Charting New Horizons in Education

T-cells, TCR, & antigen presentation

8

Immunology

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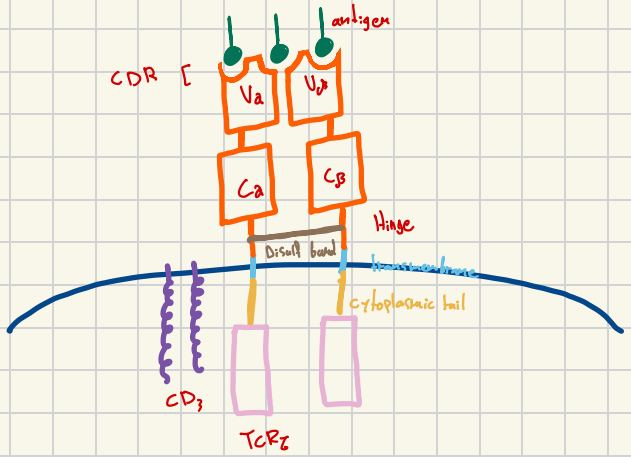
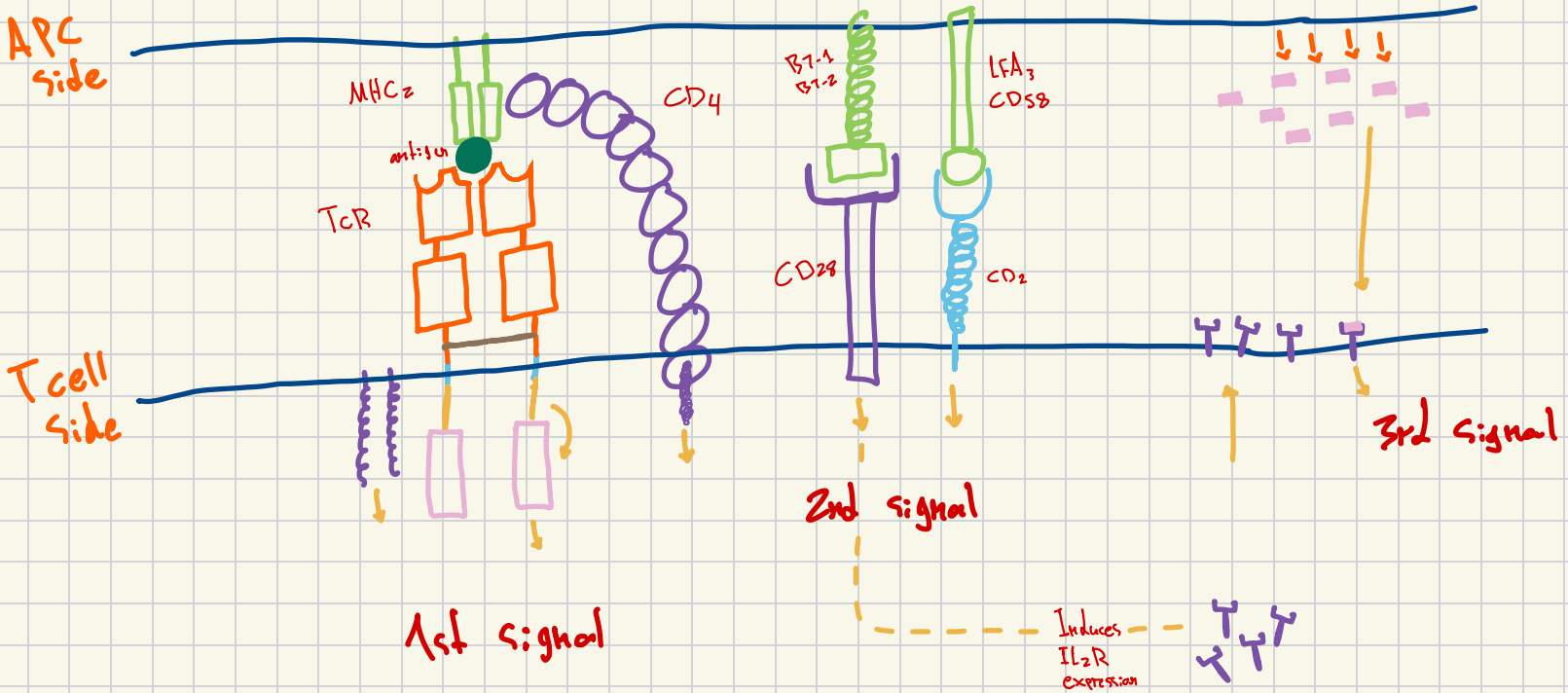
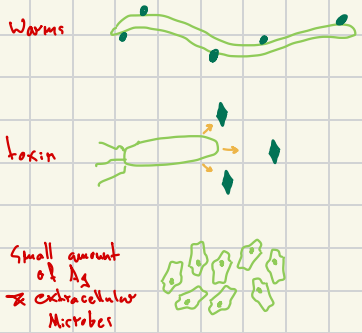
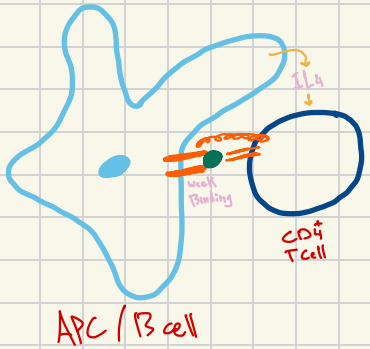
T cell Receptor









TH_2

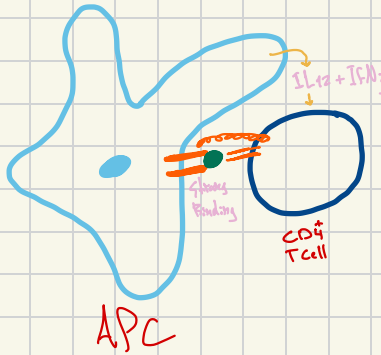
IL_4 → B cell activation → IgG_1 / IgE

IL_5 → eosinophil activation

IL_{10} & IL_4 → Macrophages Inhibition → Th_1 Inhibition

Overactivation ; Alergy + asthma

Intracellular pathogen



TH_1

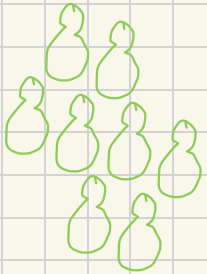
$IFN\gamma$ → Inhibit IL_4 → Inhibit Th_2

$IFN\gamma$ → Macrophage activation, Neutrophil activation → opsonization

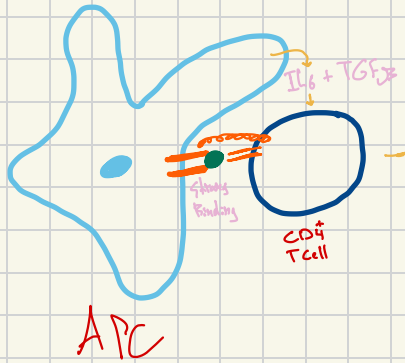
$IFN\gamma$ → activate B cells → $IgG_{1/3}$

$IFN\gamma$ → CD8 activation → Cytotoxic Tcell

over activation; Autoimmunity



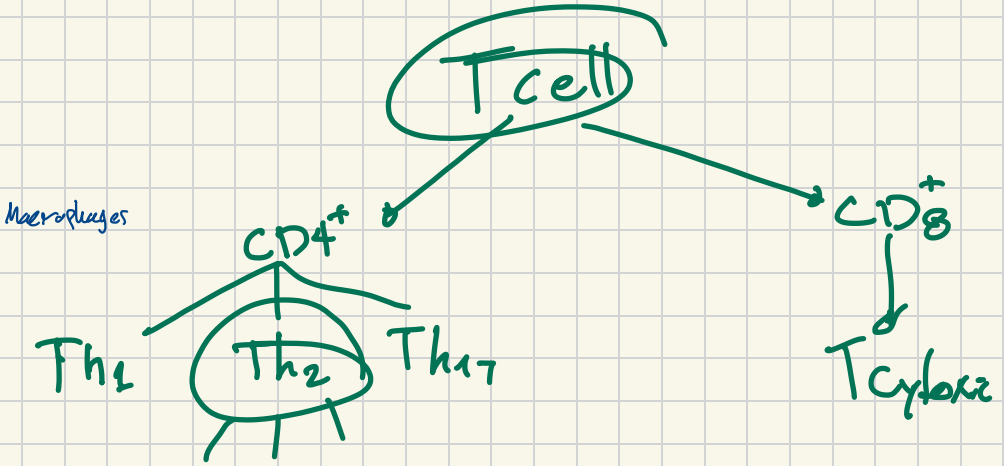
Fungi

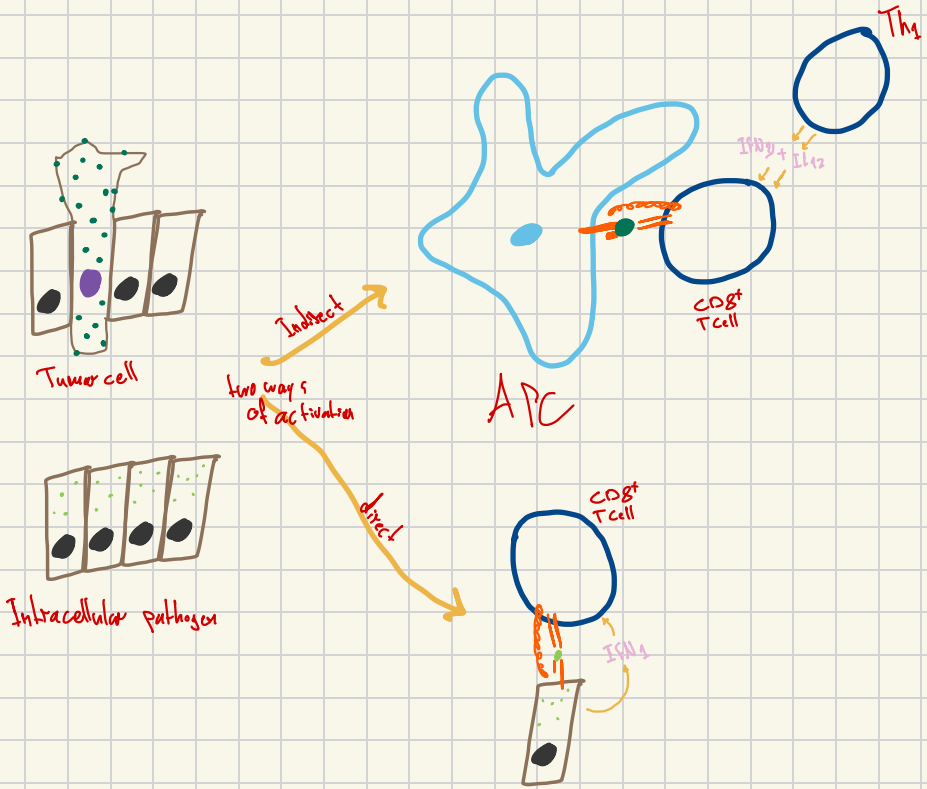


TH_{17}

IL_{17} → Inflammation

IL_{17} → recruit Neutrophils & Macrophages




Th1
IFNγ + IL12
CD8+ Tcell
APC
Indirect
two ways of activation
direct
Tumor cell
Intracellular pathogen
CD8+ Tcell
IFNγ

αß TCR

•About **90-95%** of the blood T cells.

•The receptor has two polypeptide chains: **α** and **ß**.

•Besides **TCR**, there is a **CD coreceptor** that binds **MHC**:

- **CD4+** = (**Th**) binds **MHC II**.
- **CD8+** = (**Tc**) binds **MHC I**.

•The complete **TCR** includes the **αß receptor** plus **CD3** and the **zeta (ζ) chain**.

•The **TCR complex** consists of the **αß receptor**, the **ζ chain**, and two **CD3 signaling proteins**.

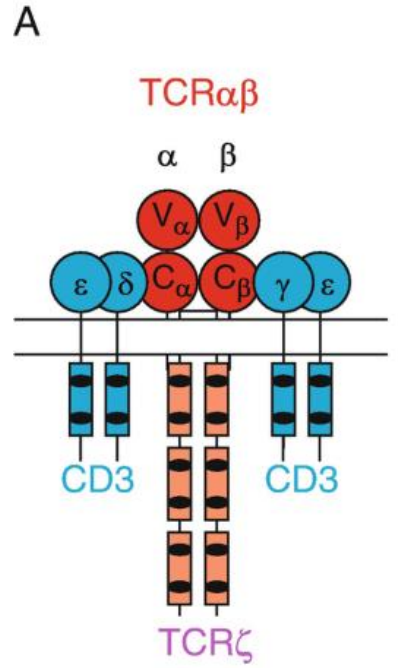
•Each chain consists of:

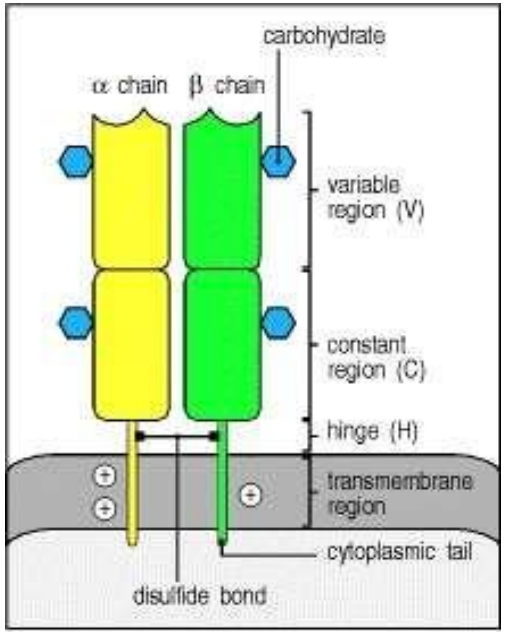
- One **variable** region
- One **constant** region
- A **hinge** region
- A **transmembrane** segment
- A **cytoplasmic tail**

•The chains are covalently linked to each other by a **disulfide bridge** between **extracellular cysteine residues**.

•The **TCR** specifically recognizes **peptide-MHC complexes**.

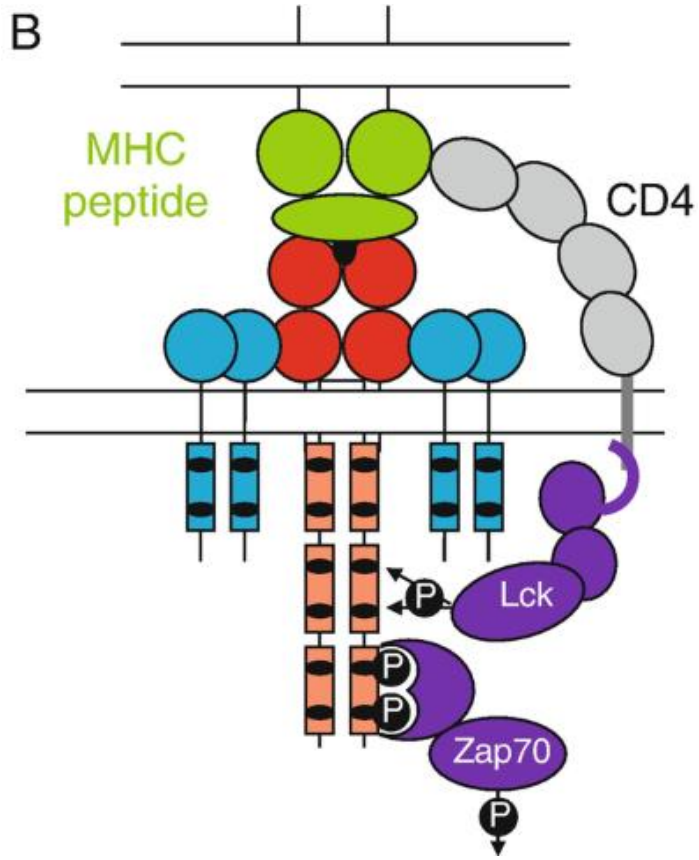
•**Hypervariable regions** on both **Vα** and **Vß** are the same as those of antibodies, located on the **Ag-binding site** and called **CDR**. There are **3 sites** for each **CDR**.





Factors Influencing the Strength of TCR Binding to Antigen

- **Antigen Binding**:
  - **TCR - CD4/8 binding** to the **antigen-MHC** complex (respectively) on antigen-presenting cells provides the **first signal**.
- **Coreceptor Binding**:
  - T cell coreceptors include **CD4** and **CD8** proteins, corresponding to **Th** (helper) or **Tc** (cytotoxic) cells, respectively.
  - **CD8** interacts with **MHC class I**, while **CD4** interacts with **MHC class II**.
  - Besides these coreceptors, **CD3** and the **zeta chain** also contribute by transmitting signals inside the T cell.



Costimulatory Receptors on T Cells:

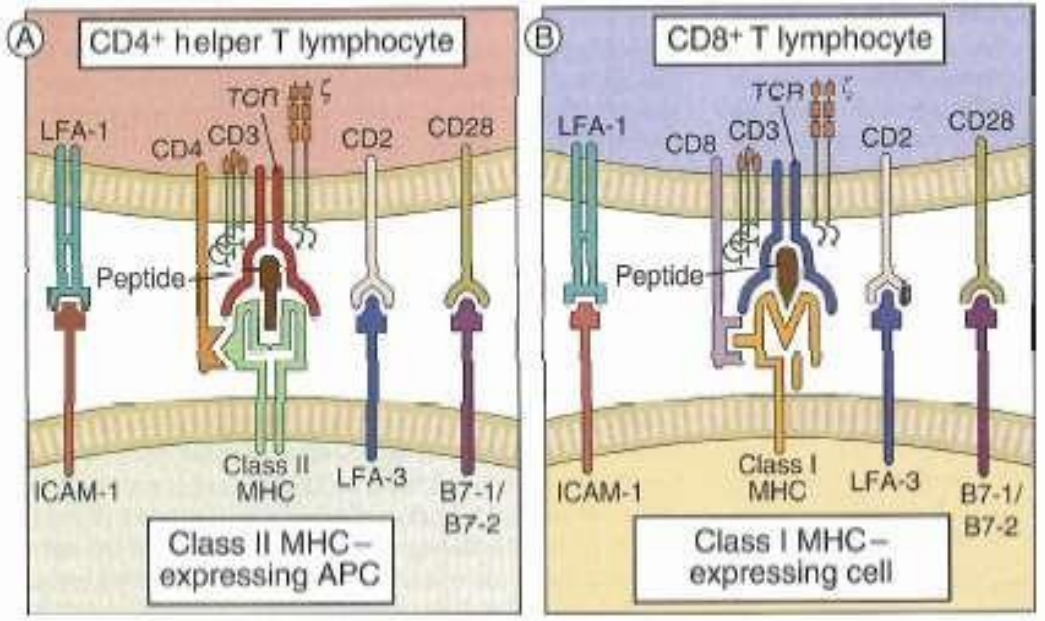
- These receptors provide the **second signals** required for lymphocyte activation.
- **CD28**
  - **CD28** is an early accessory molecule that induces signaling. When it binds to **B7** on APCs, it initiates **T cell proliferation** through the expression of the **IL-2 cytokine** and its receptor.
  - **CTLA-4** binds to **B7** after the antigen is cleared, which regulates T cell activity and leads to **T cell death**.

•**CD2**:

- CD2 is a **glycoprotein** present on over **90% of mature T cells** and **NK cells**.
- Its main ligand in humans is **leukocyte function-associated antigen 3 (LFA-3, or CD58)**.
- CD2 functions as a **signal transducer**.

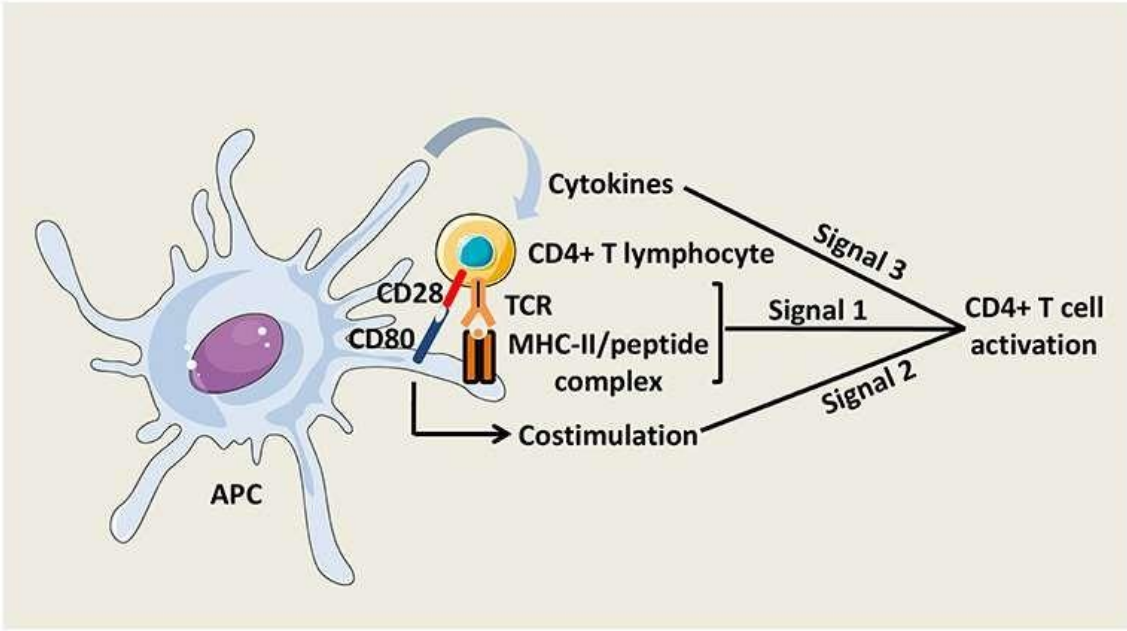
•**CD40L - CD40 Interaction**:

- This interaction occurs on **B cells** and is crucial for **B cell activation** and **isotype switching**.



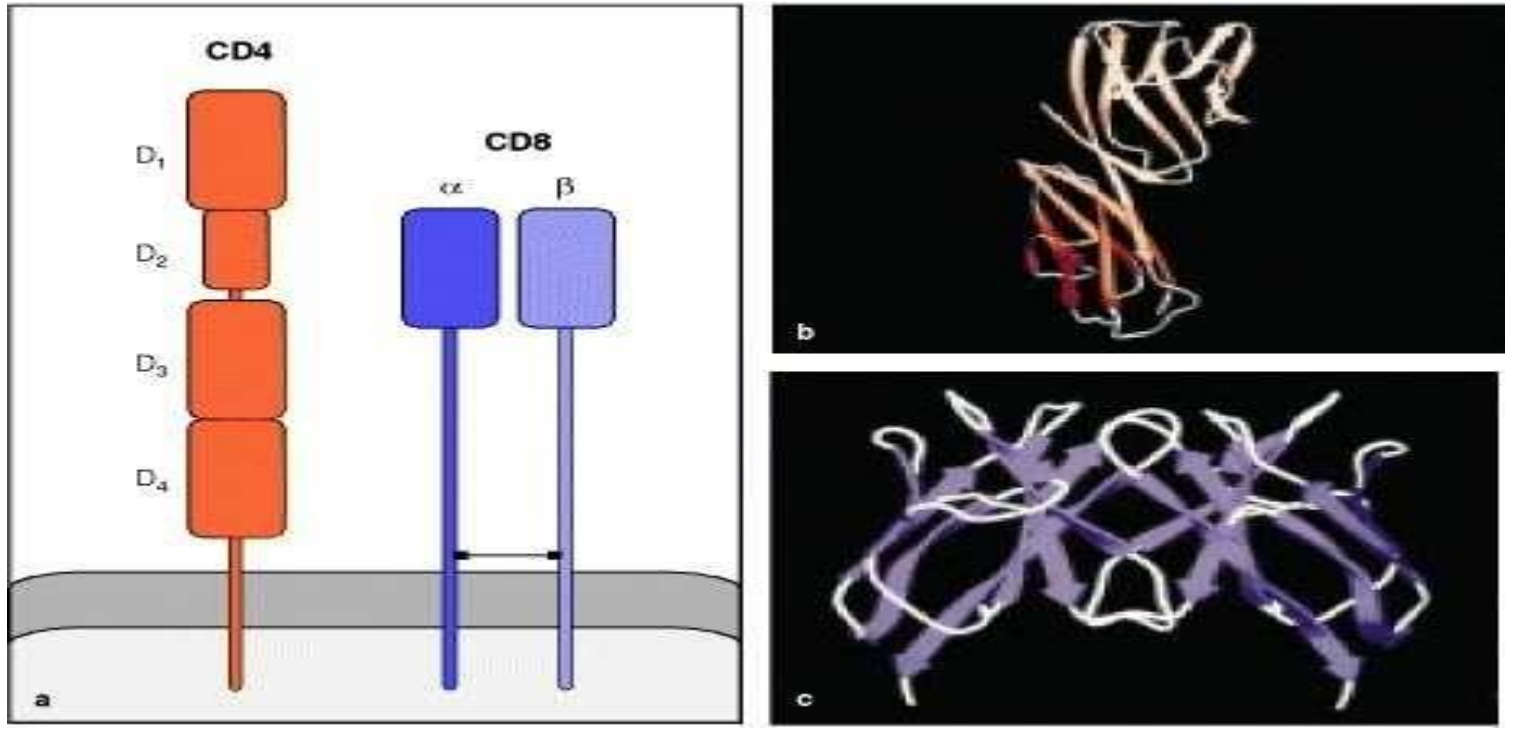
Costimulatory Receptors on T Cells:

- **Signal 3 - Cytokine Effect**:
  - T cell proliferation is stimulated by the **IL-2 growth factor**, produced by **Th** and **Tc** cells, which acts on both T cells and B cells.
- **Outcomes Based on Signal Presence**:
  - If one of these signals is absent, **T cell anergy and tolerance** occur.
  - If all signals are present, **T cell proliferation** and differentiation into **effector** and **memory cells** occur.
- **Effector Cells**:
  - For **CD4** cells, effector cells include **Th1**, **Th2**, or **Th17 lymphocytes**.
  - For **CD8** cells, the effector cell is always a **cytotoxic T lymphocyte (CTL)**



CD4 and CD8

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



T cells are involved in

- **Defense against intracellular and extracellular pathogens**
(Tc in intracellular and Th help in extracellular)
- **Tumor immune response**
- **Graft rejection**
- **Autoimmune diseases**

CD4+ Th cells

•**T cells with the CD4 marker** (a glycoprotein) represent 70% of T cells in the periphery.

•They play a central role in modulating immunity via the secretion of cytokines that modulate:

- **B cell activation** (Th2)
- **Immunoglobulin secretion** (Th2)
- **Macrophage and dendritic cell activation** (Th1)
- **Cellular chemotaxis and inflammation** (Th17)

Th1, Th2, or Th17 cells:

•**CD4+ T helper cells** can be classified into three types based on their cytokine profiles at the time of activation of CD4 and the type of antigen:

- **T helper cell type 1 (Th1)**
- **T helper cell type 2 (Th2)**
- **Th17**

Th1, Th2, or Th17 cells

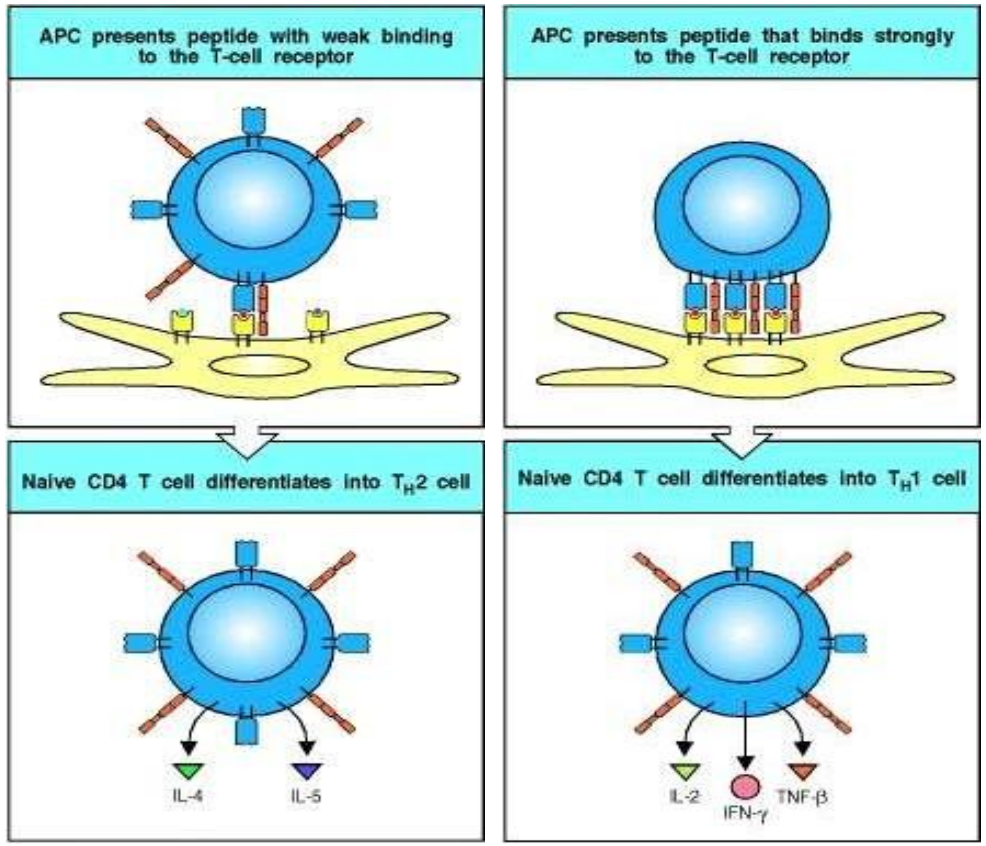
•**Naïve CD4 T cells** in the secondary lymph node are activated by antigen-presenting cells, including B cells. Then, **activated CD4+ T cells** proliferate and differentiate into effector cells.

- **Th2 differentiation** is largely mediated by:
  - Binding of CD4 cells with **B cells as APCs** in response to allergens, small extracellular microbes, or worms.
  - The presence of **IL-4** from B cells.
  - **Th2 cells secrete cytokines** to induce antibody production, specifically **IL-4 and IL-6**, which activate B cells (helping B cells).
- **Th1 differentiation** is mediated by:
  - Binding Th cells to dendritic cells (DCs) that secrete **IL-12 and IFN-gamma**.
  - Targeting intracellular pathogens multiplying within the macrophage's vesicle after engulfing infected cells.
  - Providing **helper functions to other cells** of the immune system—especially to antigen-presenting cells (APCs) such as macrophages and dendritic cells.
- **Th17 differentiation** is stimulated when DCs secrete **IL-6 and TGF-beta** in response to extracellular bacteria and fungi.
- **Treg cells** suppress the immune response and tumor activity.

Antigen effect in priming TH1, TH2, or TH17

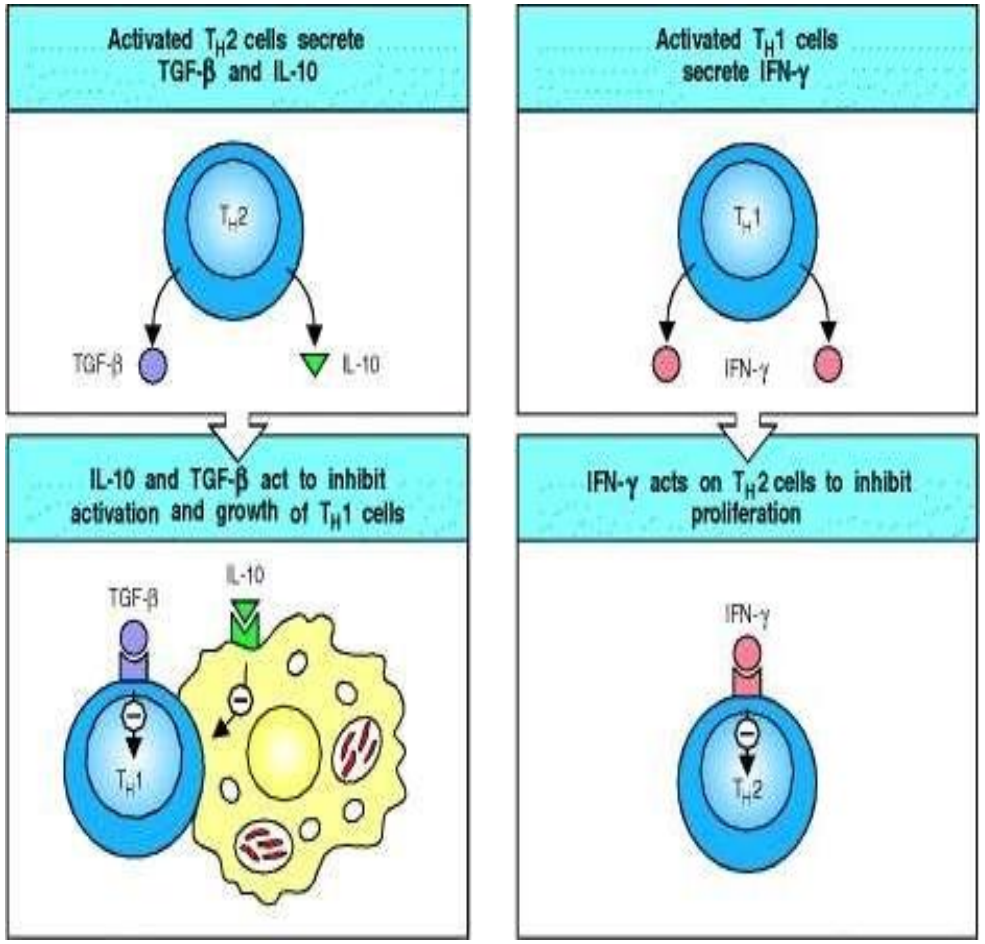
•**The nature and amount of ligand presented** to a CD4 T cell during primary stimulation can determine its functional phenotype.

- **CD4 T cells presented by B cells** with low levels of a small antigen, toxins, or worms that bind the T-cell receptor less tightly differentiate preferentially into **TH2 cells** that produce IL-4 and IL-5.
  - Such T cells are most active in stimulating naive B cells to make antibodies or in activating eosinophils.
  - The antigen in this case is typically an **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**, which secrete IFN-gamma.
  - These cells are most effective in activating macrophages, especially against intracellular pathogens multiplying within the macrophage's phagosomes.



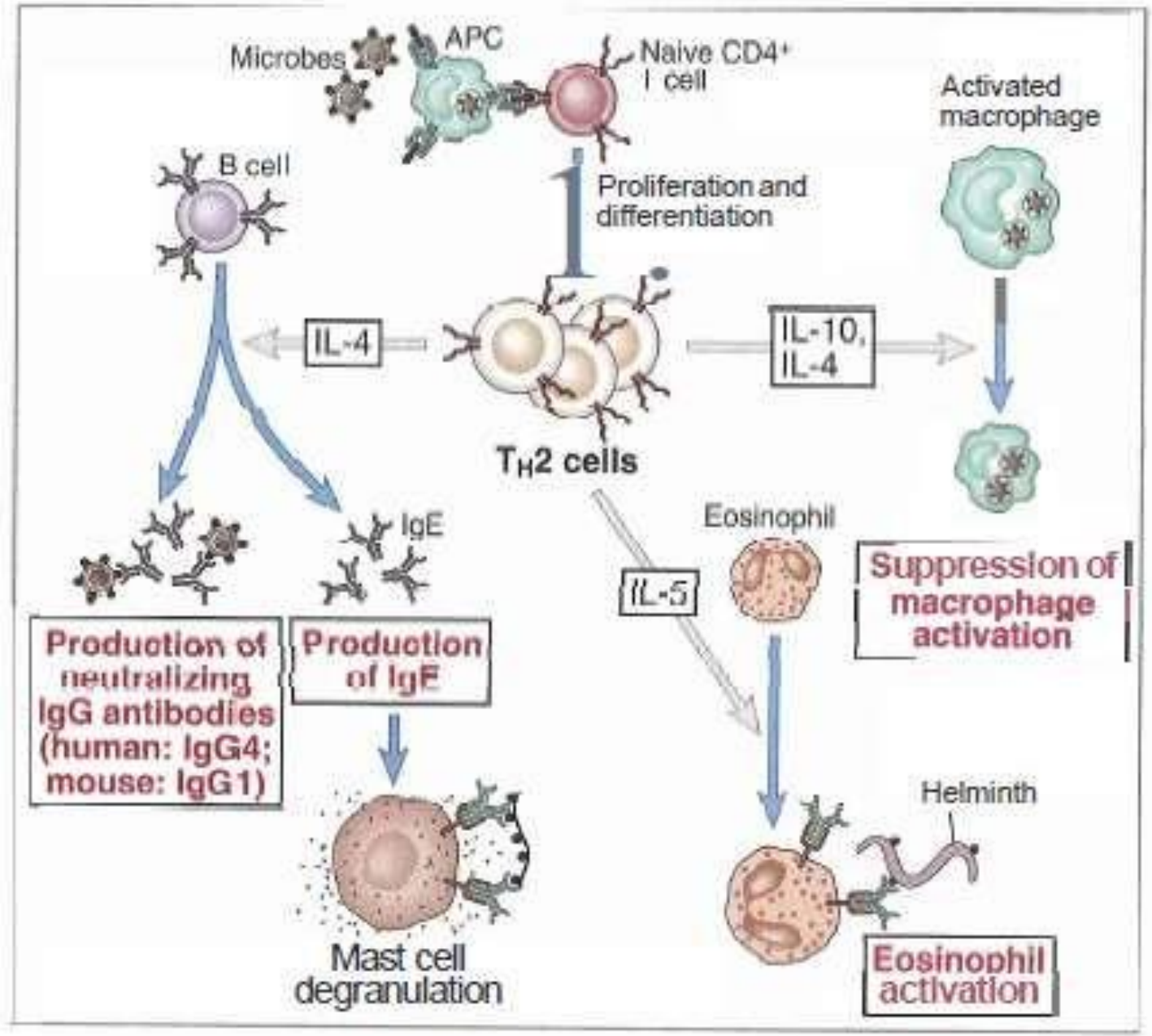
Two subsets regulate each other

- **TH2 cells** produce IL-4, which acts on macrophages to inhibit TH1 activation, thereby decreasing autoimmunity.
- **TH1 cells** secrete IFN-γ, which inhibits IL-4 and blocks the growth of TH2 cells, thereby decreasing allergy.
- These effects allow either subset to dominate a response by suppressing the outgrowth of cells from the other subset. This interaction can help in using cytokines as therapy.
- A balance toward **TH1** promotes cancer and allergy but increases autoimmunity, whereas a balance toward **TH2** decreases autoimmunity.
- **TH17** is associated with autoimmune diseases.



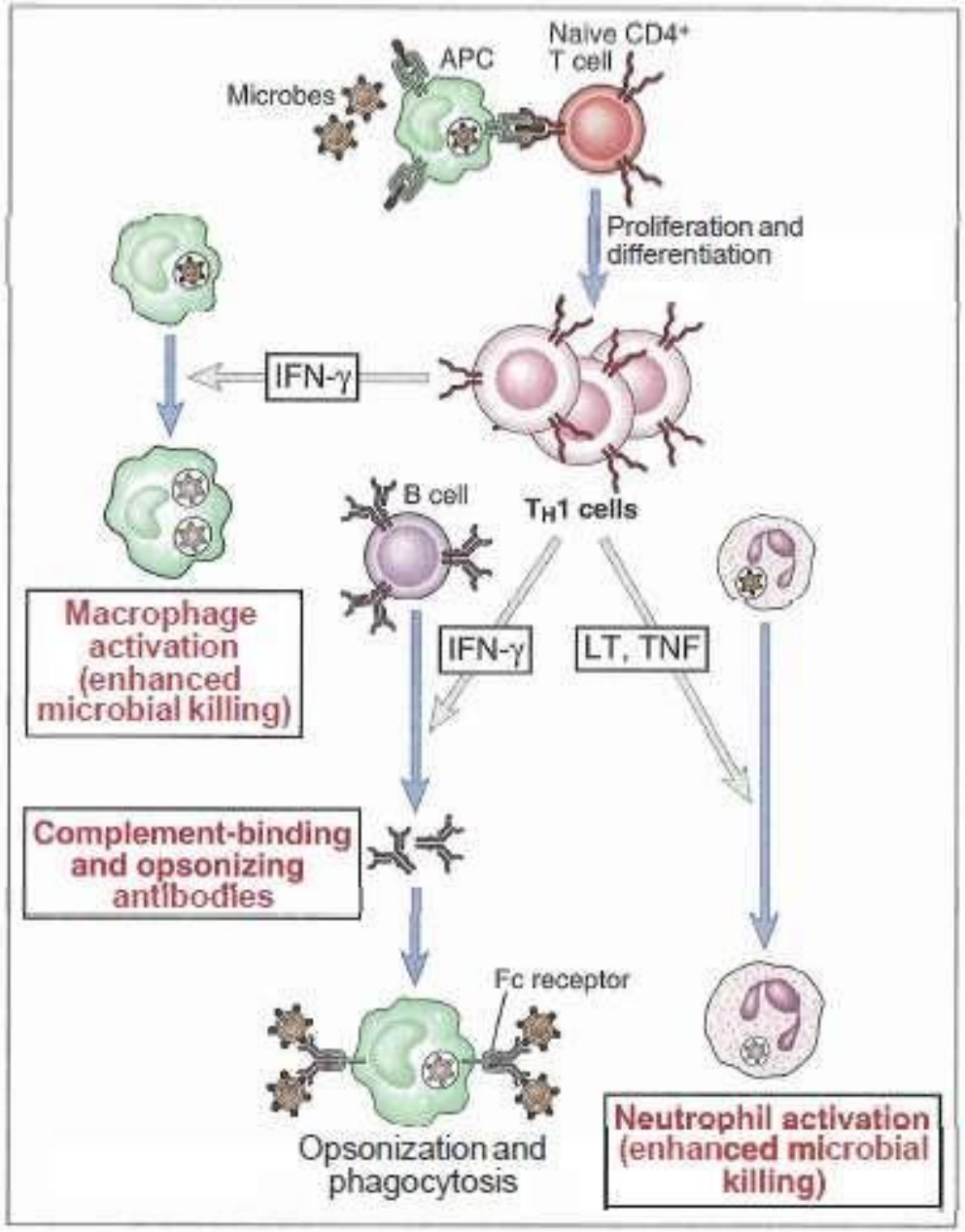
TH2 functions

- **Bind to B cells** and **secrete IL-4**, which leads to B cell activation and antibody secretion.
- **Secrete IL-5** to activate eosinophils, enabling them to react against worms.
- **Secrete IL-10**, which suppresses macrophages



TH1 functions

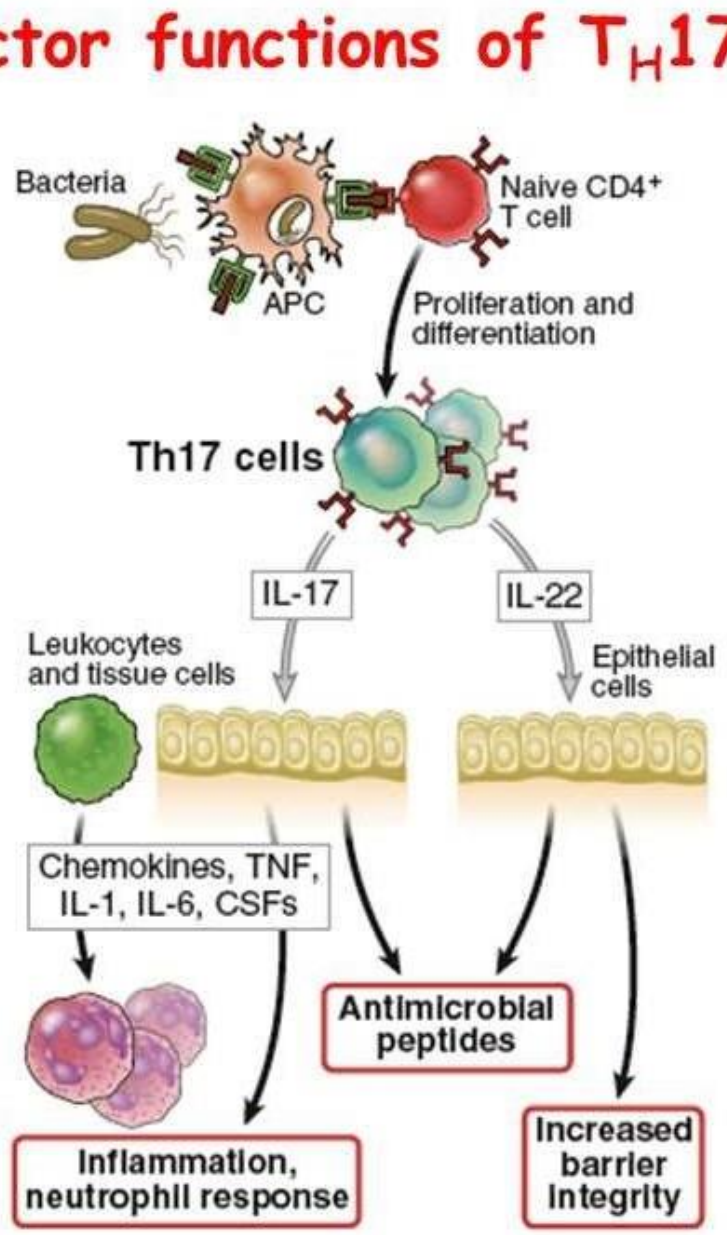
- **Activate CD8 T cells, macrophages, and NK cells** to perform direct killing of infected cells by secreting IFN-gamma and IL-2.
- **Activate B cells** to secrete opsonizing antibodies belonging to certain IgG subclasses (IgG1 and IgG3 in humans), which increase phagocytosis.
- **Help in cell-mediated immunity**
- **Facilitate neutrophil activation**



Th17 functions

•The **TH17 subset primarily produces IL-17**, which is involved in:

- **Secreting IL-17** that recruits neutrophils and macrophages to the site of infection.
- **Inducing inflammation**, which may contribute to some autoimmune diseases



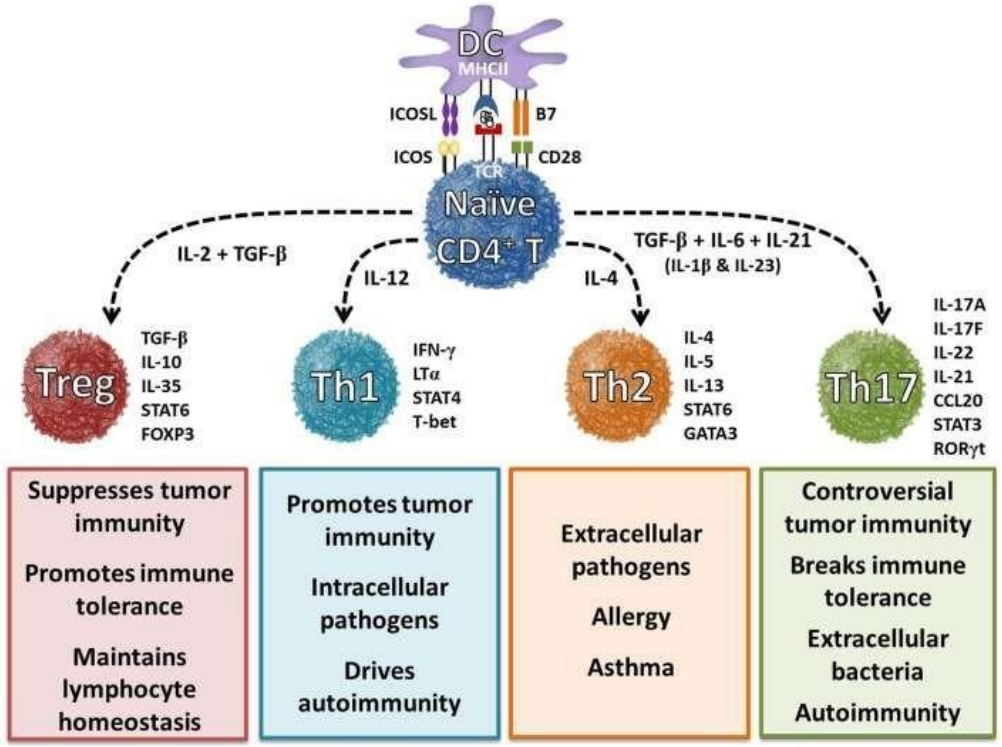
Clinical significance

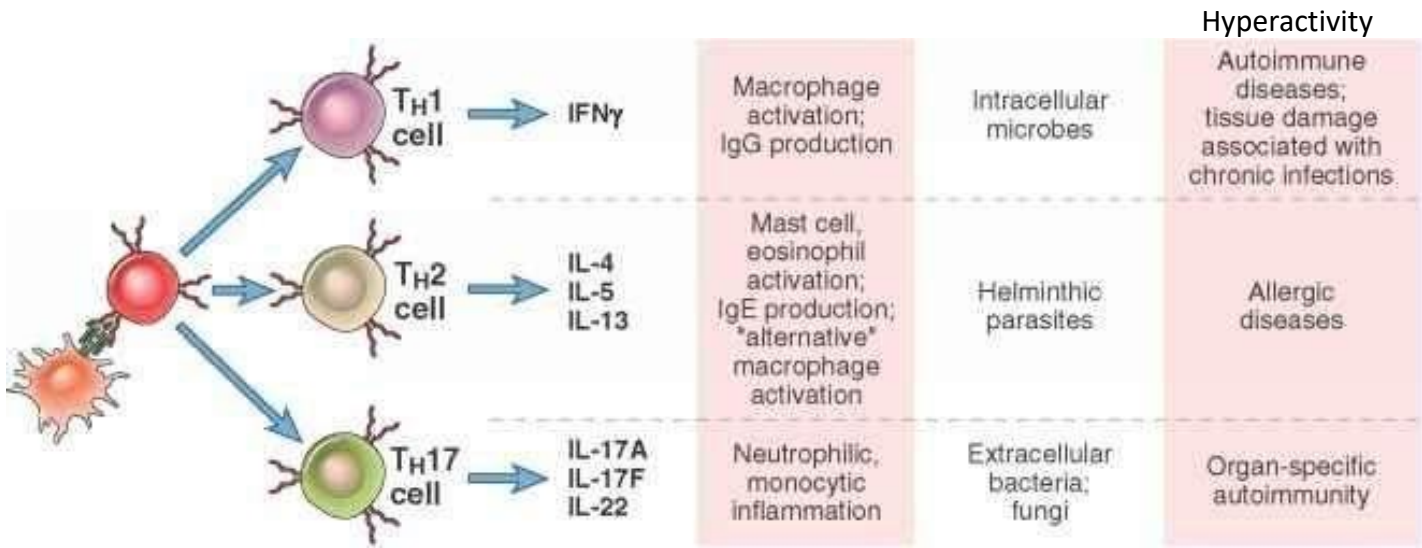
CYTOKINES & DISEASE

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*.

Summary


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


Hyperactivity
TH1 cell
IFNγ
Macrophage activation; IgG production
Intracellular microbes
Autoimmune diseases; tissue damage associated with chronic infections
TH2 cell
IL-4
IL-5
IL-13
Mast cell, eosinophil activation; IgE production; "alternative" macrophage activation
Helminthic parasites
Allergic diseases
TH17 cell
IL-17A
IL-17F
IL-22
Neutrophilic, monocytic inflammation
Extracellular bacteria; fungi
Organ-specific autoimmunity

CD8 cells

•**CD8 T cells** express the CD8 molecule on their surface and represent 30% of T cells in the periphery.

•**Naïve CD8 cells** are activated by presenting antigens on MHC class I molecules from self or antigen-presenting cells (APCs) that are infected (internally by viruses, with antigens multiplying in the cytosol) or from malformed cells (tumor cells) in the presence of IL-12 and IFN-gamma.

•They kill cells harboring microbes, such as viruses or intracellular pathogens in the cytoplasm, as well as cancer cells. By destroying the infected cells, **cytotoxic T lymphocytes (CTLs)** eliminate the reservoirs of infection.

Naïve CD8 activation:

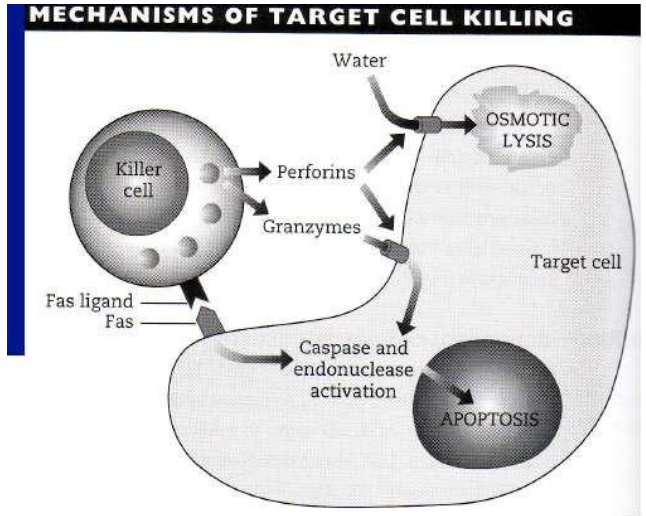
•There are **two ways for activation:**

- **Direct activation:** Presenting antigens to CD8 cells along with type 1 interferon (IFN) from infected cells.
- **Indirect activation:** TH1 cells secrete IFN-gamma to stimulate CD8 cells.

Direct Killing by CD8 cells:

•**Production of perforins** and secretion of granzymes.

•**Induction of apoptosis** by activating the FasL-Fas pathway



Fas-FasL

•The **Fas-FasL** pathway is the most important death receptor; when they bind, **caspases** are activated in the target cell, leading to apoptosis.

•This pathway helps in:

- **NK and CD8 T cell killing** of target cells.
- **T cell regulation.**
- The killing of T cells by NK cells after activation, a process known as **activation-induced cell death (AICD).**

•A mutation in the **FAS** or **FasL gene** can lead to **Autoimmune Lymphoproliferative Syndrome (ALPS)**, characterized by:

- Lymphocyte accumulation
- Defective apoptosis
- Humoral autoimmunity

«Wherever the art of medicine is loved,
there is also a love of humanity.»

- Hippocrates-

Charting New Horizons in Education