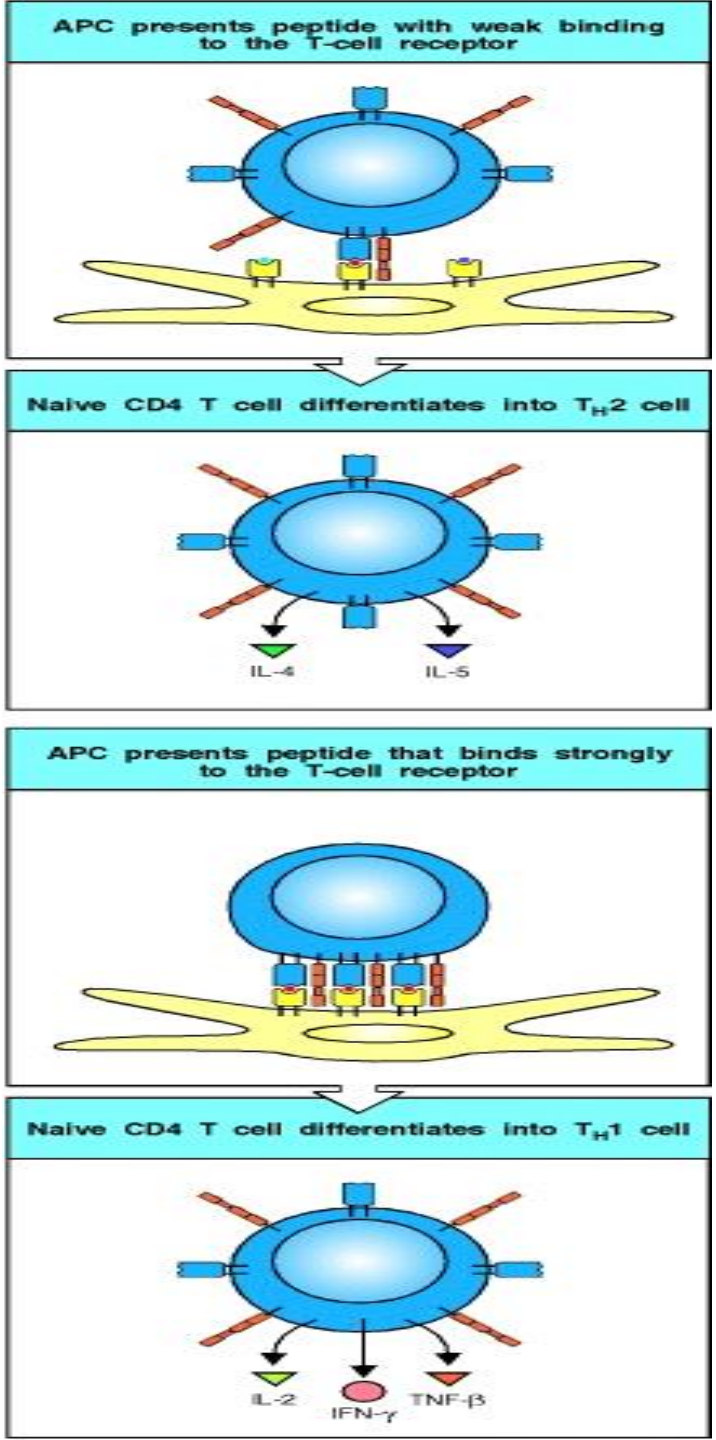
- Play central role in modulating immunity via secretion of cytokines that modulate:
  - B cell activation (Th2)
  - Immunoglobulin secretion (Th2)
  - Macrophage and dendritic cell activation (Th1)
  - Cellular chemotaxis and inflammation (Th17)

Th1 or Th2 or TH17 cells

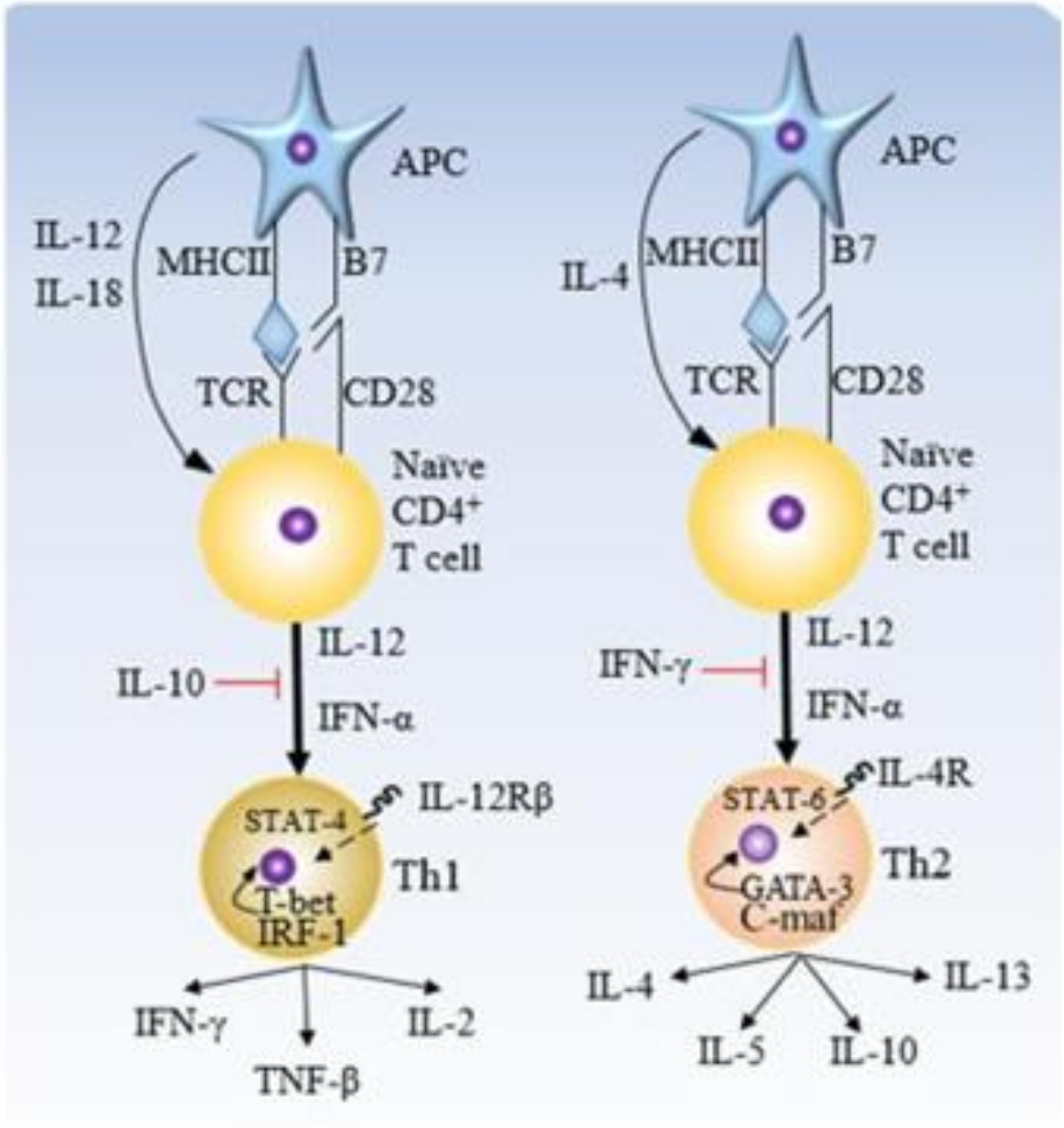
- **CD4+ T helper cells can be classified into 3 based on their cytokine profiles at time of activation of CD4 and type of antigen: T helper cell type 1 (Th1) and T helper cell type 2 (Th2). And TH17**

Antigen effect in priming TH1 or TH17 or TH2

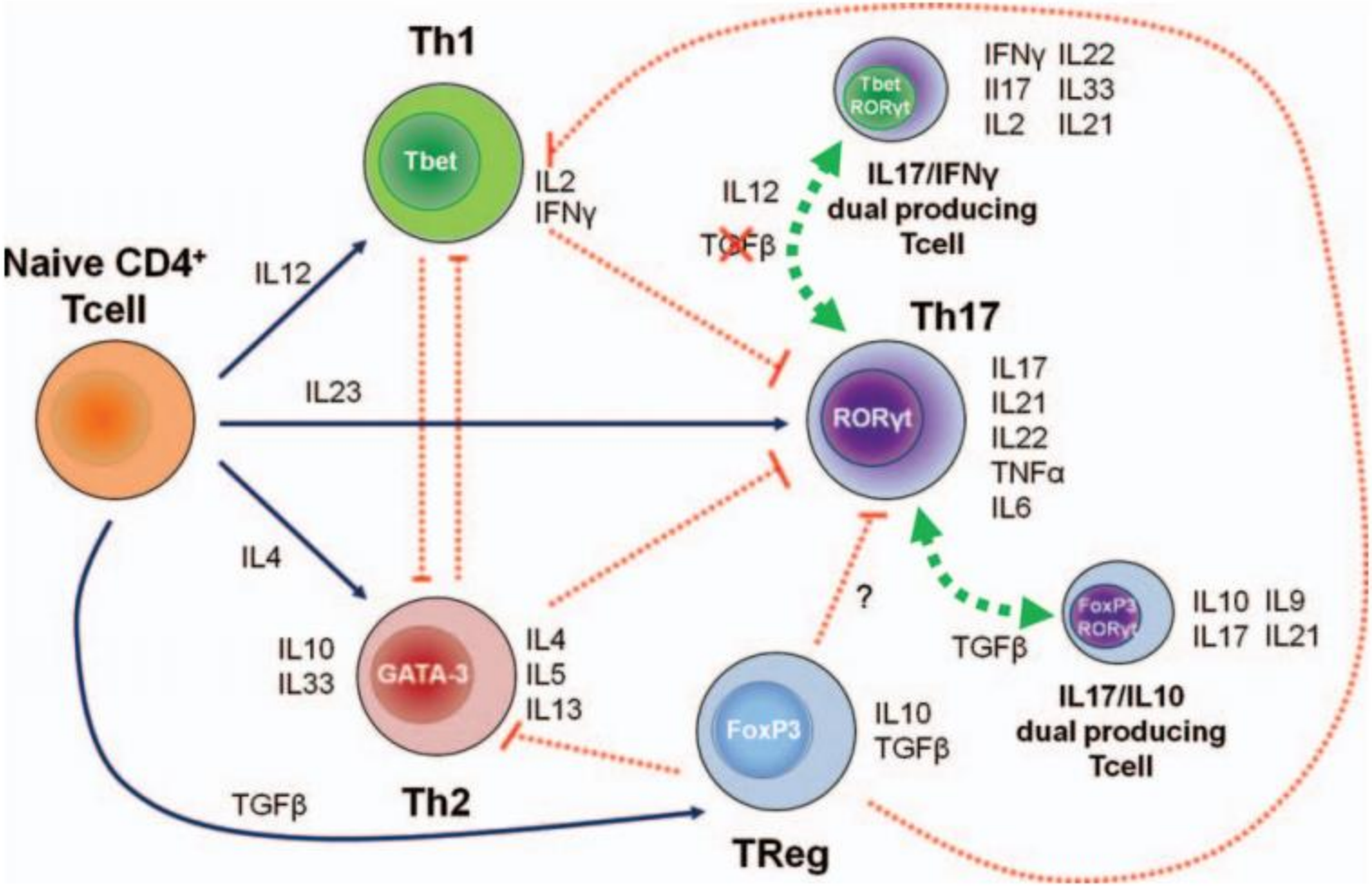
- The nature and amount of ligand presented to a CD4 T cell during primary stimulation can determine its functional phenotype.
- CD4 T cells presented by B cell with low levels of a small antigen or toxins or worms that bind the T-cell receptor less tightly, differentiate preferentially into TH2 cells 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,


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

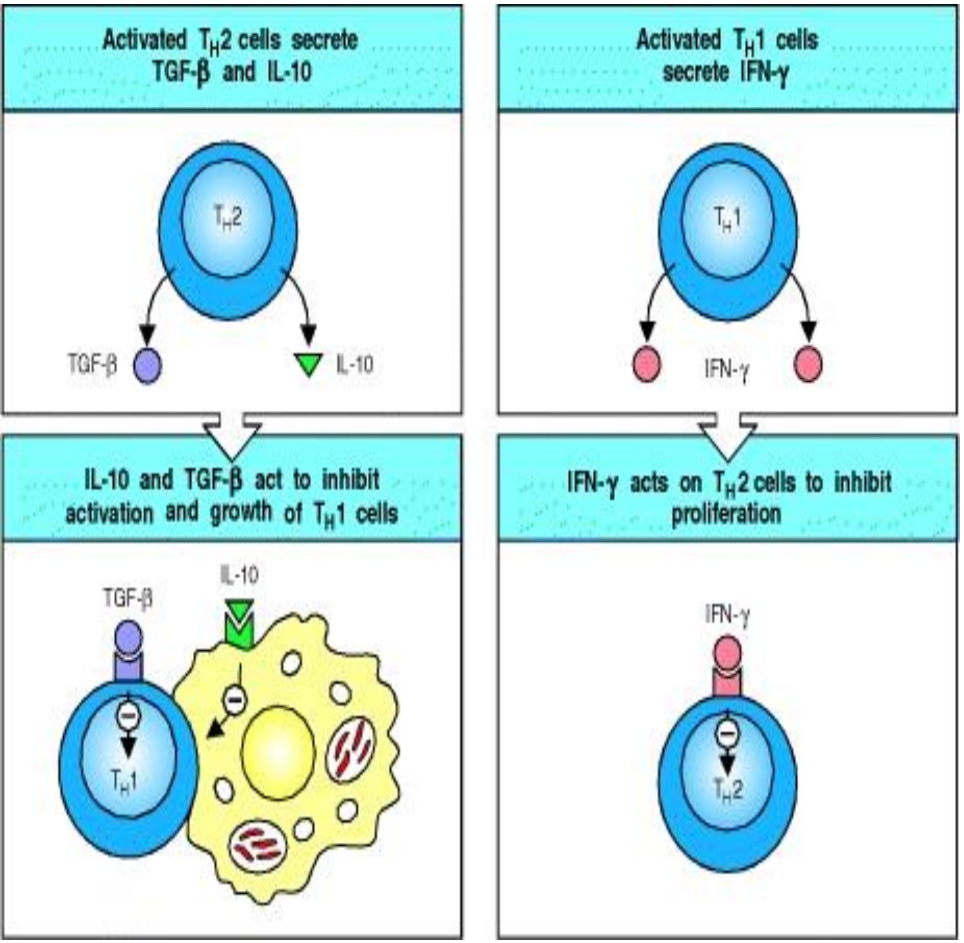
- Each subset of differentiated effector cells produces cytokines that promote its own development and may suppress the development of the other subsets
- IFN-γ secreted by TH1 cells promotes further TH1 differentiation and inhibits the generation of TH2 and TH17 cells.
- Similarly, IL-4 produced by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

Each subset inhibit other



Two subsets regulate each other



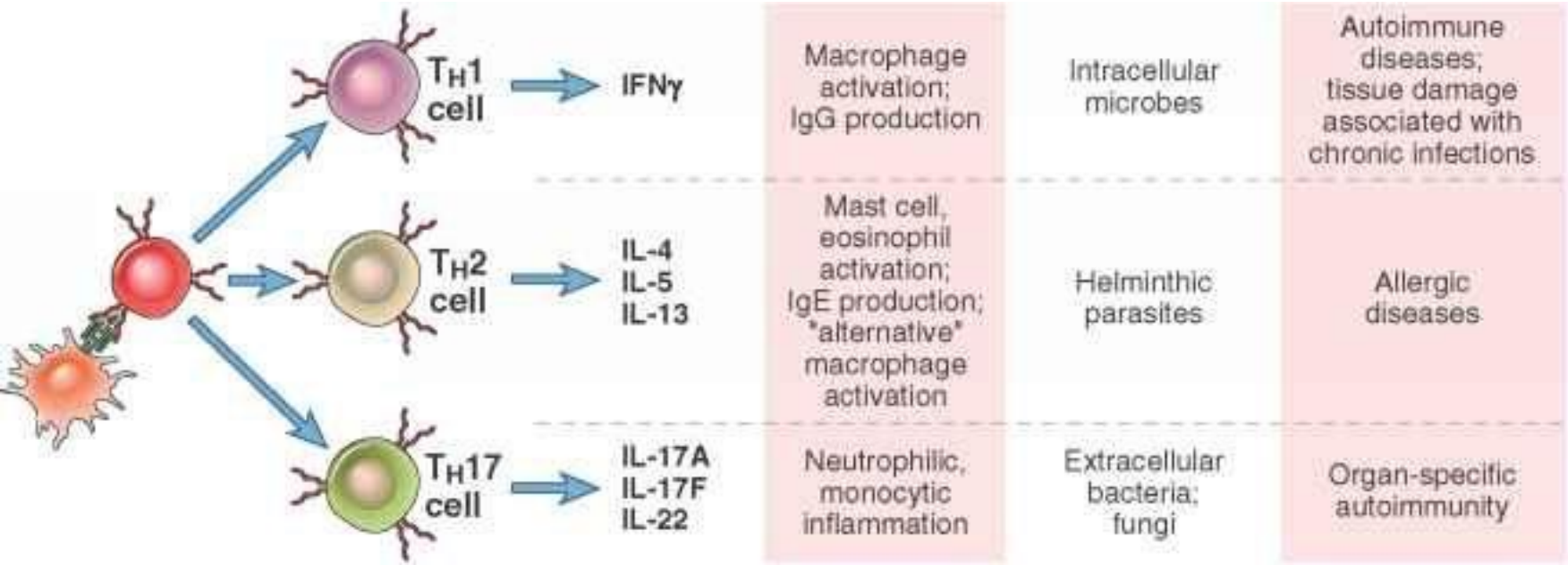
- TH2 cells make IL-4 which acts on macrophages to inhibit TH1 activation. Decrease auto-immunity
- TH1 cells make **IFN**-γ, which inhibit IL-4 and blocks the growth of TH2 cells (right panels). Decrease allergy

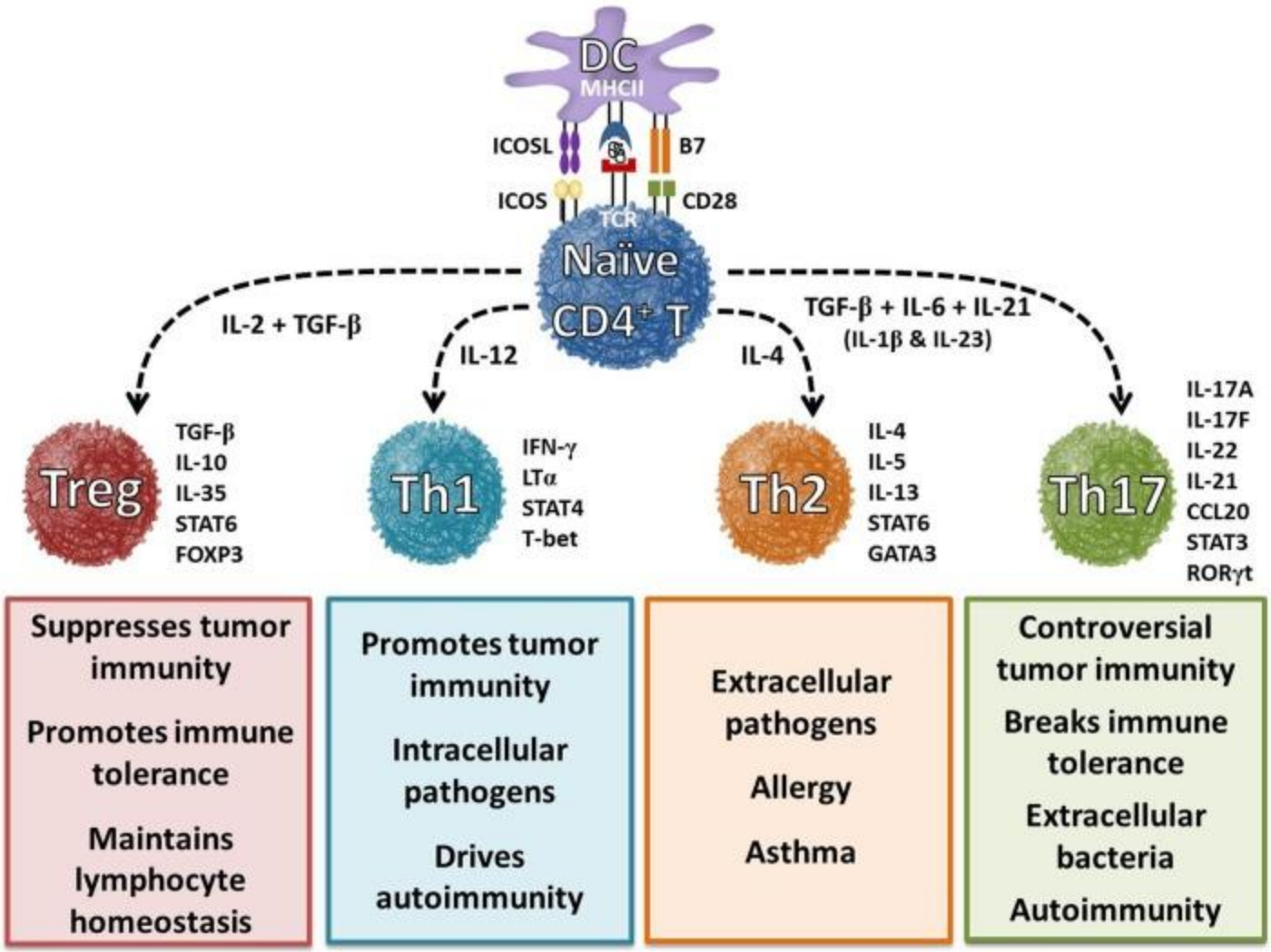
- These effects allow either subset to dominate a response by suppressing outgrowth of cells of the other subset. This help in using cytokines as therapy??.
- Balance toward TH1 help in cancer and allergy but increase autoimmunity
- Balance toward TH2 decrease autoimmunity
- Inhibition of TH17 helps in autoimmune diseases

CYTOKINES & DISEASE

Event	Development of tuberculoid leprosy	Development of lepromatous leprosy
T_H activation: cytokine production	Activation of T_H1: production of IFN-γ	Activation of T_H2: production of IL-4
Effector cell stimulation: effects on mycobacteria	Activation of macrophages: intracellular digestion of mycobacteria in cytoplasmic vesicles	Activation of B cells: antibodies have no access to intracellular mycobacteria
Resulting pathology	Some inflammatory tissue damage, but destruction of mycobacteria	Growth of mycobacteria and severe tissue damage

Table 3.3 The influence of cytokine production on disease pathogenesis following infection of macrophages by *Mycobacterium leprae*.


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

CD8 cells

- Activated CD8+ lymphocytes (CTL) result from infected DC or infected cell (antigen multiply in cytosol) presentation and the presence of IL12 and IFN gamma.
- It 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

Effector T cells

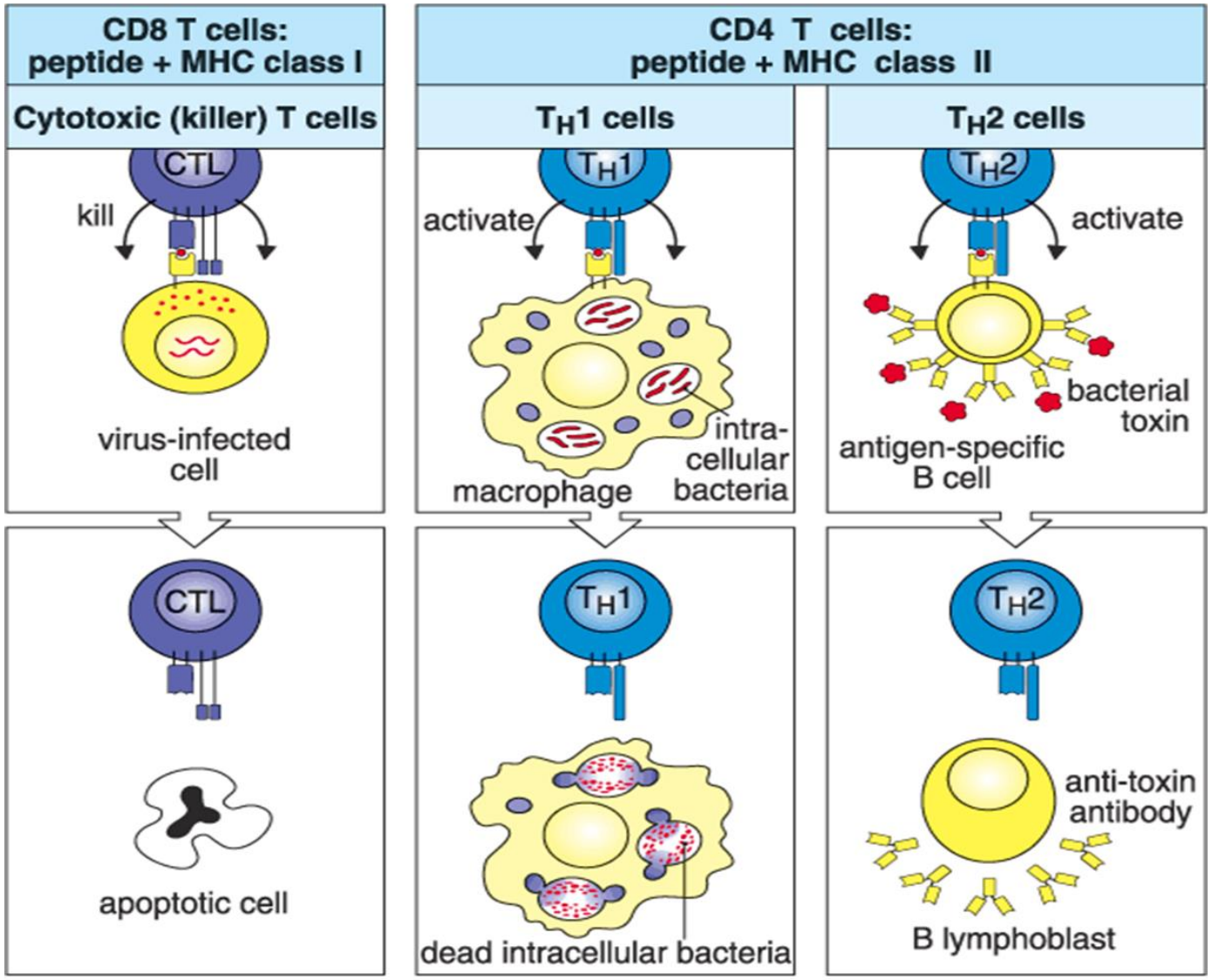
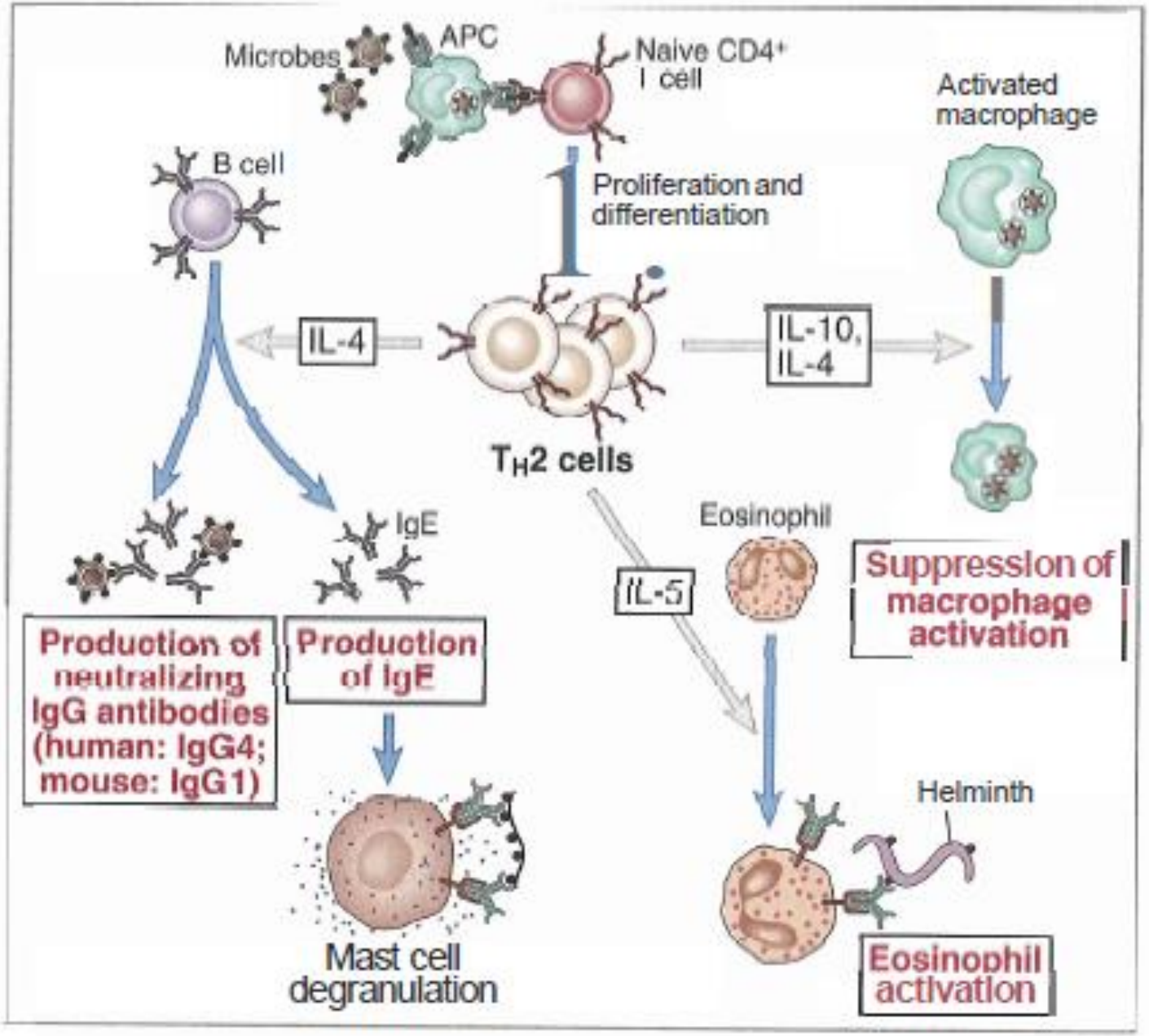


Fig 8.27 © 2001 Garland Science

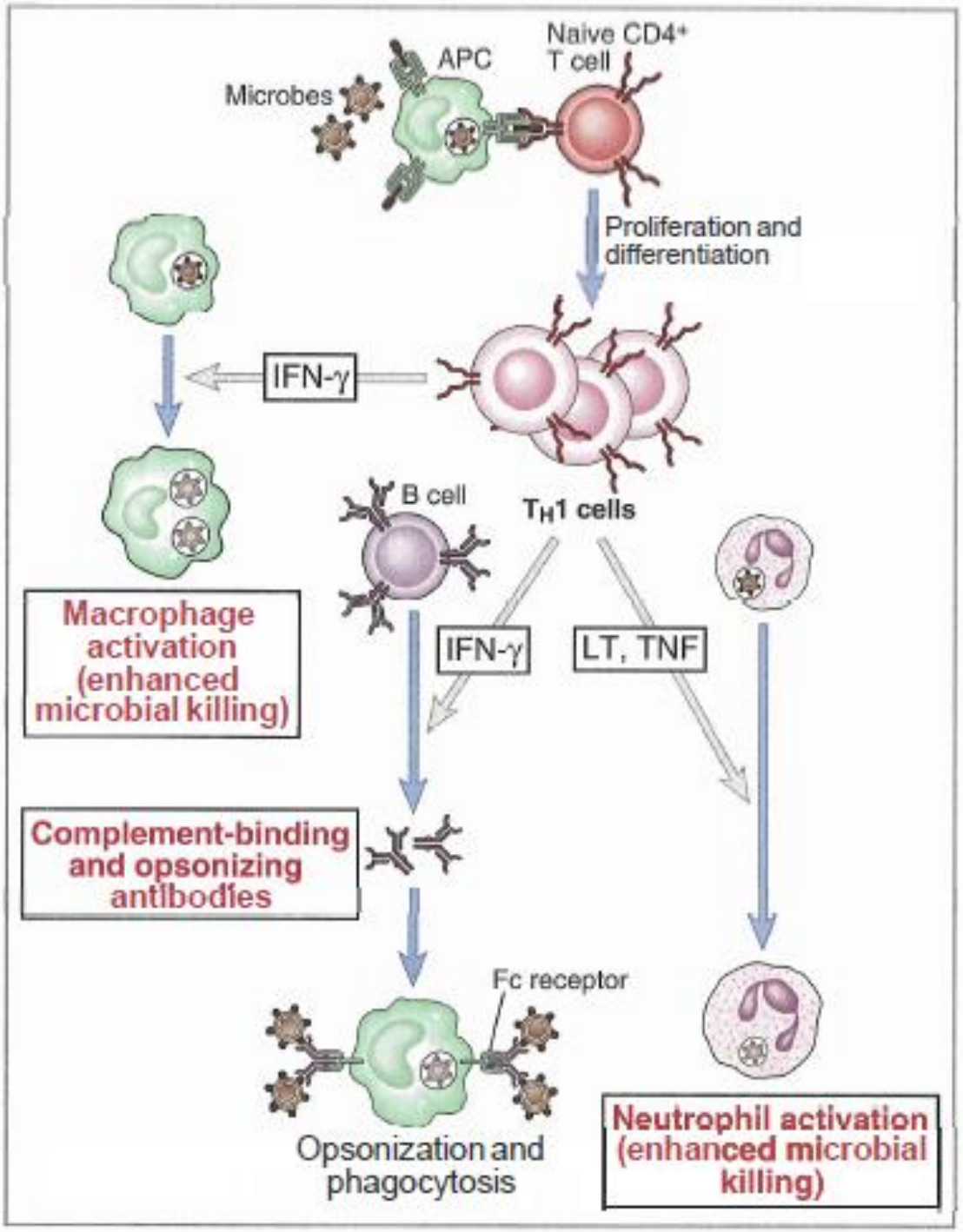
Th2

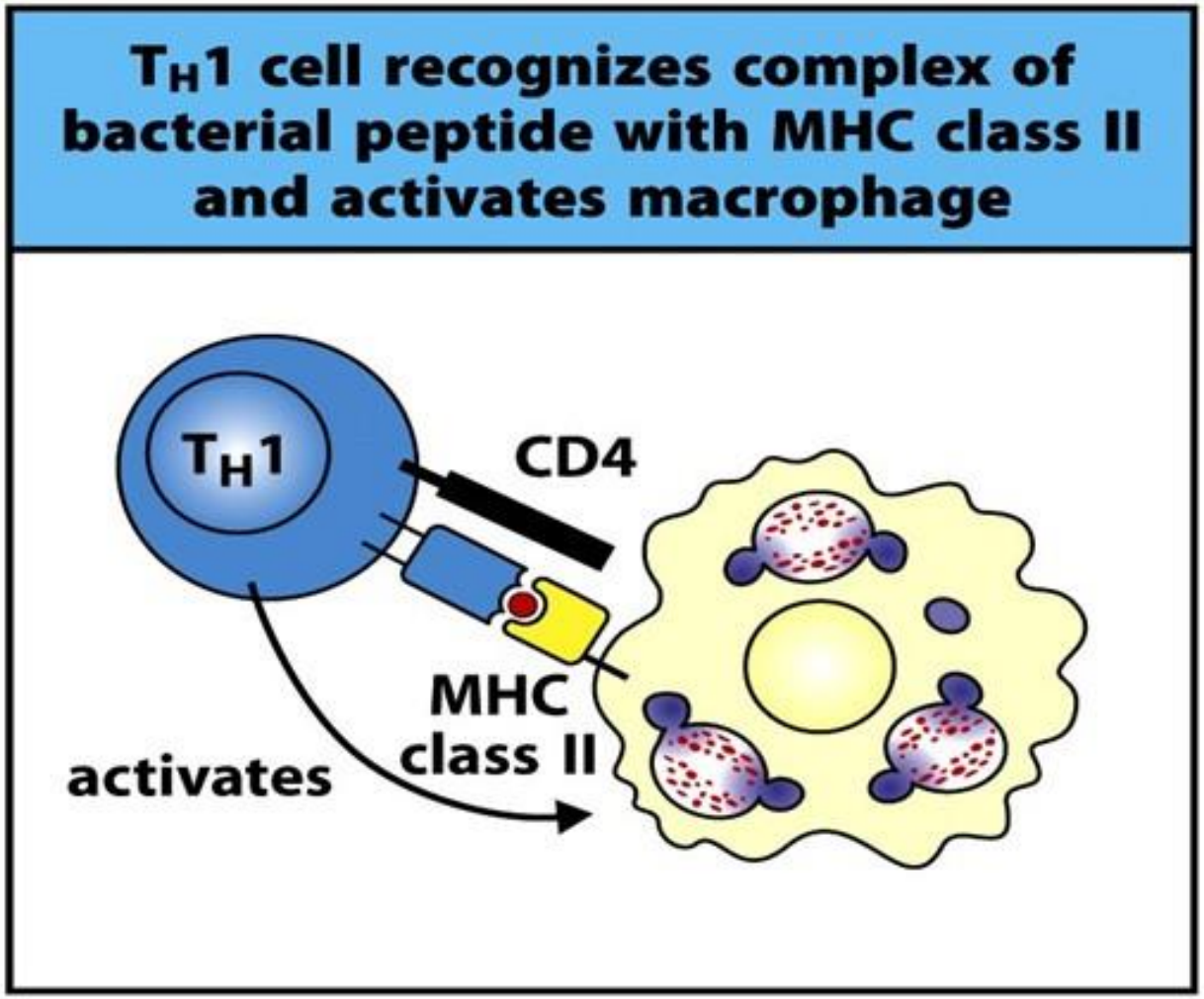
- TH2 functions
  - Bind B cell and secret IL-4 that lead to B cell activation and antibody secretion
  - Secret IL-5 to Activate eosinophils to react against worms
  - Secret IL-10 that suppress macrophages


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)



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