Biology of T-cells, TCR, and antigen presentation

Dr.Eman Albataineh,
Prof. Immunology
College of Medicine, Mutah university

αß T cells

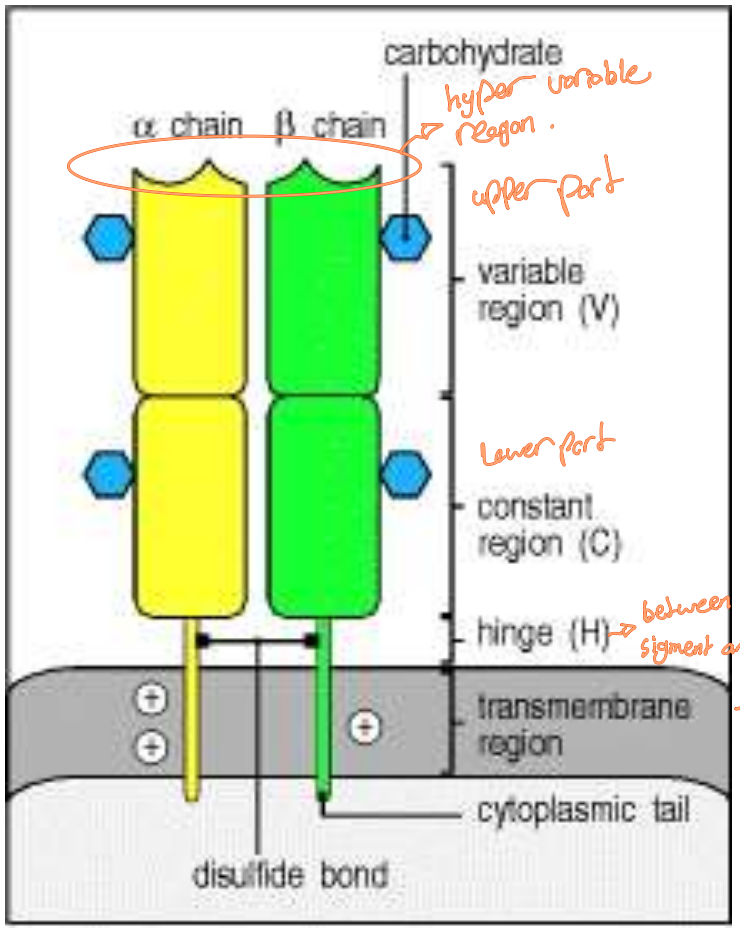
- About 90-95% of the blood T cells
- The receptor has two polypeptide chains α and ß
- Besides TCR is CD coreceptor bind MHC
  - CD4+ = (Th) bind MHC 2
  - or CD8+ = (Tc) bind MHC 1
- Complete TCR is the αß receptor plus CD3 and zeta chain

every chain has 2 sigments

Antigens must be presented on MHC to bind with Tcell

αß TCR

similar to antibody → has variable and constant bind with antigens



- TCR complex is the αß receptor plus the ζ chain and two CD3 signaling proteins
- Each chain constitute of one variable, one constant, hinge, transmembrane and cytoplasmic tail
- covalently linked to each other by a disulfide bridge between extracellular cysteine residues
- TCR that specifically recognizes peptide-MHC complexes
- Hypervariable regions on both Vα and Vß are the same as those of antibody located on Ag-binding site and called CDR and they are 3 sites for each

- T cells involved in
  - Defense against intracellular and extracellular pathogens (Tc in intracellular and Th help in extracellular) ↳CD8 ↳CD4
  - Tumor immune response
  - Graft rejection
  - Autoimmune diseases

Factors influencing the Strength binding of the TCR to antigen

There must be 2 signal to complete activation.

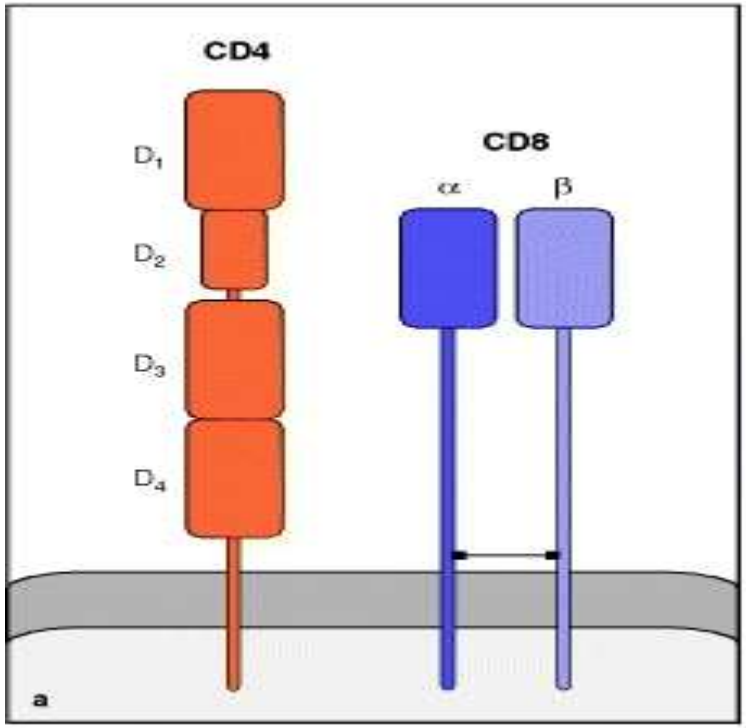
- Antigen binding increase by
- (TCR - CD4/8 binding to antigen -MHC respectively on antigen presenting cells provides the first signal).
- Coreceptors binding;
  - **T cells coreceptors** are the CD4 and CD8 proteins (Th or Tc respectively). CD8 and CD4 interact with class I and class II MHC molecules,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

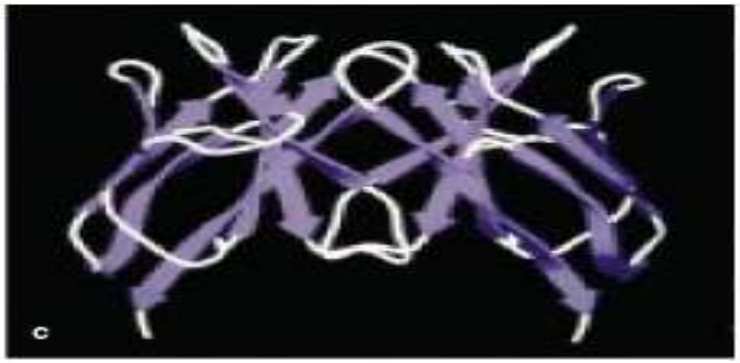
1st signal

1- present the antigen on suitable MHC
⇒ T_H ⇒ MHC II
Tc ⇒ MHC I

⇒ The antigen bind on MHC on APC
⇒ presentation the TCR
⇒ binding CD4 with MHC II
⇒ binding CD8 with MHC I
} ⇒ on APC

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

2nd signal

IL-2 → growth factor
the first cytokine
that effect to
cell to keep alive

Costimulatory receptors on T cells

- Provide so-called second signals for lymphocytes

stimulate by 2 site
- APC
- T cell → outcome

on T cell

– 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.

growth fa

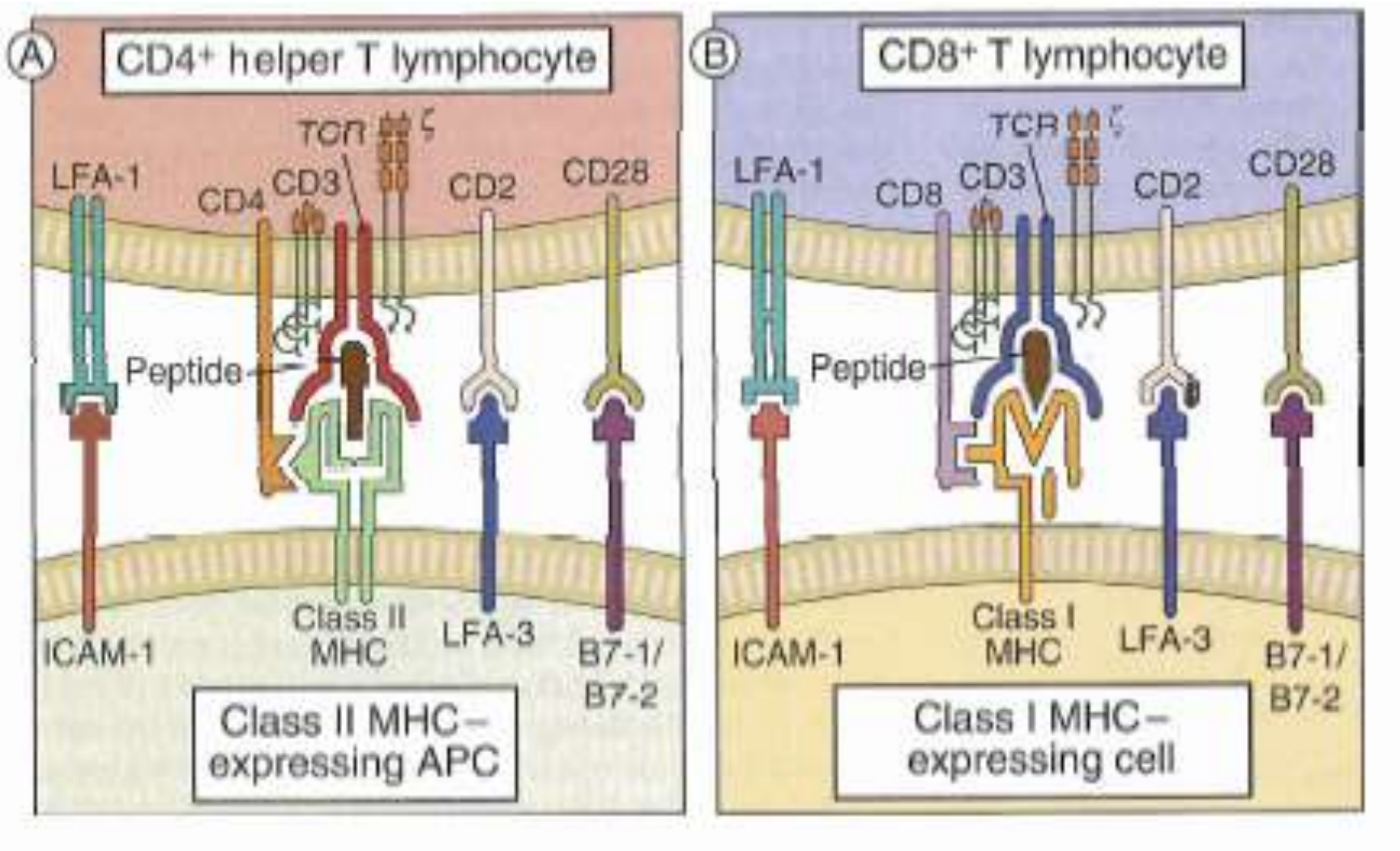
– CD2 is a glycoprotein present on more than 90% of mature T cells, and on NK cells. The principal ligand for CD2 in humans is a molecule called leukocyte function associated antigen 3 (LFA-3, or CD58), CD2 functions as a signal transducer

Natural Killer

– 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



humeral immunity => soluble in fluid
=> anti body
=> T cell has no relation.

CD4 cells or Th cells

- Naïve CD4 T cells in secondary lymph node are activated by Antigen presenting cells including B cells , then Activated CD4+ T cells proliferate and differentiate into effector cells

-Th2 differentiations are mediated largely by

helper for B cell.

– binding CD4 cells with B cells as APC in response to allergen or small extracellular microbe or worm

type of antigen :-> if it small peptide = allergen

– and the presence of IL-4 from B cells,

– Th secrete cytokine to induce antibody production; IL-4 and IL-6 which activate B cell (Help B cells)

-Th1 differentiations are mediated by -> if APC -> normal dintric cell

binding Th to DC that secret IL12 and IFN gamma, -> prodeuce by Antigen Denitric cell -> if it's take intracellular Bacteria.

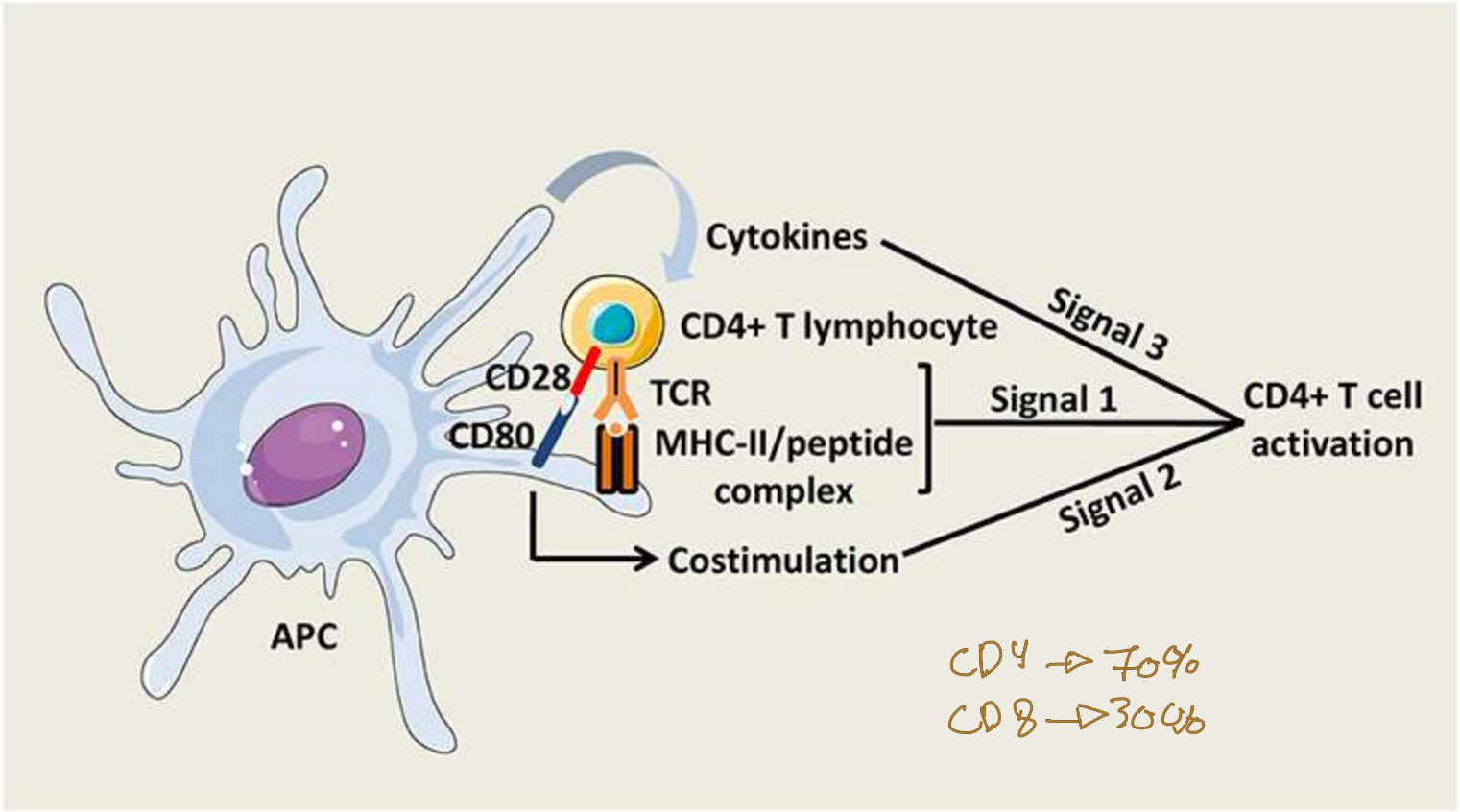
intracellular pathogen multiplying within the macrophage's vesicle after engulf infected cells,

provide helper functions to other cells of the immune system—especially the antigen-presenting cells (APCs) such as macrophages, dendritic cells, Natural Killir cell CD8 => cell mediated immunity.

-Th17; DC secret IL-6, TGF-beta in response to extracellular bacteria and fungi, => Function :-> chemotaxis => attract the macrophage, neutrophilis to the site of infection
=> Draw back:-> it increase the autoimmune disease

-T reg suppress immune response and tumor activity

T. rae :- suppress immune response and tumor activity.



CD4 → 70%
CD8 → 30%

Immune globulins → Ig
antibody

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**

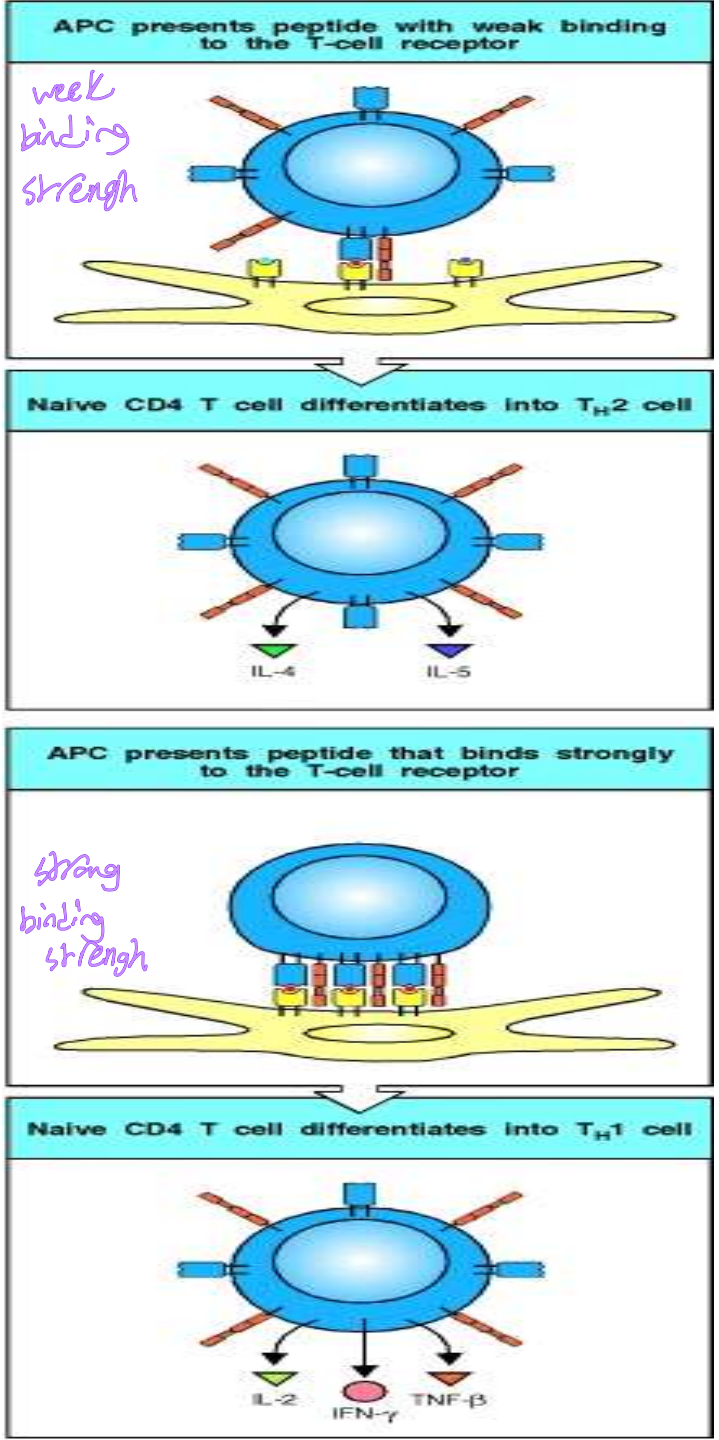
↑ Strength of binding ⇒ has role in priming of Tcell

⇒ if binding between TH + APC are very high ⇒ intracellular ⇒ TH1

⇒ " " " " " " week ⇒ extracellular ⇒ TH2

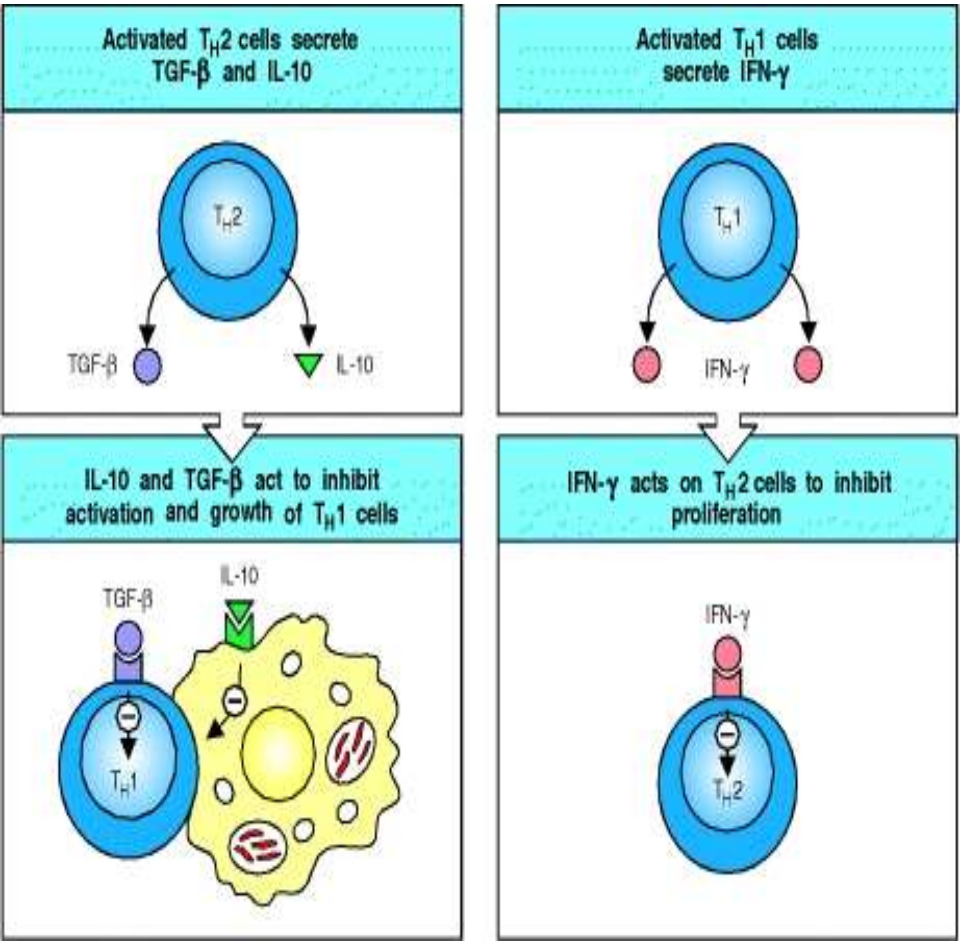
Antigen effect in priming TH1 or TH17 or TH2

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

⇒ hyper activation of TH1
⇒ hypo activation of TH2
⇒ auto immune disease
⇒ hyper activation of TH2
⇒ hypo activation of TH1
⇒ allergy

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
- TH17 helps in autoimmune diseases

* antibody will never reach the intracellular bacteria.

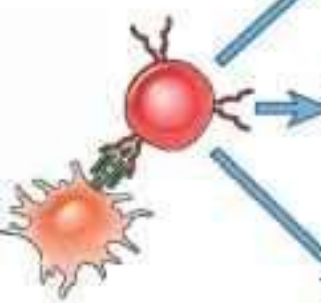
infection of mycobacterial lebel.

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

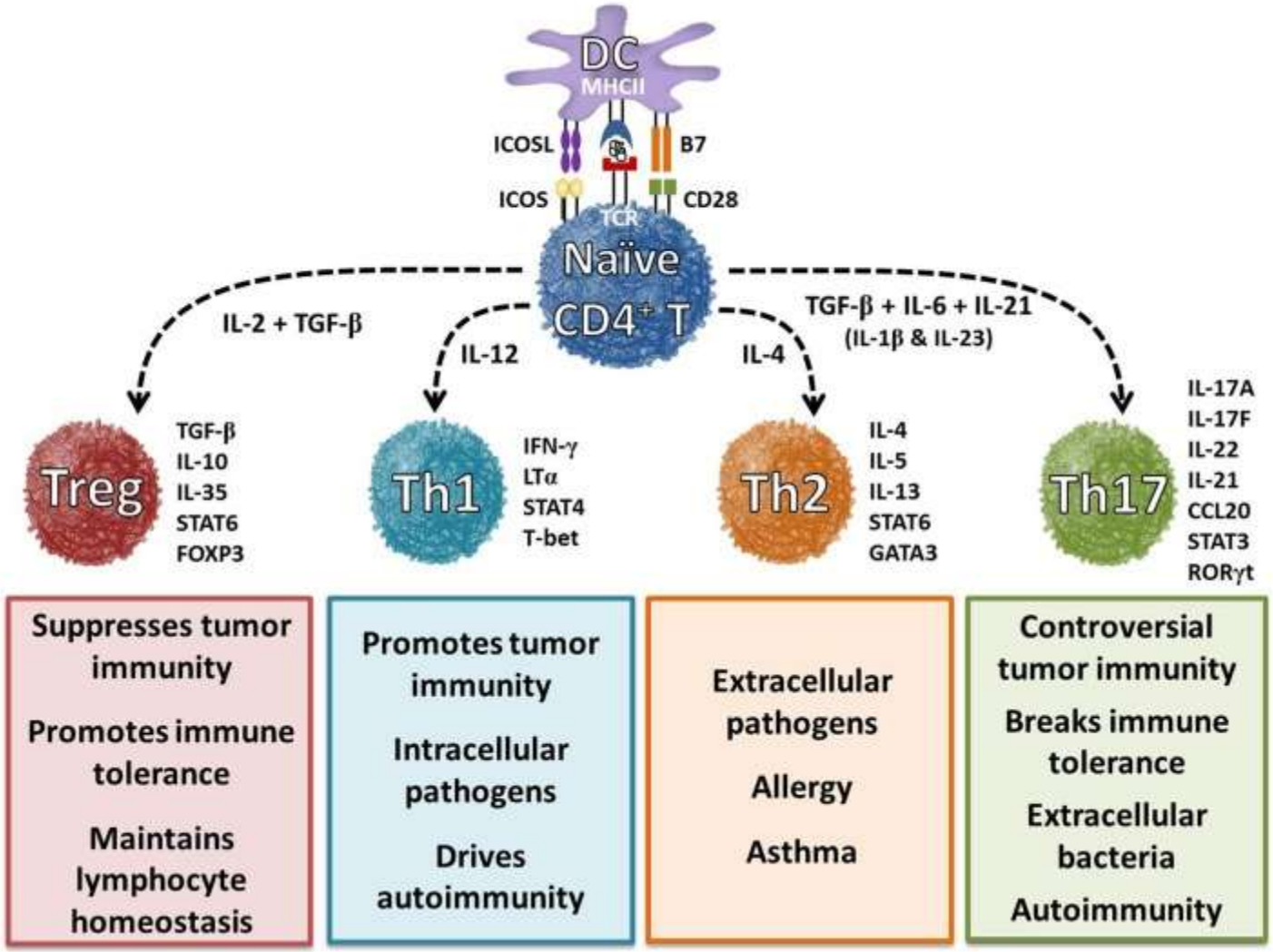
Table 3.3 The influence of cytokine production on disease pathogenesis following infection of macrophages by *Mycobacterium leprae*.

increase in the activation



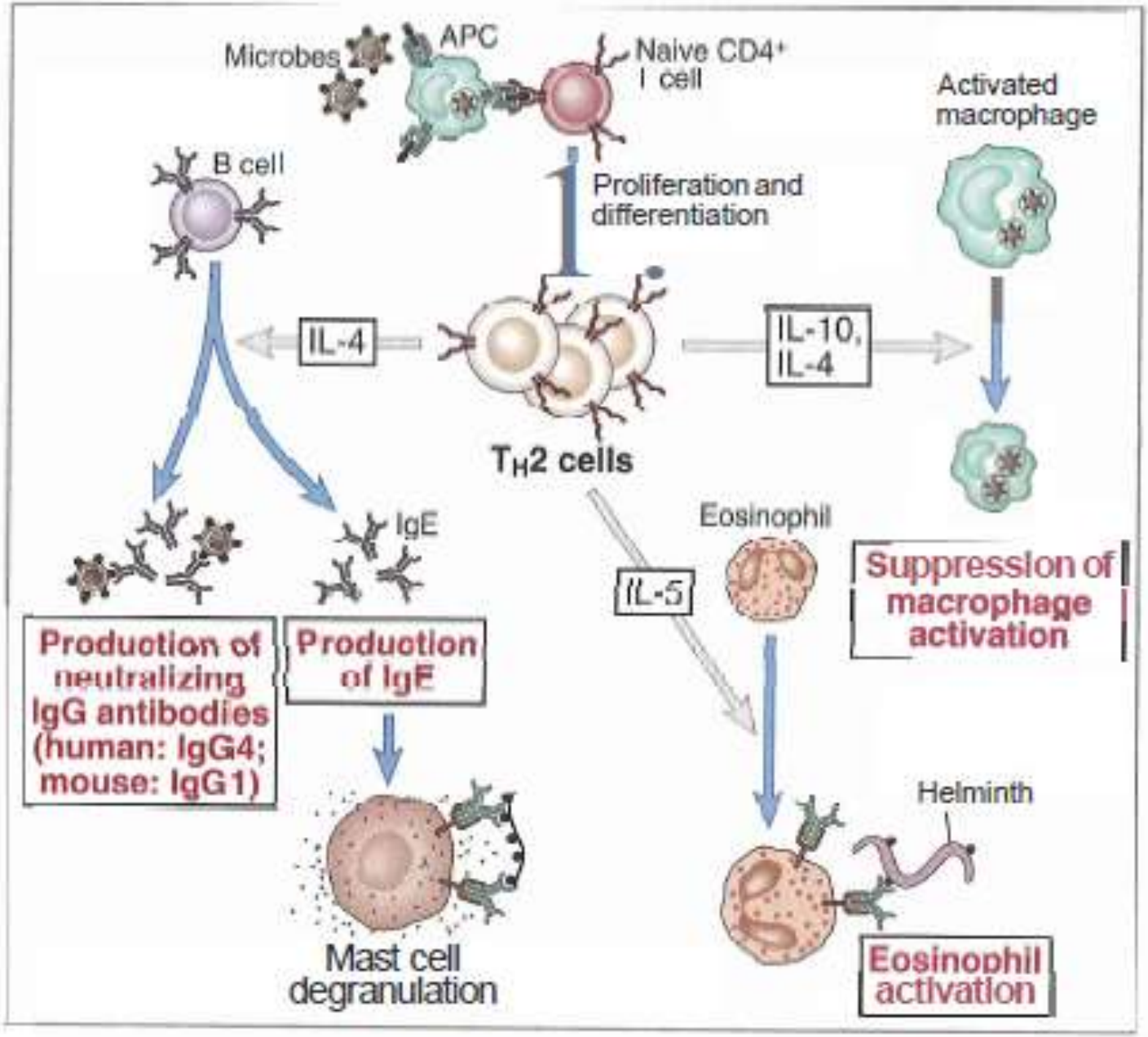
T_H1 cell	IFNγ	Macrophage activation; IgG production	Intracellular microbes	Autoimmune diseases; tissue damage associated with chronic infections
T_H2 cell	IL-4 IL-5 IL-13	Mast cell, eosinophil activation; IgE production; "alternative" macrophage activation	Helminthic parasites	Allergic diseases
T_H17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

in allergy.


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

Th2

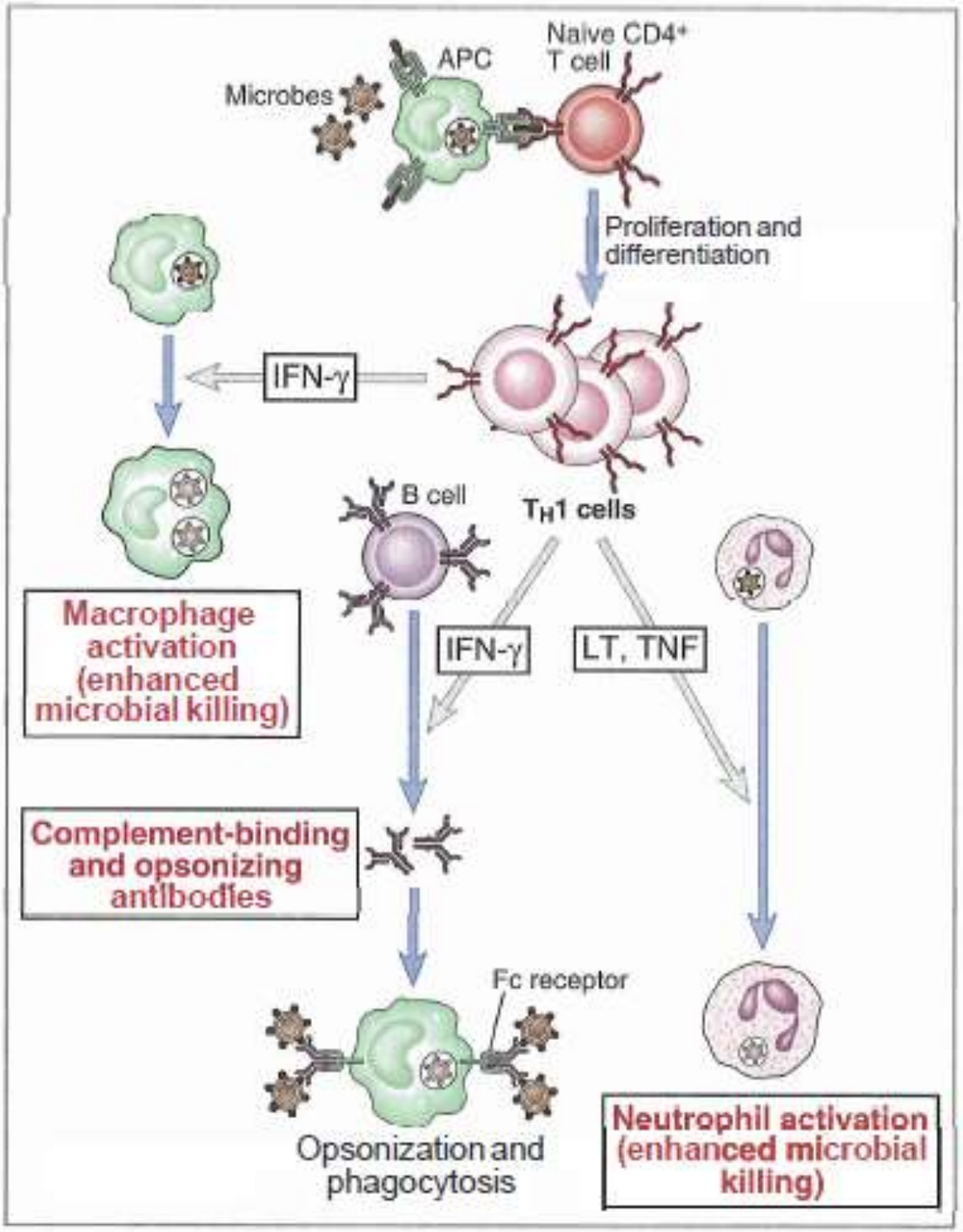
– TH2 functions
  - Bind B cell and secret IL-4 that lead to B cell activation and antibody secretion
  - Secret IL-5 to Activate eosinophils to react against worms
  - Secret IL-10 that suppress macrophages


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

IgG:- obsonizing antibody
⇒ put a mark on microscope to facilitate aken by immune cells

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)

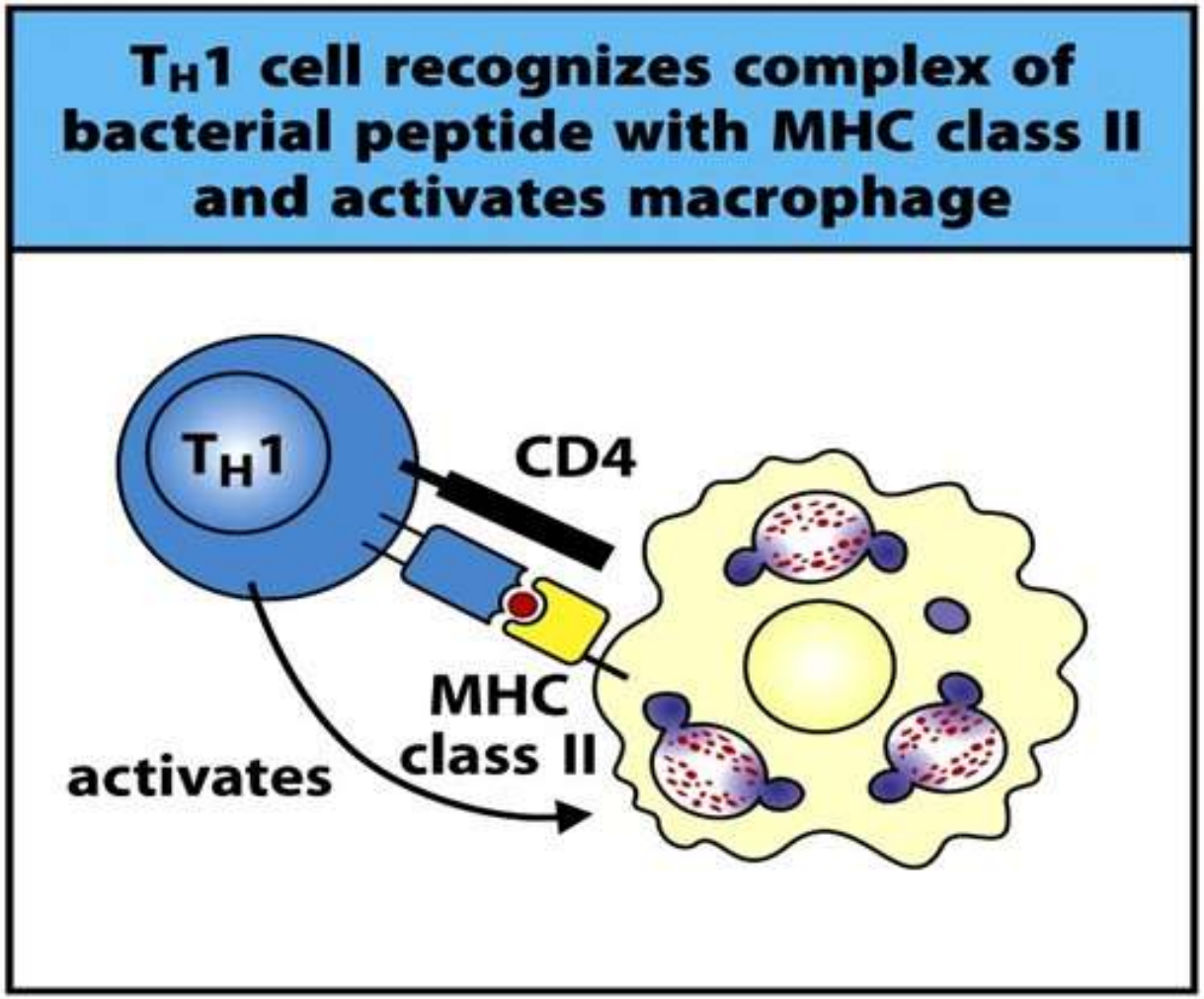


Figure 1-33 Immunobiology, 7ed. (© Garland Science 2008)

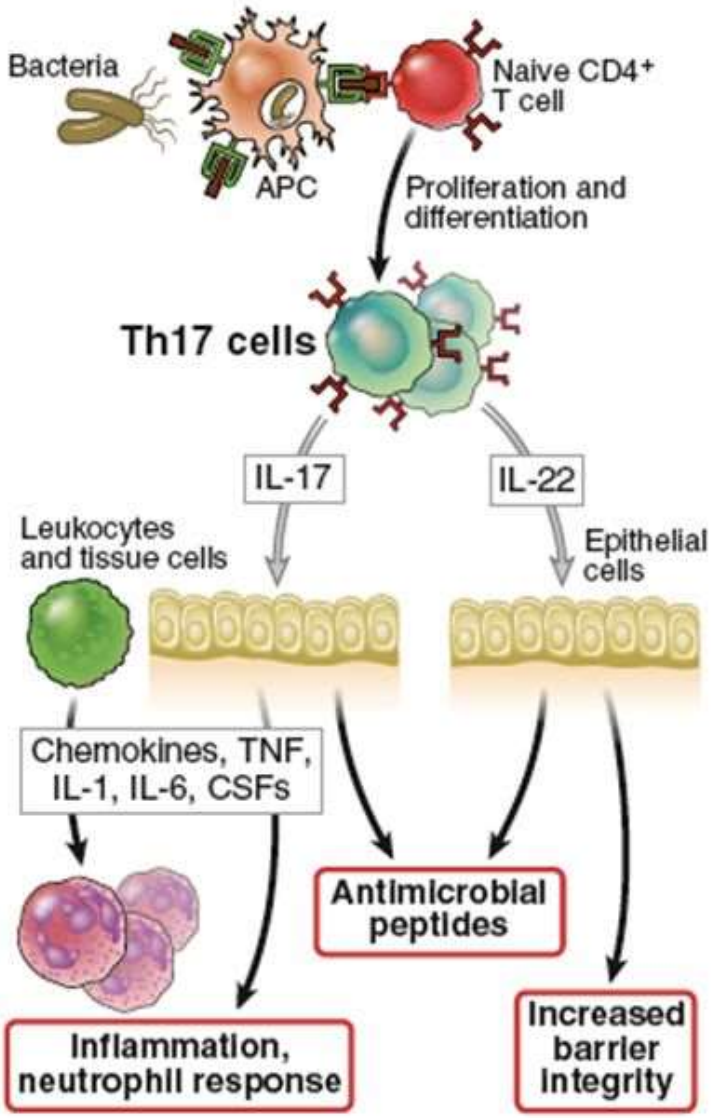
Effector function of Th17

- The TH17 subset is primarily produce IL-17 that involved in
  - Secret IL-17 that recruit neutrophils and macrophages to site of infection,
  - inducing inflammation
  - may cause some autoimmune diseases.

*any cells that dameg the intracellular bacteria like :- TH1
- macrophage.
- CD8
- TH17

⇒ that could loss of regulation ⇒ autoimmune disease.

Effector functions of T_H17 Cells



CD8 cells = T cytotoxic.

- T cells that express CD8 molecule on their surface and they represent 30% of T cells in the periphery
- Naïve CD8 cells are activated by presenting antigen on MHC1 on self or APC infected (internally by virus, antigen multiply in cytosol) or malformed cells (tumor) and the presence of IL12 and IFN gamma. → in intracellular infection.
- 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

↳ Activated form of TC. CD8.

Naïve CD8 activation

- 2 ways for activation

1-Directly. , present antigen to CD8 cells and type 1 IFN (interferon) from infected cells

2-indirectly by TH1 cells that secret IFN gamma to stimulate CD8

Direct Killing by CD8 cells

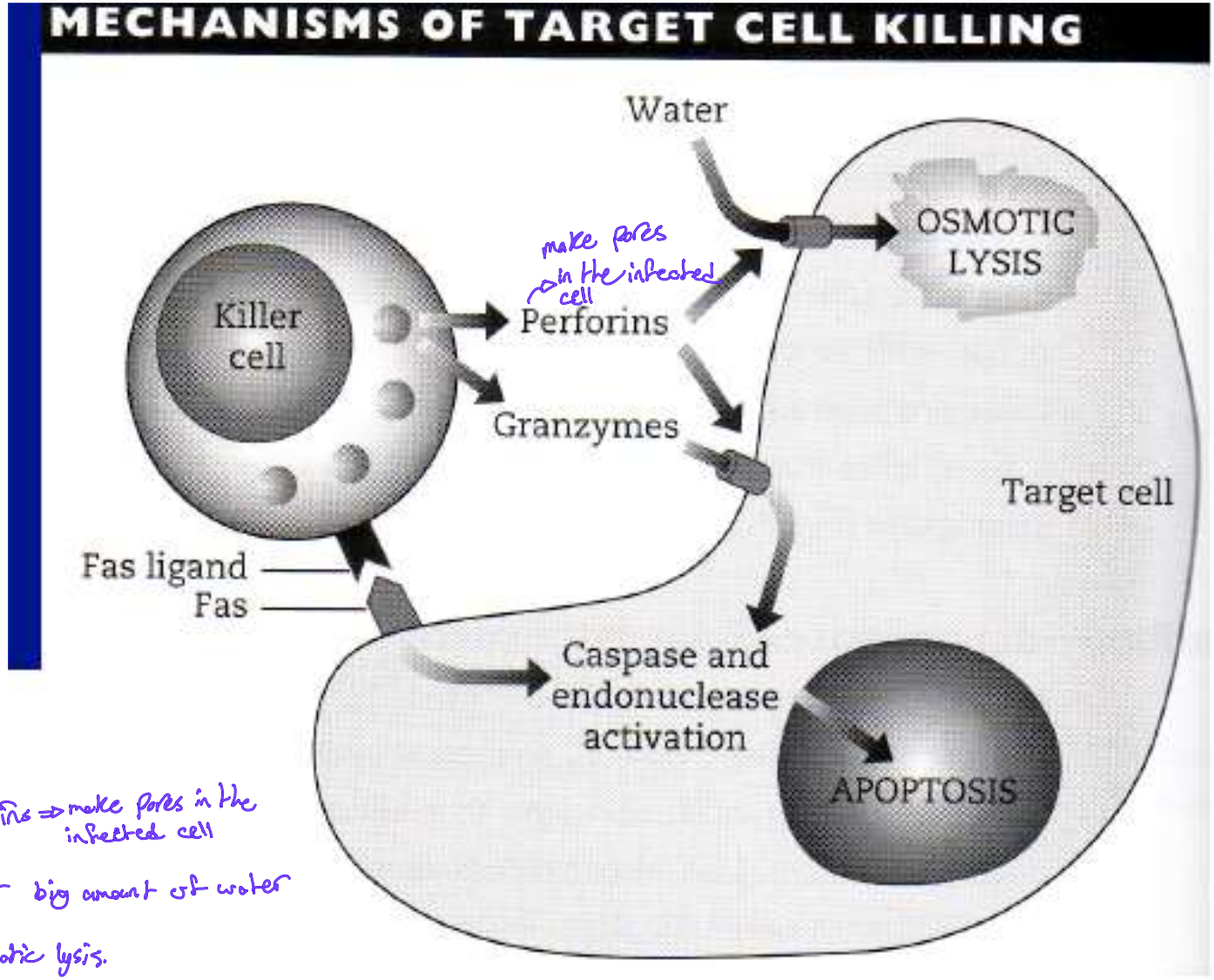
1- production of perforins and secretion of granzymes

2-induction of apoptosis by activation fasL-fas pathway ⇒ expression of the cell receptor that bind it ligand on the effected cell

Fas-FasL ⇒ produce by killer cell

- Most important death receptor, when they bound the caspases will be activated in target cell and then apoptosis
- Help in NK and CD8 killing of target cell
- Help in T cell regulation
  - Killing of T cell by NK after activation (activation induced cell death (AICD)
  - Mutation in FAS or fas L gene lead to AUTOIMMUNE LYMPHOPROLIFERATIVE SYN (alps): lymphocyte accumulation, defective apoptosis and humeral autoimmunity

Natural Killer some pathway of killing of CD8



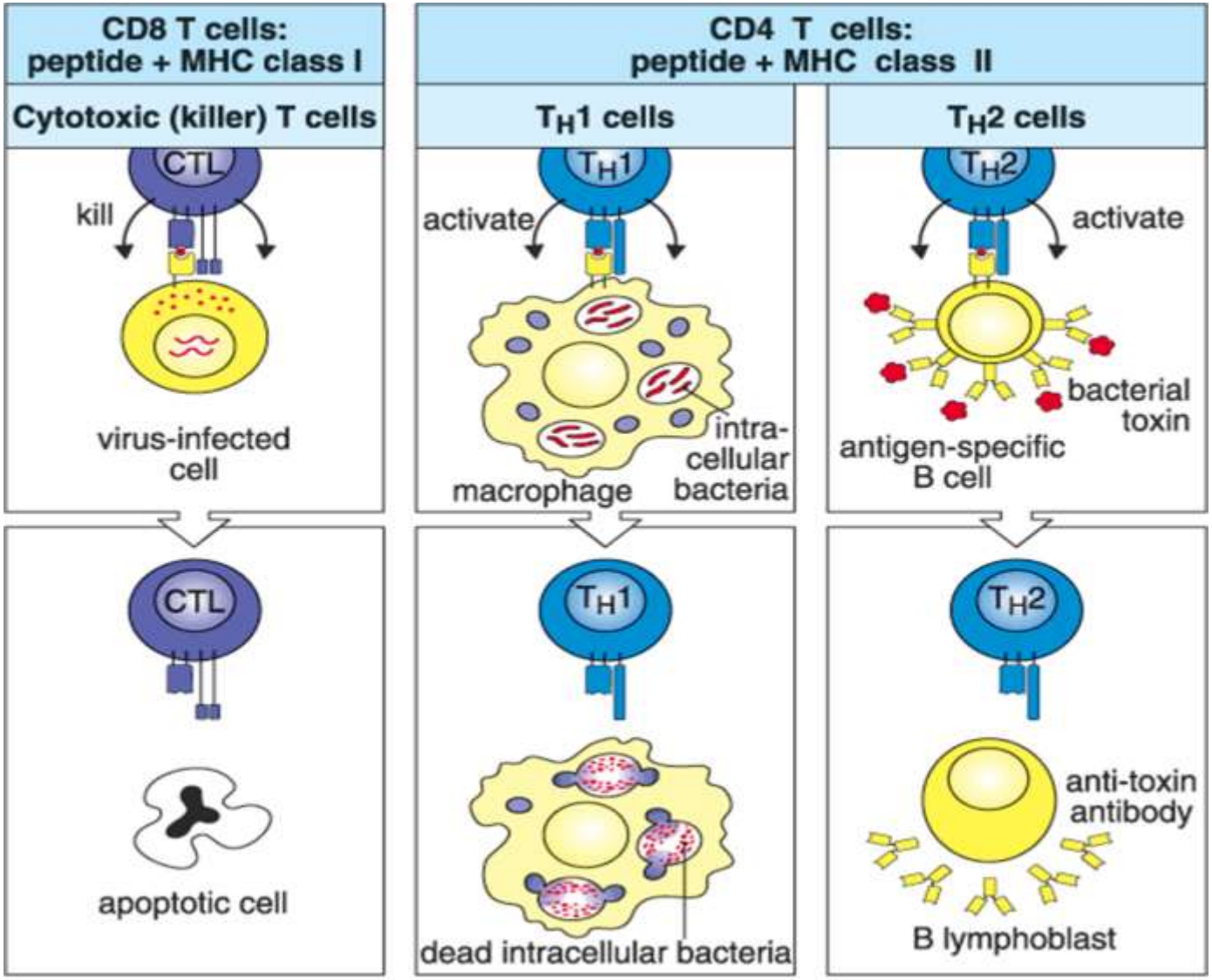
* perforins => make pores in the infected cell

=> enter big amount of water

=> Osmotic lysis.

* Granzymes enzyme => stimulate the enzyme that responsible for Apoptosis (caspases) => death cell => same as Fas-L.

Effector T cells



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