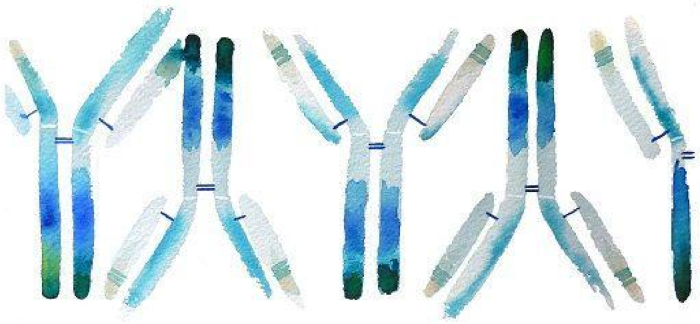
بسم الله الرحمن الرحيم

Medical Immunology



Anas Abu-Humaidan
M.D. Ph.D.

Lecture 10

Innate immunity

"استعن بالله ولا تعجز"

- In this lecture we will discuss

- Main topics:

Immune responses to intracellular pathogens

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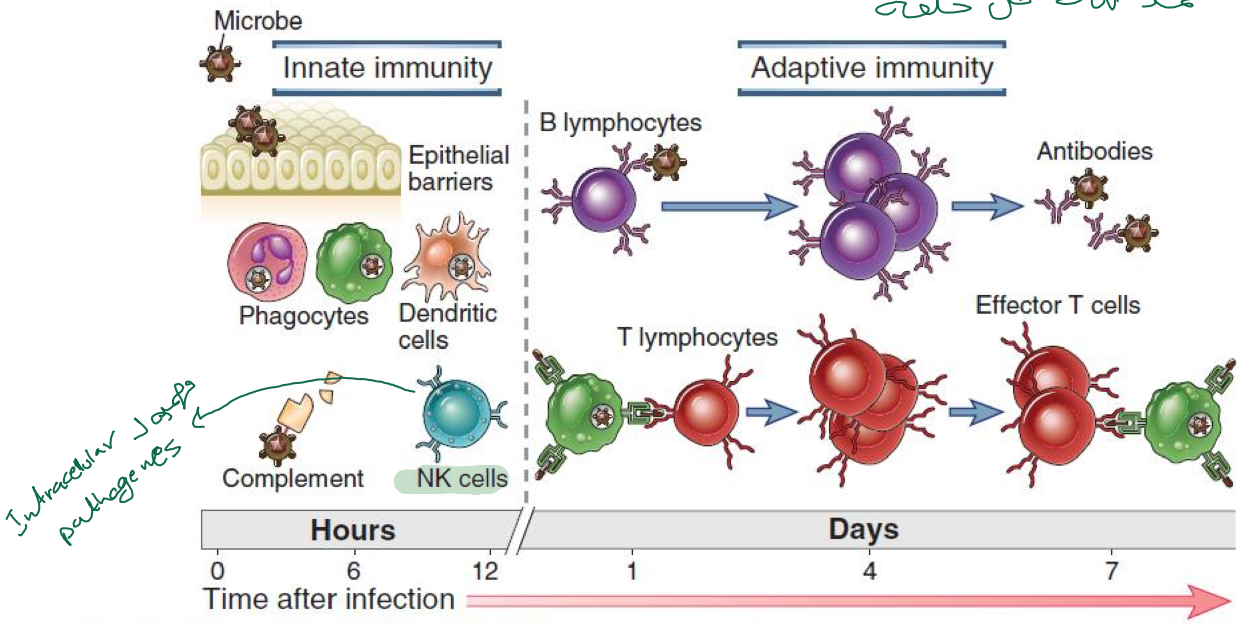

FIGURE 1–1 Innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

Immunity to Intracellular bacteria

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- The innate immune response to **intracellular bacteria** is mediated mainly by phagocytes and natural killer (NK) cells

- Phagocytes, initially neutrophils and later macrophages, ingest and attempt to destroy these microbes, but pathogenic intracellular bacteria are resistant to degradation within phagocytes.

زيادة بكتيريا extracellular

- Products of these bacteria are recognized by TLRs and cytoplasmic proteins of the NOD like **receptor (NLR) family**, resulting in activation of the phagocytes.

- Intracellular bacteria activate NK cells by **inducing expression of NK cell–activating ligands on infected cells** and by **stimulating dendritic cell and macrophage production of IL-12 and IL-15**, both of which are NK cell–activating cytokines.

- The major protective immune response against intracellular bacteria is **T cell–mediated immunity.**

Immunity to Intracellular pathogens / Natural killer (NK) cells

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- NK are lymphocytes important in innate immunity. The term natural killer derives from the fact that these cells are capable of performing their killing function without a need for clonal expansion and differentiation.

- NK cells distinguish infected and stressed cells from healthy cells, and NK cell activation is regulated **by a balance between signals** that are generated from activating receptors and inhibitory receptors.

- In general, the **activating receptors** recognize ligands on **infected and injured cells**, and the inhibitory receptors recognize healthy normal cells. Most NK cells express **inhibitory receptors** that recognize **class I major histocompatibility complex** (MHC) molecules.

- This ability of NK cells to become activated by host cells that lack class I MHC has been called **recognition of missing self**.

Immunity to Intracellular pathogens / Natural killer (NK) cells

FCγRI ... on phagocytes

- Antibodies that bind to antigens can be recognised by **FcγRIII** (CD16) receptors expressed on NK cells, resulting in NK activation, release of cytolytic granules and consequent cell apoptosis. This allows NK cells to **target cells against which a humoral response** has been gone through and to lyse cells through antibody-dependant cytotoxicity (**ADCC**).

- NK cells work to **control viral infections** by secreting **IFNγ and TNFα**. IFNγ activates macrophages for phagocytosis and lysis, and TNFα acts to promote direct NK tumor cell killing.

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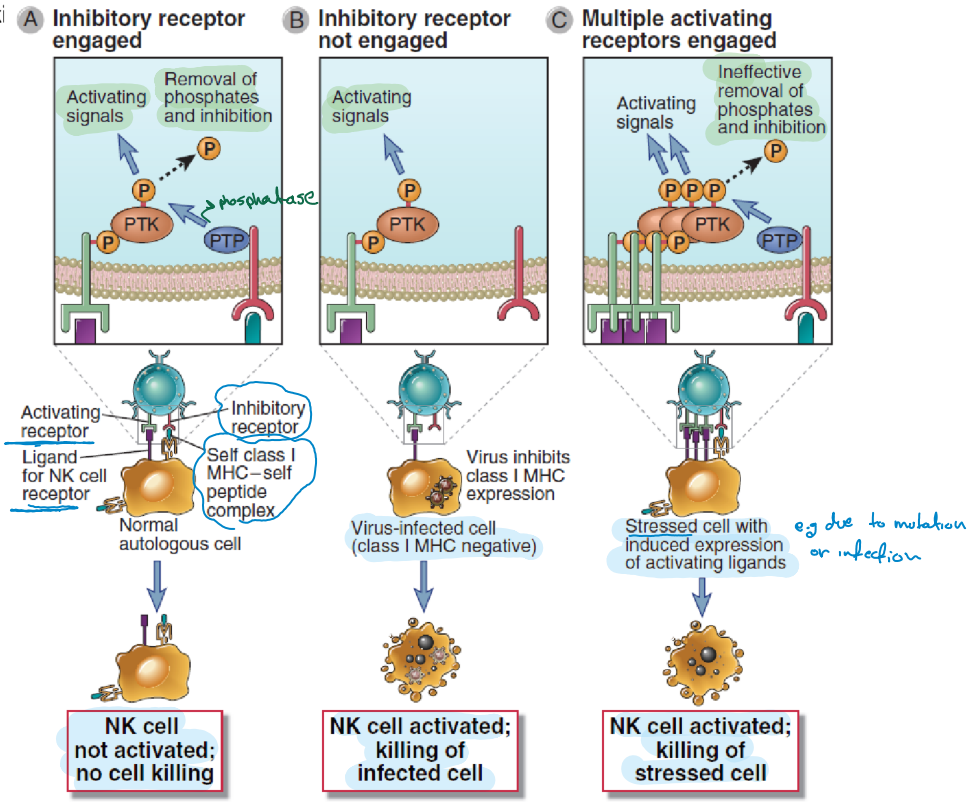
Immunity to Intracellular pathogens / Natural ki

A, Activating receptors of NK cells recognize ligands on target cells and activate protein tyrosine kinase (PTK), whose activity is inhibited by inhibitory receptors that recognize class I MHC molecules and activate protein tyrosine phosphatases (PTP). NK cells do not efficiently kill class I MHC–expressing healthy cells.

B, If a virus infection or other stress inhibits class I MHC expression on infected cells and induces expression of additional activating ligands, the NK cell inhibitory receptor is not engaged and the activating receptor functions unopposed to trigger responses of NK cells, such as killing of target cells and cytokine secretion.

C. Cells stressed by infection or neoplastic transformation may express increased amounts of activating ligands, which bind NK cell activating receptors and induce more tyrosine phosphorylation than can be removed by inhibitory receptor associated phosphatases, resulting in killing of the stressed cells



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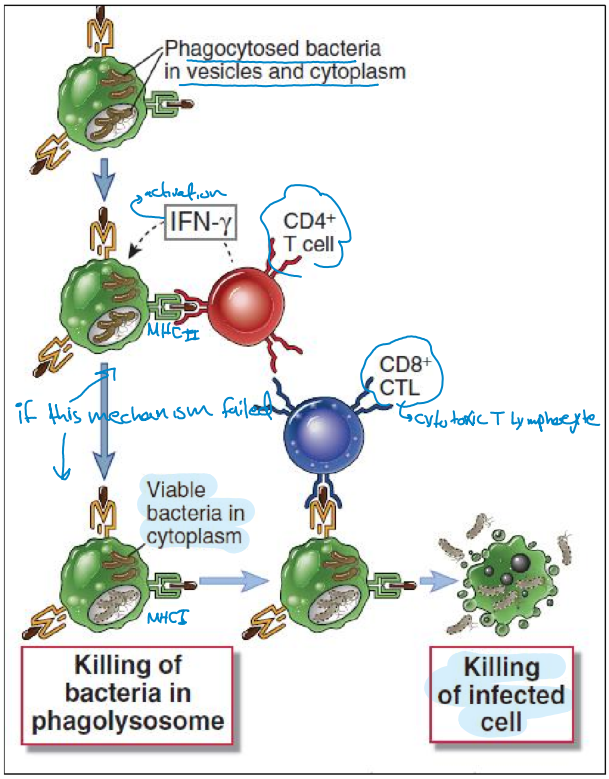
Immunity to Intracellular bacteria / Adaptive immunity

- Cooperation of CD4+ and CD8+ T cells in defense against intracellular microbes. Intracellular bacteria such as L. monocytogenes are phagocytosed by macrophages and may survive in phagosomes and escape into the cytoplasm.

- CD4+ T cells respond to class II MHC–associated peptide antigens derived from the intravesicular bacteria. These T cells produce IFN-γ, which activates macrophages to destroy the microbes in phagosomes. CD8+ T cells respond to class I–associated peptides derived from cytosolic antigens and kill the infected cells.



Immunity to Intracellular bacteria

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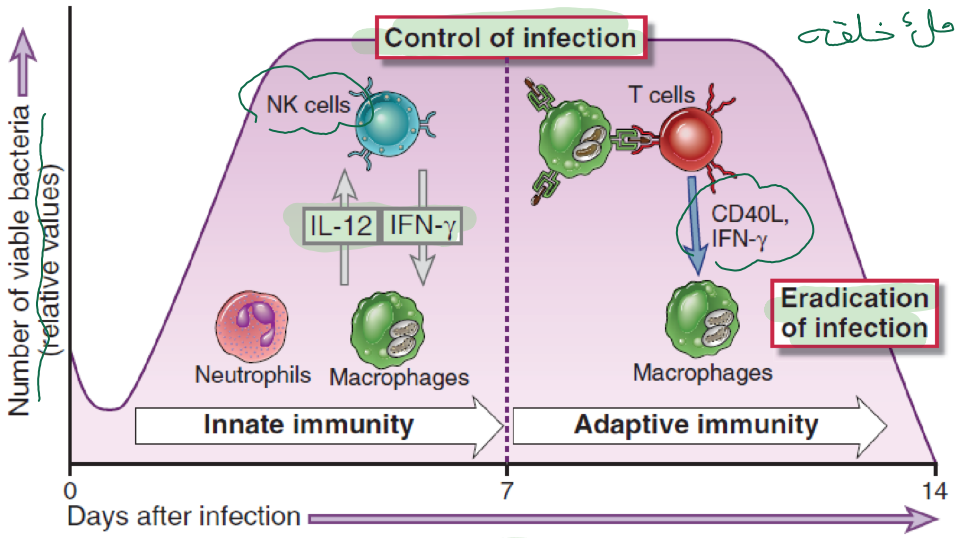

FIGURE 15–3 Innate and adaptive immunity to intracellular bacteria. The innate immune response to intracellular bacteria consists of phagocytes and NK cells, interactions among which are mediated by cytokines (IL-12 and IFN-γ). The typical adaptive immune response to these microbes is cell-mediated immunity, in which T cells activate phagocytes to eliminate the microbes. Innate immunity may control bacterial growth, but elimination of the bacteria requires adaptive immunity. These principles are based largely on analysis of *Listeria monocytogenes* infection in mice; the numbers of viable bacteria shown on the y-axis are relative values of bacterial colonies that can be grown from the tissues of infected mice. *(Data from Unanue ER. Studies in listeriosis show the strong symbiosis between the innate cellular system and the T-cell response. Immunological Reviews 158: 11-25, 1997.)*

Immunity to Intracellular pathogens / Interferons

أستغفر الله

- The major way by which the innate immune system deals with **viral infections** is to induce the expression of type I interferons. Type I interferons are a large family of structurally related cytokines that mediate the **early innate immune response to viral infections**.
- Type I interferons, signaling through the type I interferon receptor, activate transcription of several genes that confer on the cells a resistance to viral infection, called an **antiviral state**.
- Type I interferons cause **sequestration of lymphocytes in lymph nodes**, thus maximizing the opportunity for encounter with microbial antigens.
- Type I interferons **increase the cytotoxicity of NK cells** and **CD8+ CTLs**
- **Upregulate expression of class I MHC** molecules and thereby increase the probability that virally infected cells will be recognized and killed by CD8+ CTLs.

Immunity to Intracellular pathogens / Interferons

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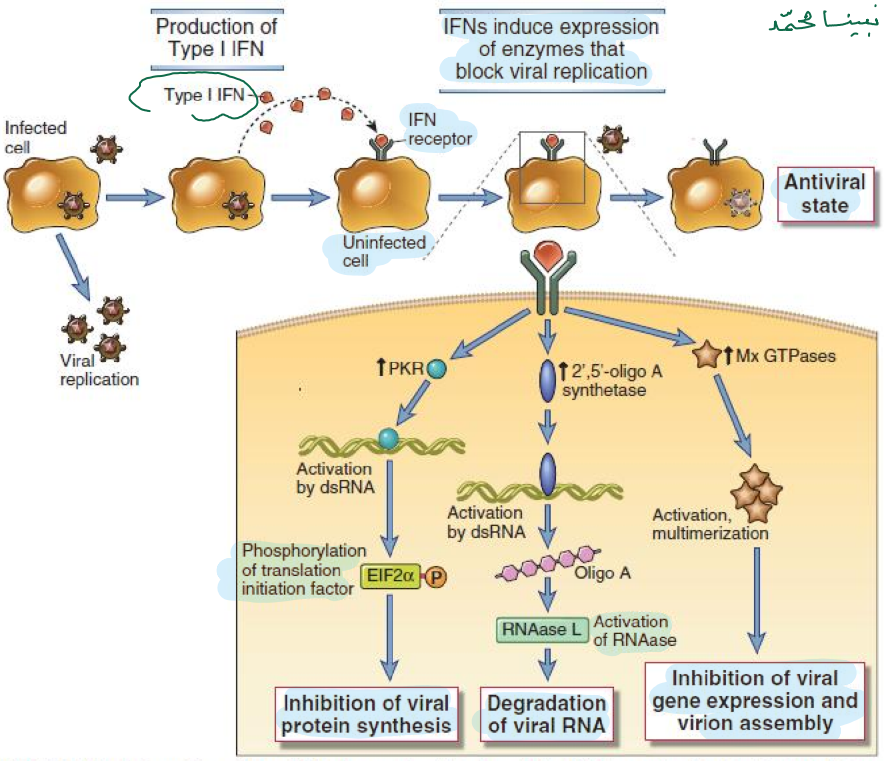

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Immunity to Intracellular pathogens / Interferons

Clinical Correlate

Therapeutic Use of Interferons

Since the first description of interferons (IFN) almost 50 years ago, a multitude of dramatic immunomodulatory roles have been discovered for this group of proteins. As a group, IFNs induce increases in the expression of class I and II MHC molecules and augment NK cell activity. They increase the efficiency of presentation of antigens to both cytotoxic and helper cell populations. Cloning of the genes that encode IFNs α, β, and γ has made it possible to produce sufficient amounts to make their use clinically practical.

- **Interferon-α** has well-known antiviral activity and has been used in the treatment of hepatitis B and C infections. Within cancer therapy, IFN-α has shown promise in treatment of hairy B-cell leukemia, chronic myelogenous leukemia, and Kaposi sarcoma.
- **Interferon-β** was the first drug shown to have a positive effect on young adults with multiple sclerosis. Patients treated with IFN-β enjoy longer periods of remission and reduced severity of relapses.
- **Interferon-γ** is being used in the treatment of chronic granulomatous disease (CGD). This molecule is a potent inducer of macrophage activation and a promoter of inflammatory responses. Its application appears to significantly reverse the CGD patient's inability to generate toxic oxygen metabolites inside phagocytic cells.

The side effects of IFN therapy are fortunately mild and can be managed with acetaminophen. They include headache, fever, chills, and fatigue, and they diminish with continued treatment.

Immunity to Intracellular pathogens / Interferons

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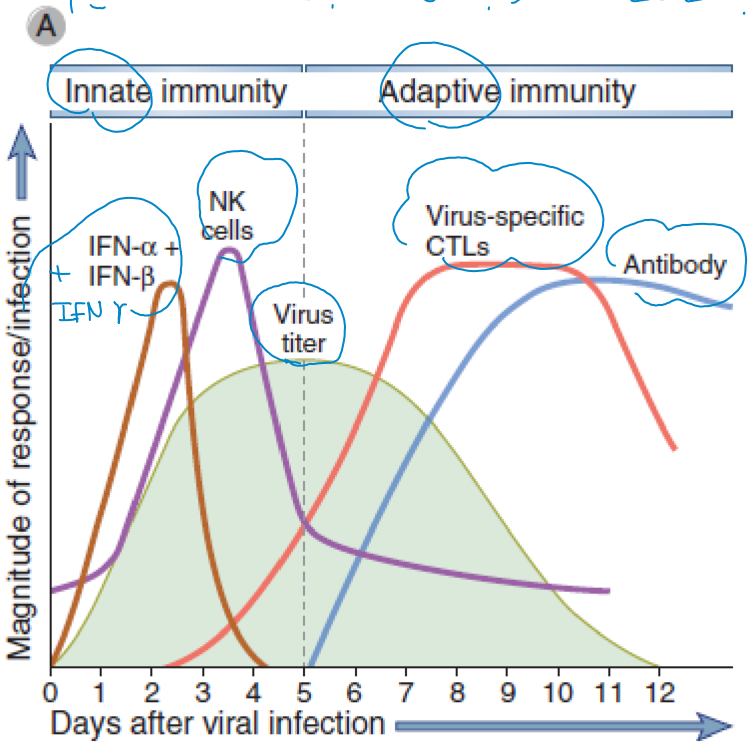

Innate immunity/ Innate Immunity to Intracellular Pathogens

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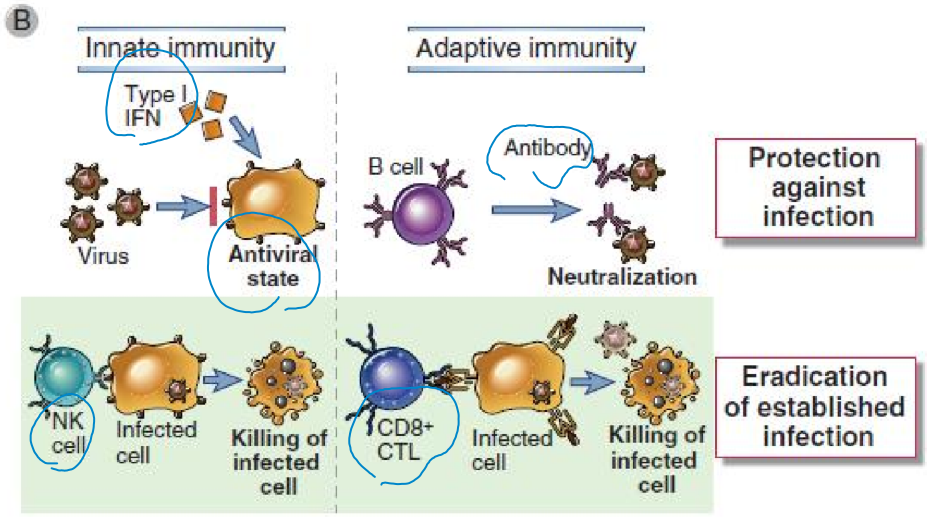

Immunity to Intracellular pathogens / Effector T cells

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- Effector T cells of the CD4+ lineage link specific recognition of microbes with the recruitment and activation of other leukocytes that destroy the microbes.

- The adaptive immune response to microbes that are phagocytosed and live within the phagosomes of macrophages is mediated by TH1 cells, which recognize microbial antigens and activate the phagocytes to destroy the ingested microbes.

- The response to extracellular microbes, including many fungi and bacteria, is mediated by TH17 cells. While The response to helminthic parasites is mediated by TH2 cells,

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- The adaptive immune response to microbes that infect and replicate in the cytoplasm of various cell types, including nonphagocytic cells, is mediated by CD8+ cytotoxic T lymphocytes (CTLs), which kill infected cells and eliminate the reservoirs of infection.

- T cell–dependent inflammation may damage normal tissues. This T cell–dependent injurious reaction is called delayed-type hypersensitivity (DTH), the term hypersensitivity referring to tissue damage caused by an immune response.

SIGNALS FOR T LYMPHOCYTE ACTIVATION

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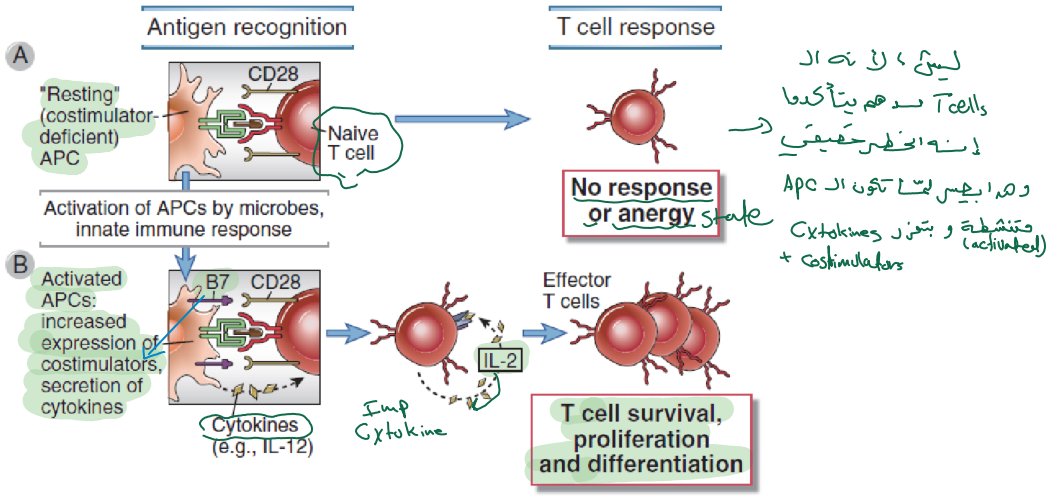

- The proliferation of T lymphocytes and their differentiation into effector and memory cells require **antigen recognition**, **costimulation**, and **cytokines** that are produced by the T cells themselves and by APCs and other cells at the site of antigen recognition.

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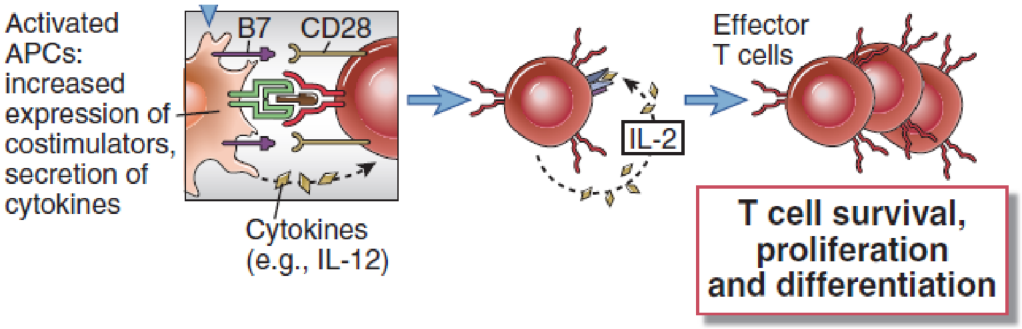
SIGNALS FOR T LYMPHOCYTE ACTIVATION



- The best characterized costimulatory pathway in T cell activation involves the T cell surface receptor **CD28**, which binds the costimulatory molecules **B7**-1 (CD80) and B7-2 (CD86) expressed on activated APCs.

- The outcome of T cell activation is influenced by a balance between engagement of activating and inhibitory receptors of the CD28 family. **Inhibitory receptors** include CTLA-4 (cytotoxic T lymphocyte antigen 4, and PD-1 (programmed death 1).

SIGNALS FOR T LYMPHOCYTE ACTIVATION

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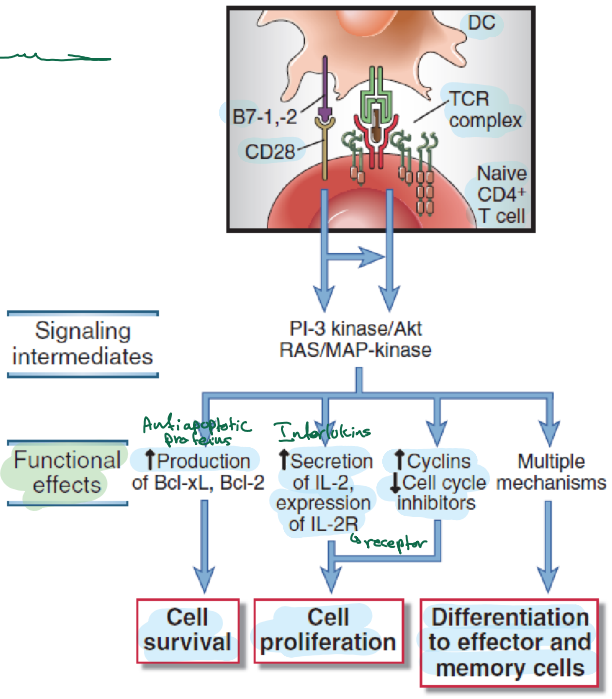
- APCs must express molecules in addition to antigen that are required for T cell activation. These molecules are called **costimulators**, and the "second signal" for T cell activation is called costimulation because it functions together with antigen ("signal 1") to stimulate T cells.



SIGNALS FOR T LYMPHOCYTE ACTIVATION

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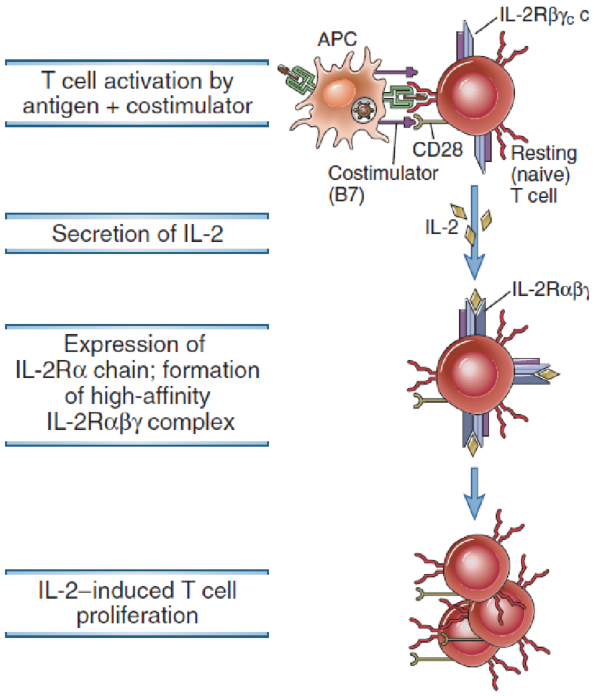
- The most important cytokine produced by T cells early after activation, often within 2 to 4 hours after recognition of antigen and costimulators, is **interleukin-2 (IL-2).**
- IL-2 stimulates the **survival, proliferation, and differentiation** of antigen-activated T cells.
- T cell proliferation in response to antigen recognition is mediated primarily by a combination of signals from the antigen receptor, costimulators, and autocrine growth factors, **primarily IL-2**.



MIGRATION OF EFFECTOR T LYMPHOCYTES TO SITES OF INFECTION

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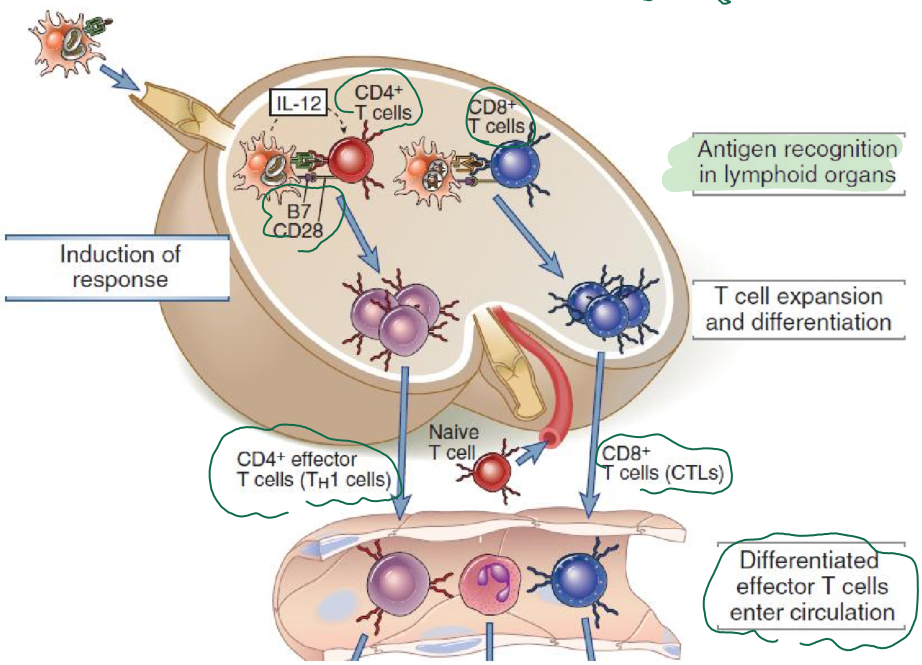

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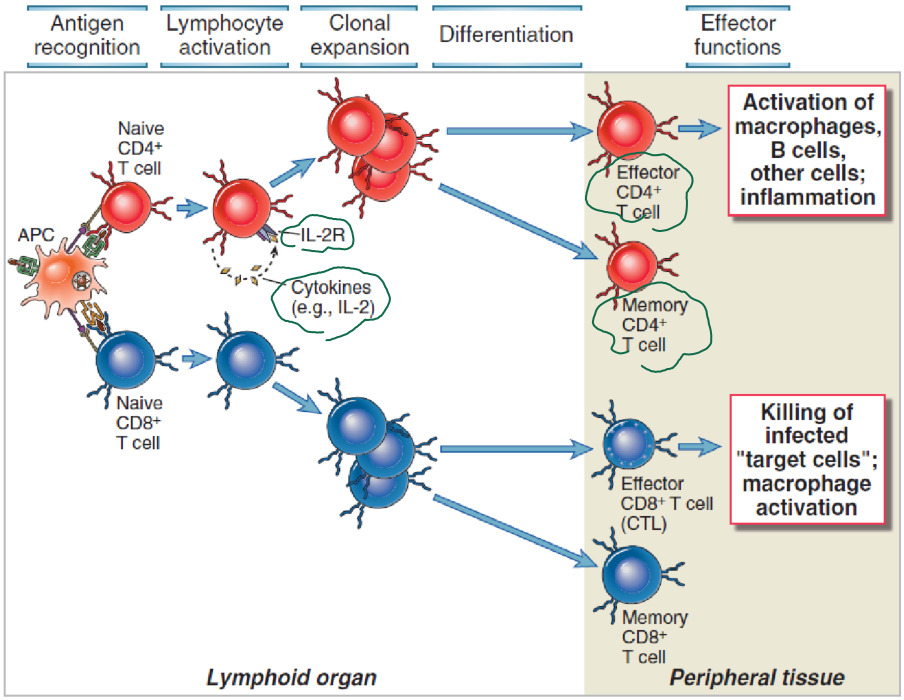
MIGRATION OF EFFECTOR T LYMPHOCYTES TO SITES OF INFECTION



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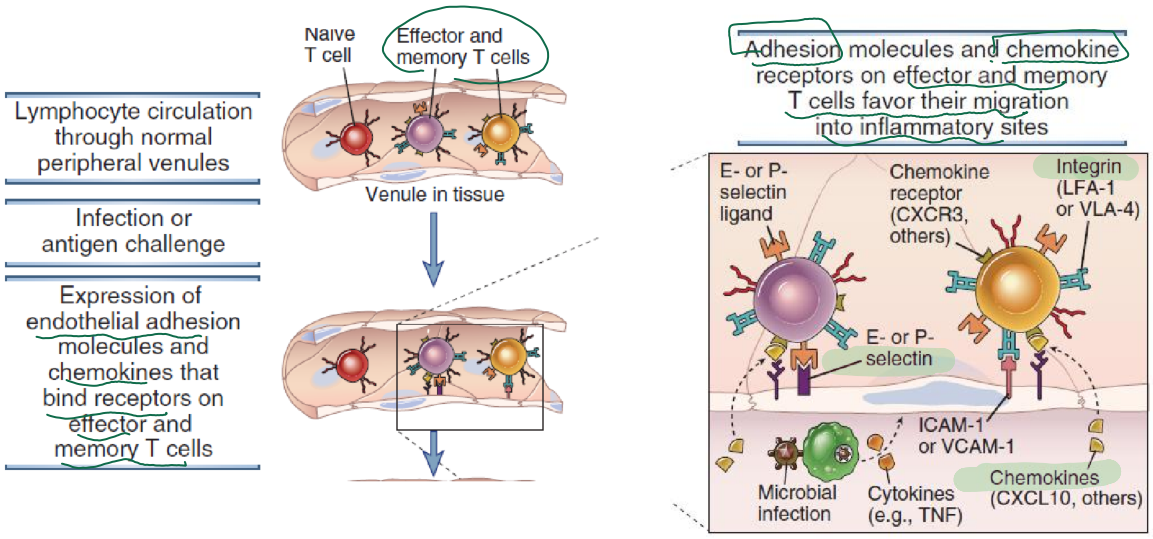
MIGRATION OF EFFECTOR T LYMPHOCYTES TO SITES OF INFECTION



Migration and retention of effector and memory T cells at sites of infection. Previously activated effector and memory T cells, but not naive cells, migrate through endothelium that is activated by cytokines (e.g., TNF) produced at a site of infection. and then they stay at the site of infection for long time until the pathogen comes again

EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS

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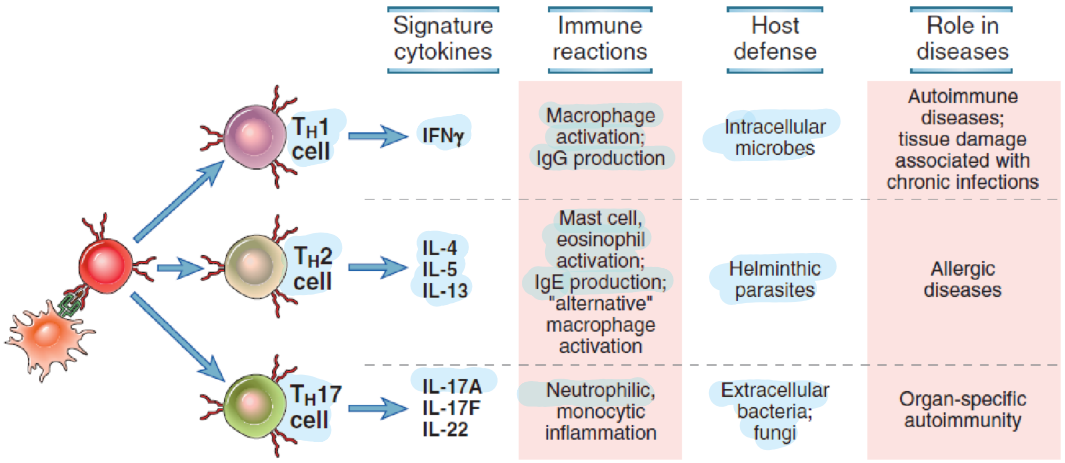
- There are three distinct subsets of CD4+ T cells, called **TH1, TH2, and TH17**, that function in host defense against different types of infectious pathogens and are involved in different types of tissue injury in immunologic diseases



EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/

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- The cytokines that drive the development of CD4+ T cell subsets are **produced by APCs** (primarily dendritic cells and macrophages) and **other immune cells** (such as NK cells and basophils or mast cells) present at the site of the immune response.

- Differentiation of each subset is induced by the types of microbes which that subset is best able to combat.

الدكتور اختصر اللاية بالشكل بس كل معلوماتها الموجودة اشرحت شغل متعرق

EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/ Functions of TH1 Cells

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- The principal function of TH1 cells is to activate macrophages to ingest and destroy microbes. Indeed, **phagocytosed intracellular microbes** are powerful stimuli for the generation of TH1 cells.
- The signature cytokine of TH1 cells is **IFN-γ**. TH1 cells also produce TNF, some chemokines, and other cytokines.
- IFN-γ is the principal **macrophage-activating cytokine** and serves critical functions in immunity against intracellular microbes.
- The actions of IFN-γ together result in **increased ingestion of microbes** and the **destruction of the ingested pathogens**.
- CD4+ TH1 cells activate macrophages by contact-mediated signals delivered by **CD40L-CD40** interactions and by IFN-γ

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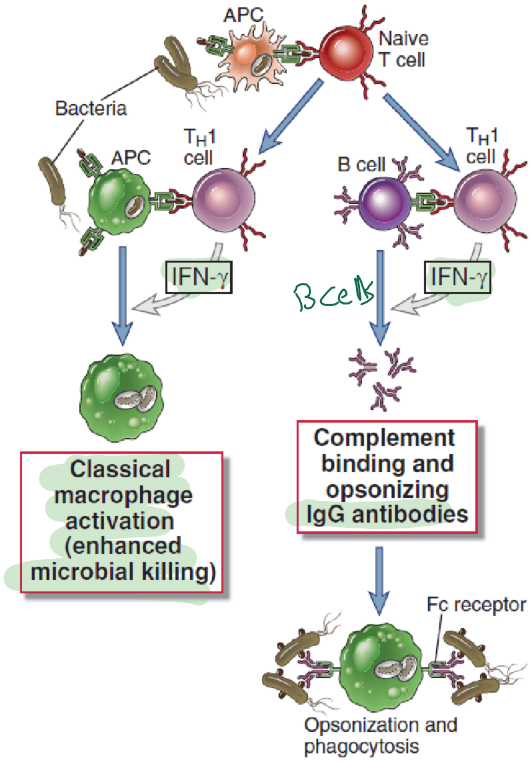
EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/ Functions of TH1 Cells

- IFN-γ acts on B cells to promote switching to certain **IgG subclasses**
- IFN-γ **promotes the differentiation** of CD4+ T cells to the **TH1 subset** and inhibits the differentiation of TH2 and TH17 cells.
- IFN-γ stimulates expression of several different proteins that contribute to **enhanced MHC-associated antigen presentation** and the initiation and amplification of T cell–dependent immune responses.



EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/ Functions of TH1 Cells

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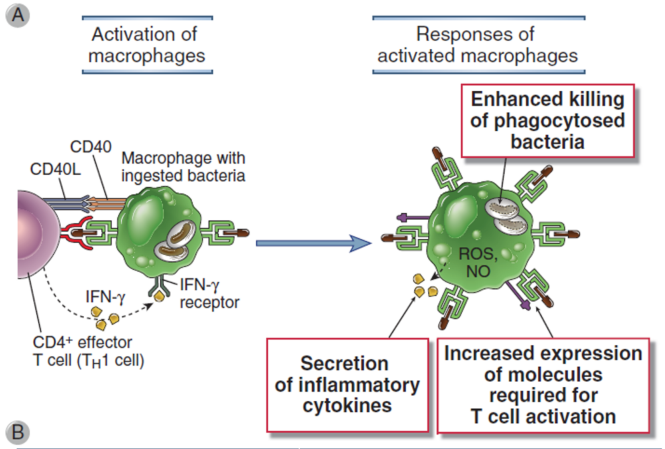

B

Macrophage response	Role in cell-mediated immunity
Production of reactive oxygen species, nitric oxide, increased lysosomal enzymes	Killing of microbes in phagolysosomes (effector function of macrophages)
Secretion of cytokines (TNF, IL-1, IL-12) and chemokines	TNF, IL-1, chemokines: leukocyte recruitment (inflammation) IL-12: T_H1 differentiation, IFN-γ production
Increased expression of B7 costimulators, MHC molecules	Increased T cell activation (amplification of T cell response)

EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/ Functions of TH2 Cells

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- The principal function of TH2 cells is **stimulate IgE- and eosinophil-mediated reactions** that serve to eradicate helminthic infections.
- The functions of TH2 cells are mediated by **IL-4, which induces IgE antibody responses**; **IL-5, which activates eosinophils; and IL-13, which has diverse actions**.
- The functions of TH2 cells are mediated by IL-4, which induces IgE antibody responses; IL-5, which activates eosinophils; and IL-13, which has diverse actions.
- IL-4 stimulates B cell Ig heavy chain **class switching to the IgE isotype**.
- IL-4 **stimulates the development of TH2 cells** and functions as an autocrine growth factor for differentiated TH2.
- IL-4, together with IL-13, contributes to an **alternative form of macrophage activation to** express enzymes that promote collagen synthesis and fibrosis**.**

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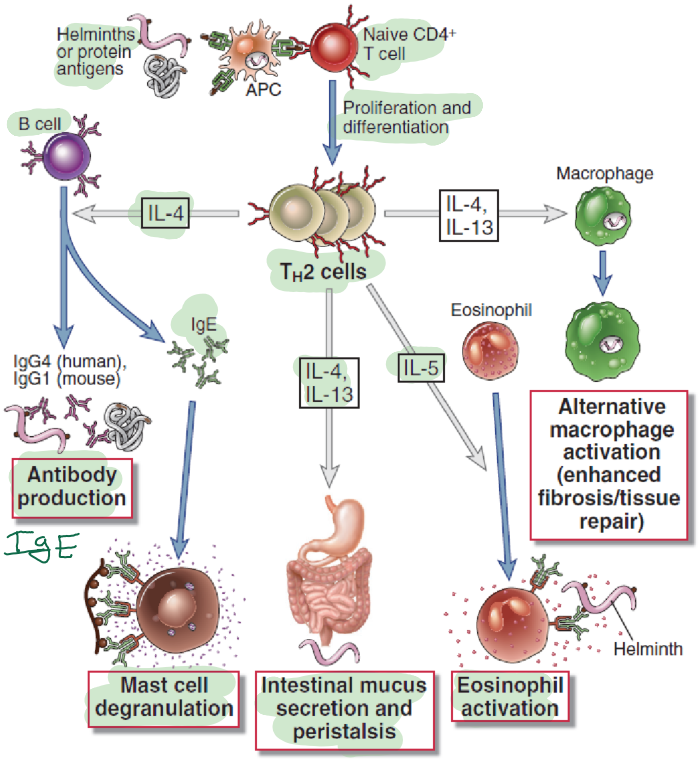
EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/ Functions of TH2 Cells

- **IL-5** is an **activator of eosinophils** and serves as the principal link between T cell activation and eosinophilic inflammation.
- Cytokines produced by TH2 cells are involved in **blocking entry and promoting expulsion of microbes** from mucosal organs. For instance, **IL-13** stimulates mucus production, and IL-4 and IL-13 may stimulate peristalsis in the gastrointestinal system.



EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/ Functions of TH17 Cells

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- **TH17 cells** secrete cytokines that **recruit leukocytes**, mainly **neutrophils**, to sites of infection.
- Because neutrophils are a major defense mechanism **against extracellular bacteria** and fungi, **TH17 cells** play an especially important role in defense against these infections.
- TH17 cells produce several cytokines. Most of the inflammatory actions of these cells are mediated by **IL-17**.

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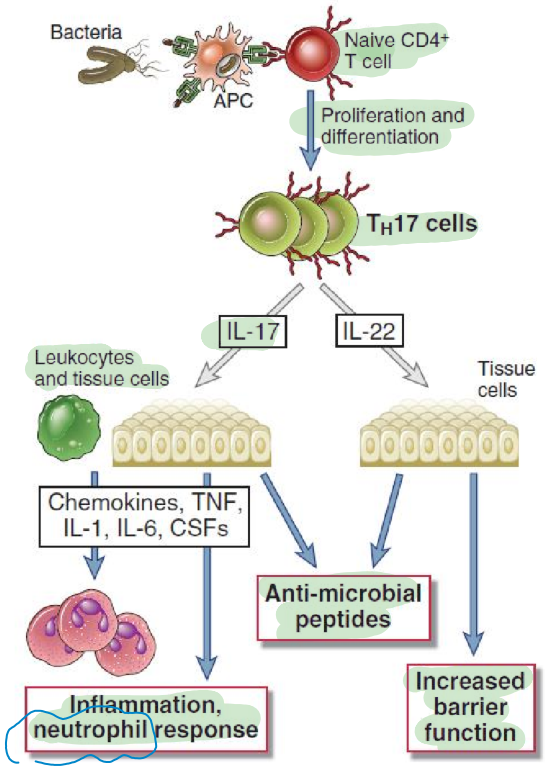
EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/ Functions of TH17 Cells

- IL-17 induces neutrophil-rich inflammatory reactions.
- IL-17 stimulates the production of antimicrobial substances, including defensins, from numerous cell types.
- The principal effector function of TH17 cells is to induce neutrophilic inflammation, which serves to destroy **extracellular bacteria and fungi**



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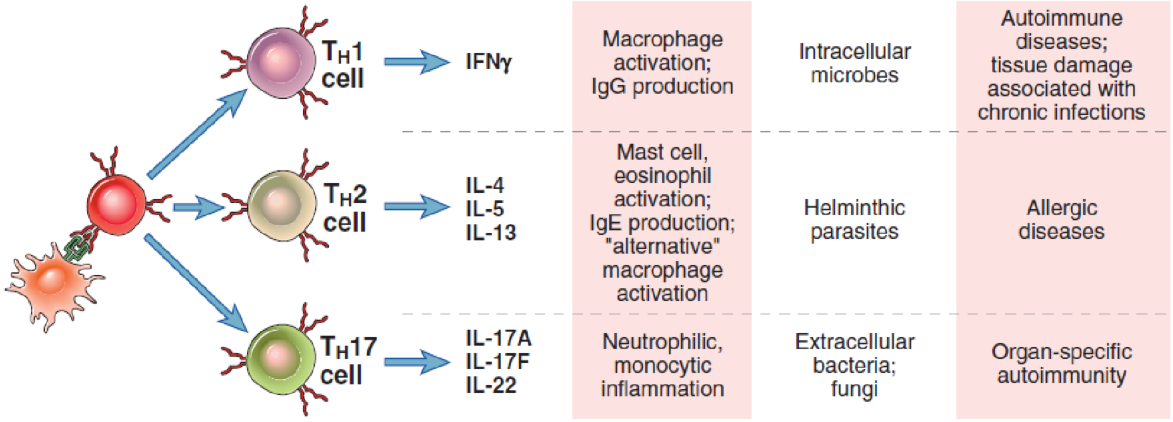

EFFECTOR FUNCTIONS OF CD8+ HELPER T CELLS

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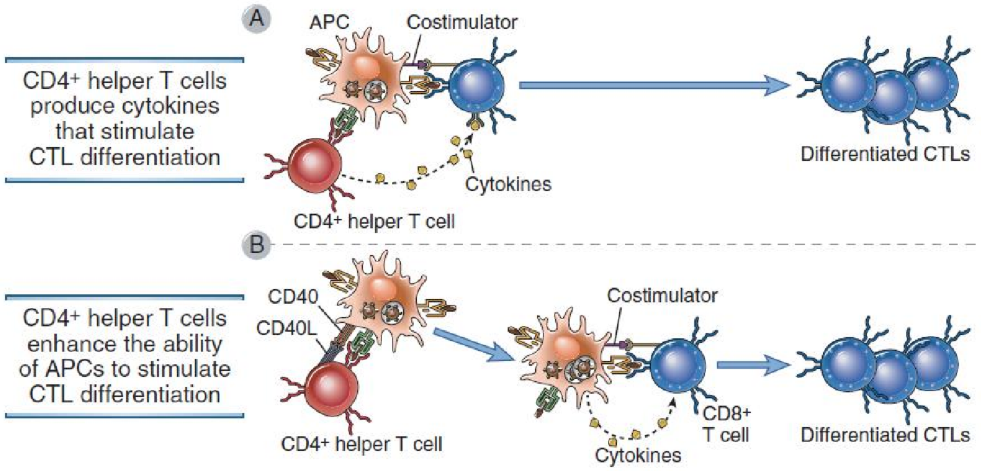
- The full activation of naive CD8+ T cells and their differentiation into **functional CTLs** and **memory cells** may require the **participation of CD4+ helper cells**.



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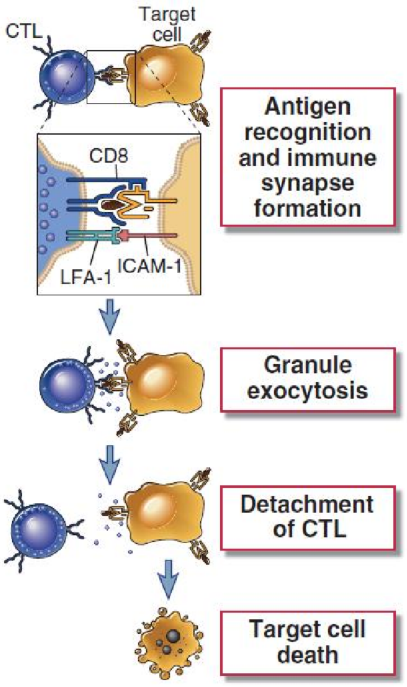
EFFECTOR FUNCTIONS OF CD8+ T CELLS

- **CD8+ CTLs** eliminate intracellular microbes mainly by **killing infected cells**
- CTL-mediated killing involves specific recognition of target cells and delivery of proteins that **induce cell death**.
- Within a few minutes of a CTL's antigen receptor recognizing its antigen on a target cell, the target cell undergoes changes that induce it to die by apoptosis.
- The cytotoxic proteins in the granules of CTLs (and NK cells) include **granzymes** and **perforin**.



EFFECTOR FUNCTIONS OF CD8+ T CELLS

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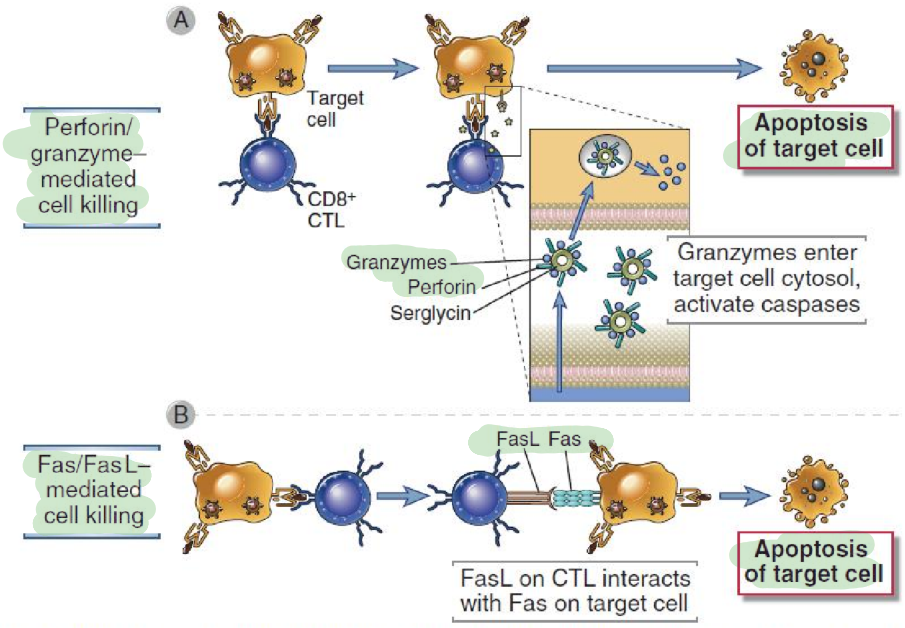

FIGURE 10–13 Mechanisms of CTL-mediated killing of target cells. CTLs kill target cells by two main mechanisms. **A,** Complexes of perforin and granzymes are released from the CTL by granule exocytosis and enter target cells. The granzymes are delivered into the cytoplasm of the target cells by a perforin-dependent mechanism, and they induce apoptosis. **B,** FasL is expressed on activated CTLs, engages Fas on the surface of target cells, and induces apoptosis.

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EFFECTOR FUNCTIONS OF Regulatory T (TReg) cells

- Treg cells express the biomarkers **CD4, FOXP3, and CD25** and are thought to be derived from the same lineage as naïve CD4+ cells
- Regulatory T (TReg) cells are essential for maintaining **peripheral tolerance**, preventing autoimmunity and limiting chronic inflammatory diseases. However, they also limit beneficial responses by suppressing sterilizing immunity and limiting anti-tumour immunity.
- TReg cells have multiple mechanisms at their disposal to mediate their suppressive effects.
- Suppression by inhibitory cytokines: **interleukin-10 (IL-10), transforming growth factor-β (TGFβ)** and the newly identified IL-35 are key mediators of TReg-cell function.

اللهم صل وسلم على نبينا محمد

Immunity to Fungi

- Fungal infections, also called mycoses, are important causes of morbidity and mortality in humans. Some fungal infections are endemic, and these infections are usually caused by fungi that are present in the environment and whose spores enter humans

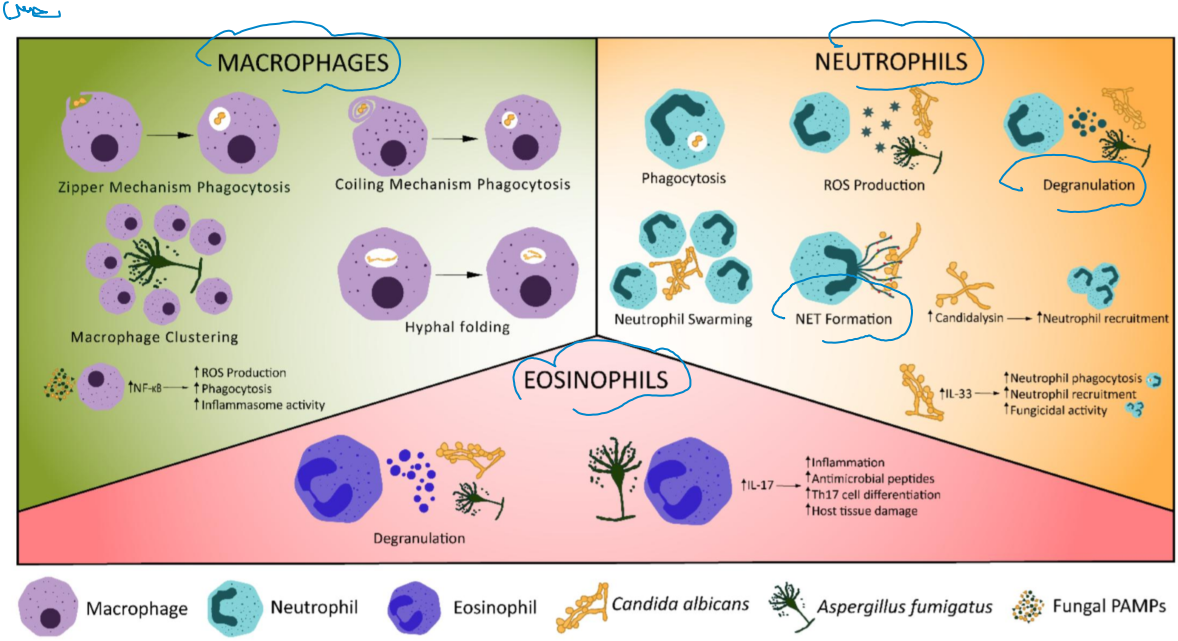
- The principal mediators of innate immunity against fungi are **neutrophils and macrophages**. Patients with **neutropenia are extremely susceptible to opportunistic fungal infections**.

- less is known about antifungal immunity than about immunity against bacteria and viruses. This lack of knowledge is partly due to the paucity of animal models for mycoses and partly due to the fact that these infections typically occur in individuals who are incapable of mounting effective immune responses.

Immunity to Fungi

أستغفر الله العظيم اللهم صل وسلم على نبينا محمد

Extracellular نفس الـ bacteria



Burgess TB, Condliffe AM, Elks PM. A Fun-Guide to Innate Immune Responses to Fungal Infections. *Journal of Fungi*. 2022; 8(8):805. https://doi.org/10.3390/jof8080805

Immunity to Helminths

اللهم صلِّ وسلِّم على نبينا محمد

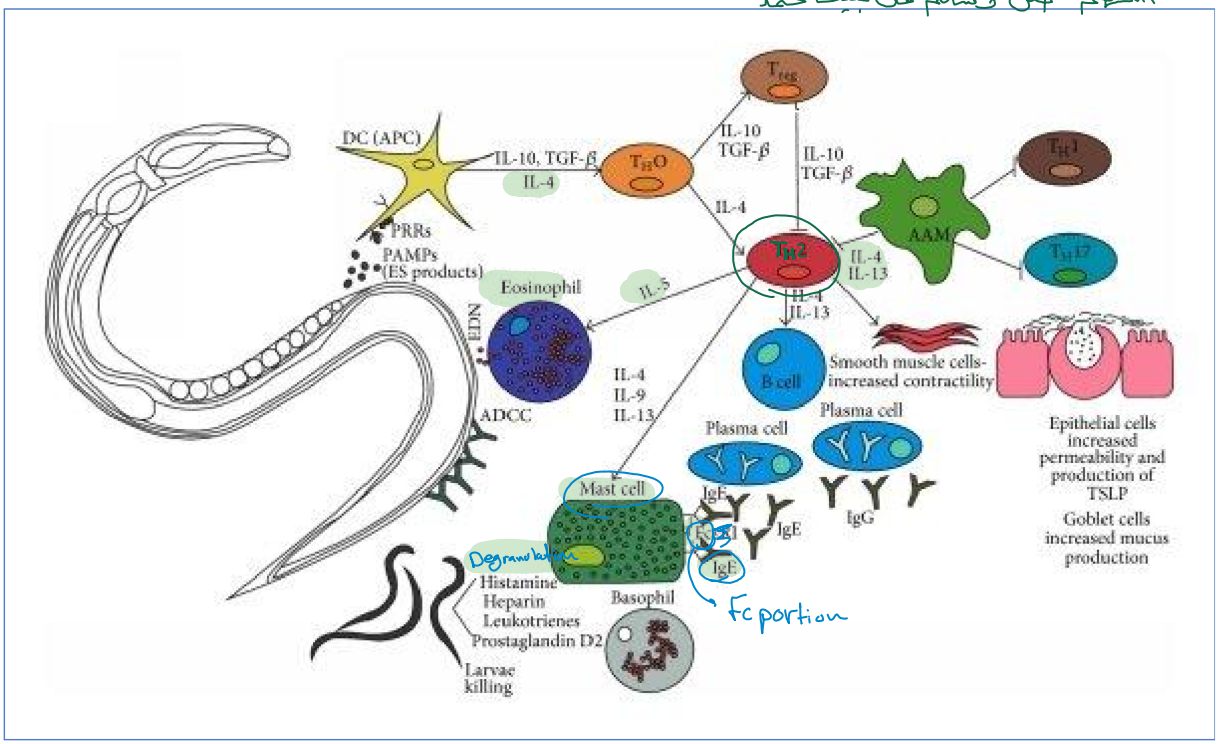
- **Antibodies**, **mast cells**, and **eosinophils** function with antibodies to mediate the expulsion and killing of some helminthic parasites. Helminths (worms) are too large to be engulfed by phagocytes, and their integuments are relatively resistant to the microbicidal products of neutrophils and macrophages.

- **IgE, IgG, and IgA** antibodies that coat helminths can bind to Fc receptors on eosinophils and cause the **degranulation of these cells**, releasing the **major basic protein**, a **toxic cationic protein**, present in the granules of eosinophils. Other eosinophil granule contents also aid in killing the parasites.

- **IgE antibodies** that recognize antigens on the surface of the helminths may initiate local **mast cell degranulation** through the **high-affinity IgE receptor**. Mast cell mediators may induce **bronchoconstriction and increased local motility**, contributing to the **expulsion** of worms.

Immunity to Helminths

اللهم صلِّ وسلِّم على نبينا محمد



Effector mechanisms of humoral immunity/ Antibody-Mediated Clearance of Helminths

الحمد لله عدد خلقه

الحمد لله ملء خلقه

Review Article

Harnessing the Helminth Secretome for Therapeutic Immunomodulators

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Helminths are the largest and most complex pathogens to invade and live within the human body. Since they are not able to outpace the immune system by rapid antigen variation or faster cell division or retreat into protective niches not accessible to immune effector mechanisms, their long-term survival depends on influencing and regulating the immune responses away from the mode of action most damaging to them. Immunologists have focused on the excretory and secretory products that are released by the helminths, since they can change the host environment by modulating the immune system. Here we give a brief overview of the helminth-associated immune response and the currently available helminth secretome data. We introduce some major secretome-derived immunomodulatory molecules and describe their potential mode of action. Finally, the applicability of helminth-derived therapeutic proteins in the treatment of allergic and autoimmune inflammatory disease is discussed.

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 4. Innate immunity
Chapter 15. Immunity to microbes

حديث الصادة

اللهم صلِّ وسلِّم على نبينا محمد
وارزقنا اتباع هديه وسنته