ÉCOLE POLYTECHNIQUE
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VI.
T cell effector response

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Outline

Introduction: 2 types of cell-mediated immune responses

VI-1 General characteristics of T cells

VI-2 CD4 effector T cells

VI-3 CD8 effector T cells (CTLs)

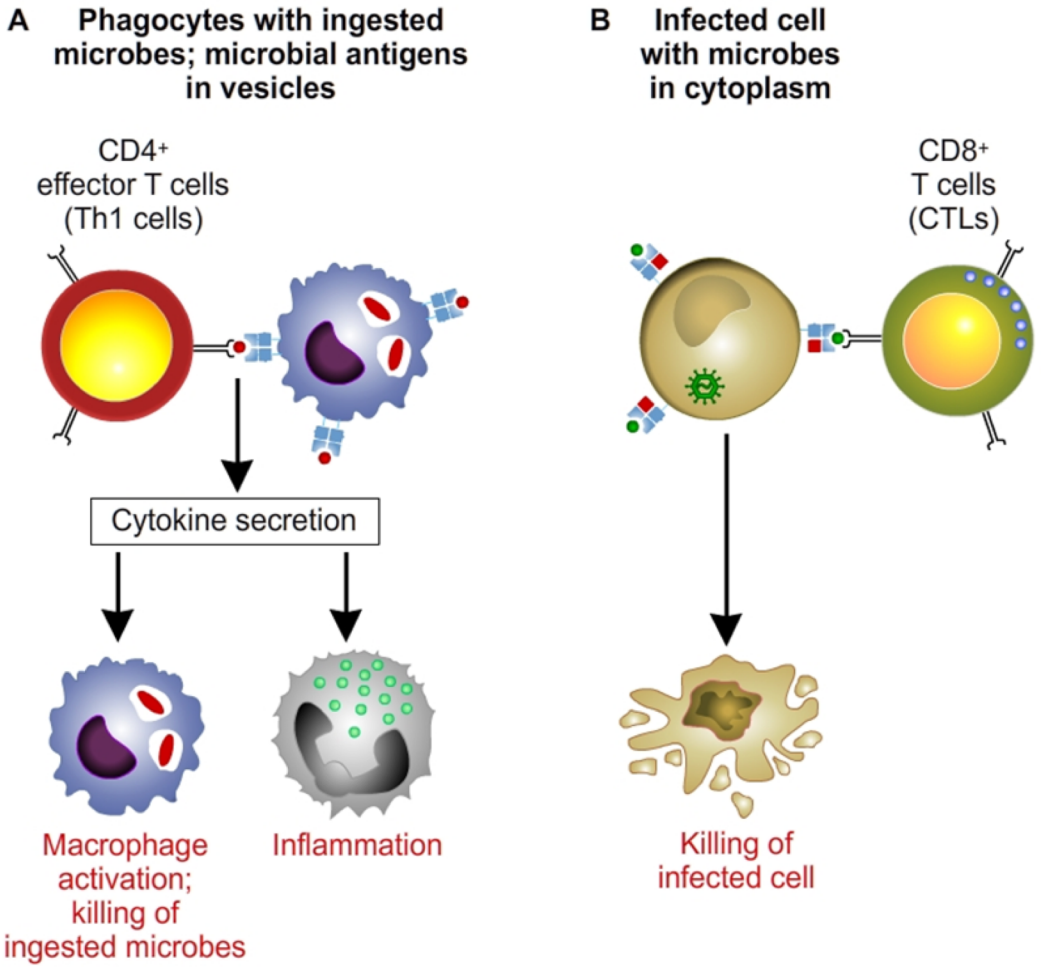
VI-4 End of T cell effector response

VI-5 Evasion of T cell-mediated immunity

2 main types of T cell-mediated immunity

- **CD4+ helper T cells (Th)** activate phagocytes to destroy microbes residing in the vesicles of these phagocytes.

- **CD8+ cytotoxic T cells (CTLs)** kill any cell containing microbes or microbial proteins in the cytoplasm, thereby eliminating the reservoir of infection.

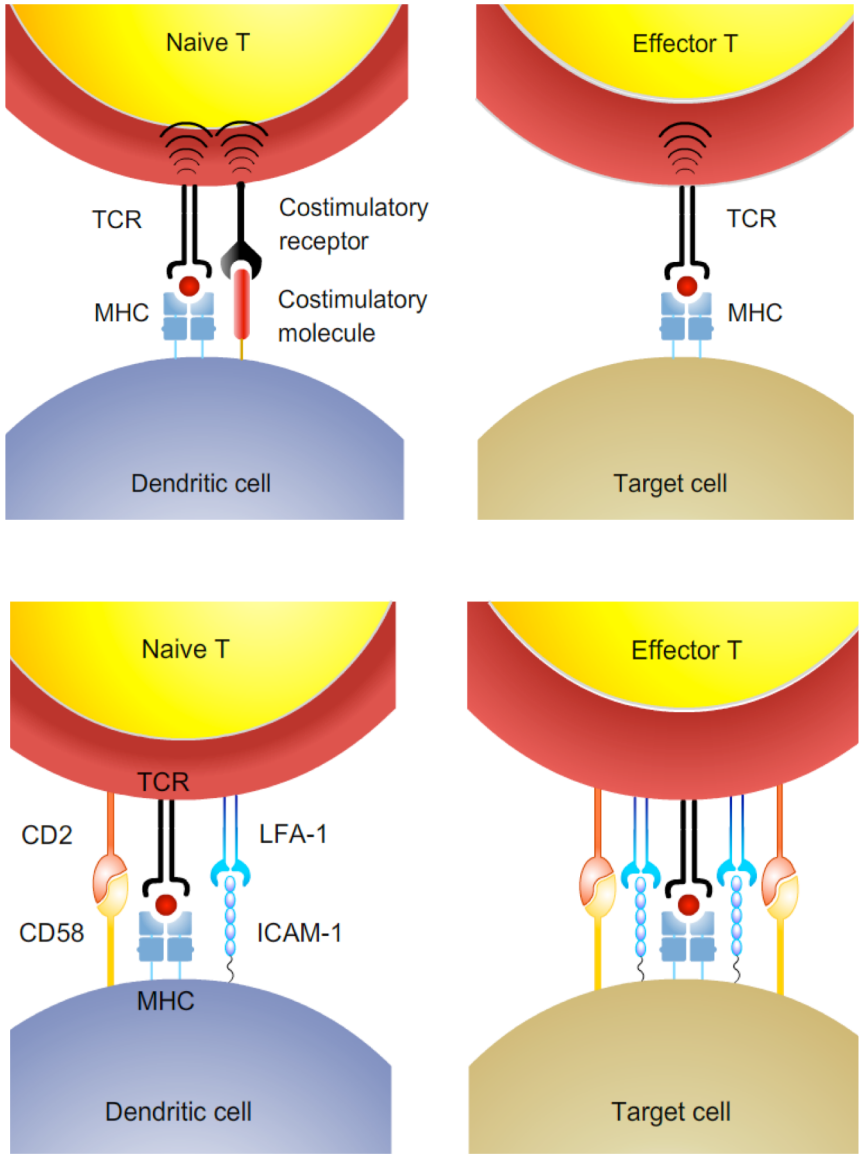


Adapted from Abbas, Cellular and Molecular Immunology

VI-1
General characteristics of T cells

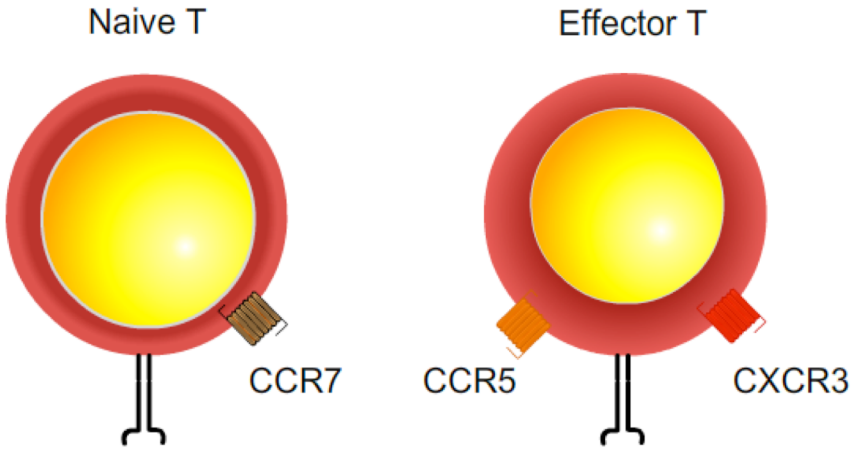
Antigen recognition and Adhesion

- T cells **recognize protein antigens** at two stages:
  - **naive T cells** recognize antigens in lymphoid tissues and respond by proliferating and by differentiating into effector cells
  - **effector T cells** recognize the same antigens anywhere in the body and respond by eliminating these microbes
- Effector T cells increase cell surface expression of **cell adhesion molecules** to allow greater and prolonged interaction with
  - APCs for CD4+ Th cells
  - Target cells for CD8+ CTLs

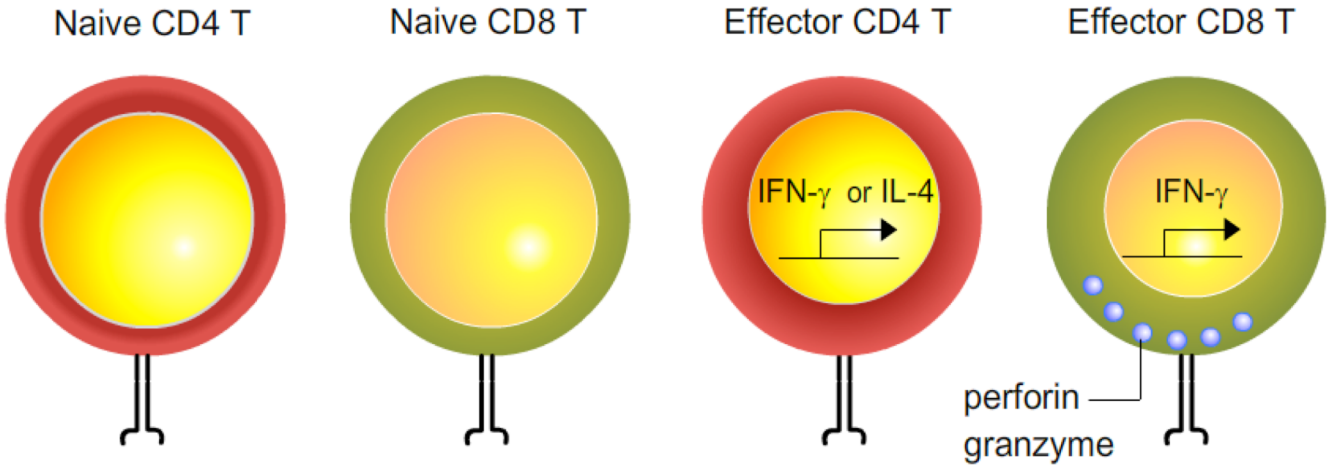


Migration and effector molecules

- T cells alter their expression of lymphocyte **homing receptors**, allowing them to leave the lymphoid organ where they were activated, enter peripheral tissues, and **migrate** to the site of pathogen entry or inflammation



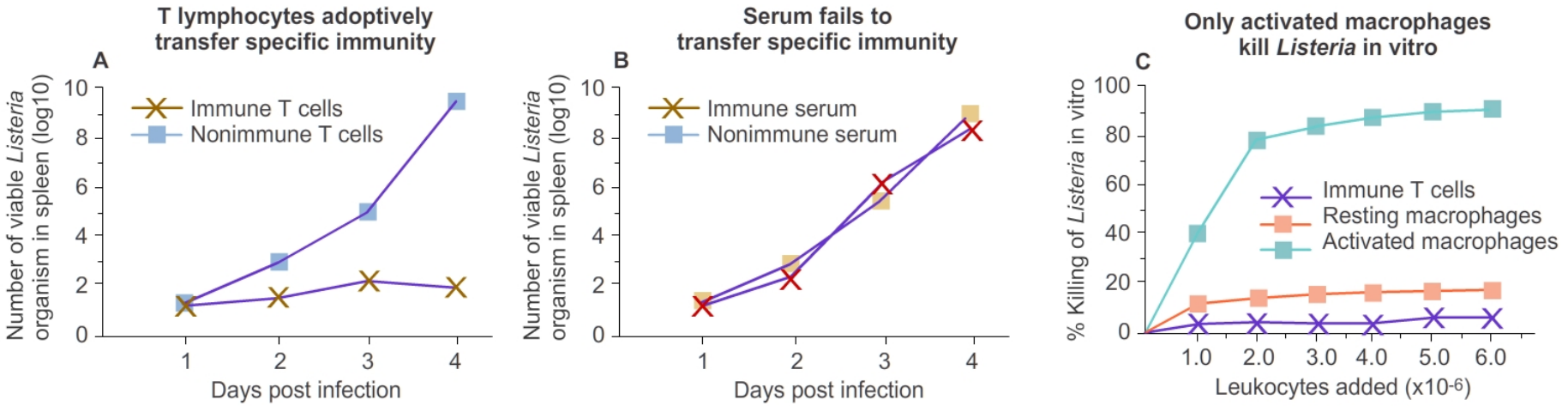
- Effector T cells express many **membrane-bound receptors** (e.g. FasL, CD40Lβ), **cytokines**, and **enzymes** that are absent in naïve T cells



VI-2
CD4+ effector T cells

- Role of Th1 T cells
- Role of Th2 T cells
- Th1 / Th2 balance
- Role of Th17 T cells
- Role of Treg T cells

Th1 T cell response: macrophage activation



Transfer

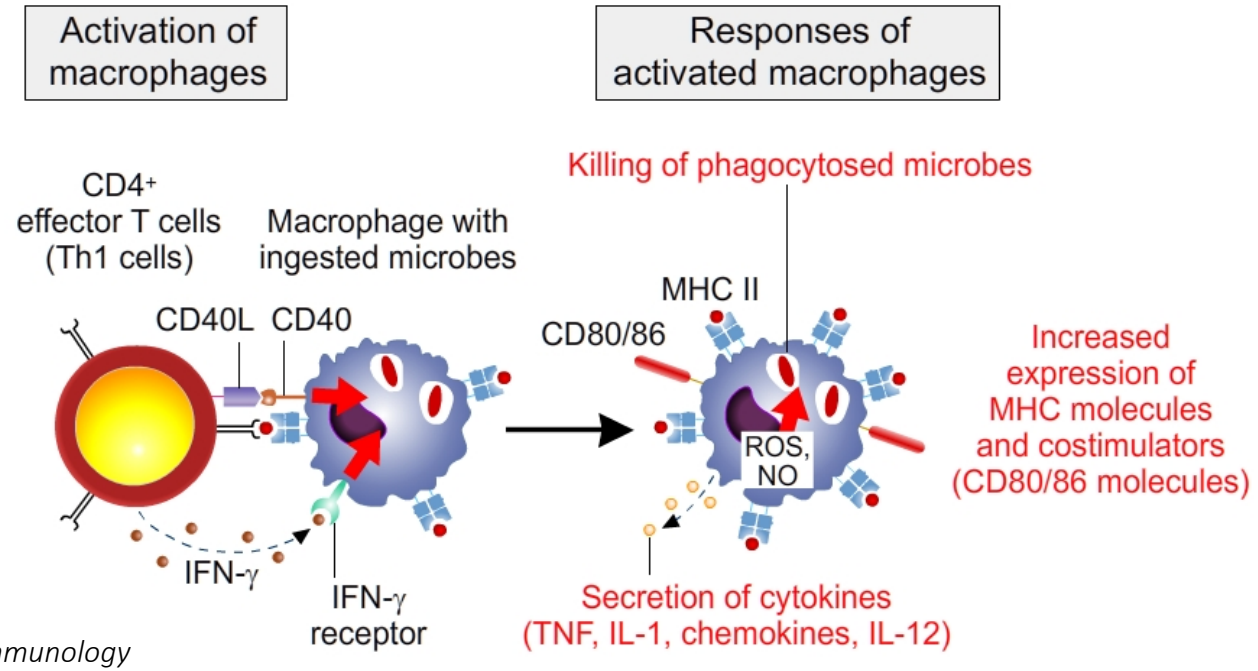
In vitro

(A-B) In this experiment, a sample of lymphocytes or serum (a source of antibodies) was taken from a mouse that had previously been exposed to a sub-lethal dose of Listeria organisms (immune mouse) and transferred to a normal (naive) mouse, and the recipient of the "adoptive transfer" was challenged with the bacteria. The numbers of bacteria were measured in the spleen of the recipient mouse to determine if the transfer had conferred immunity.

Adapted from Abbas, Cellular and Molecular Immunology

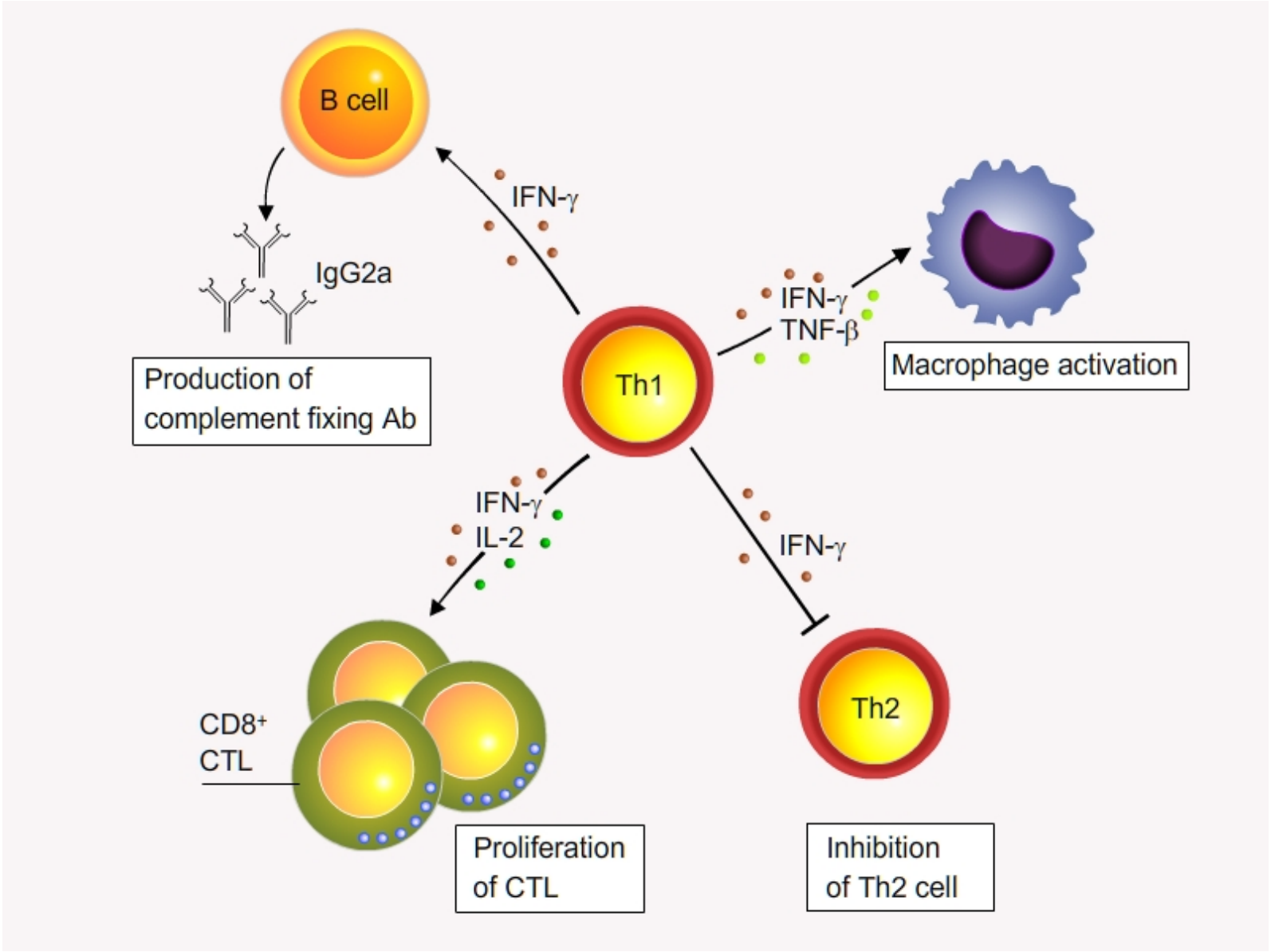
Th1 T cell response: macrophage activation

- is mediated by CD4+ Th1 T Cells
- is triggered upon:
  - recognition of MHCII associated peptide and interaction CD40L/CD40
  - production of IFNγ
- induces transcription factors → lysosomal enzymes, ROS, NOS
- is pro-inflammatory and leads to tissue damage
- macrophages produce IL-12 which drives the Th1 response → bidirectional interaction between innate and adaptive immunity



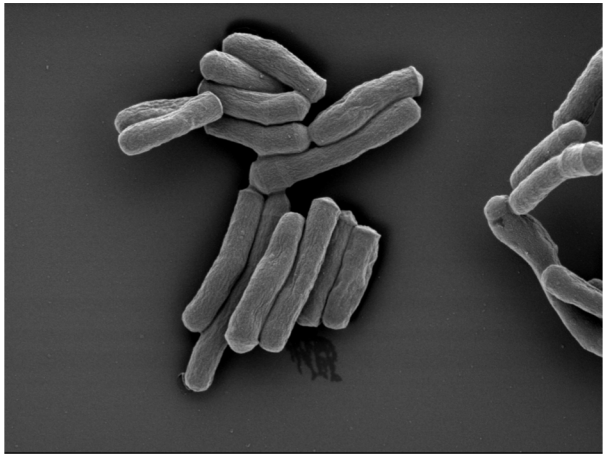
Adapted from Abbas, Cellular and Molecular Immunology

Th1 T cell response: cytokine production

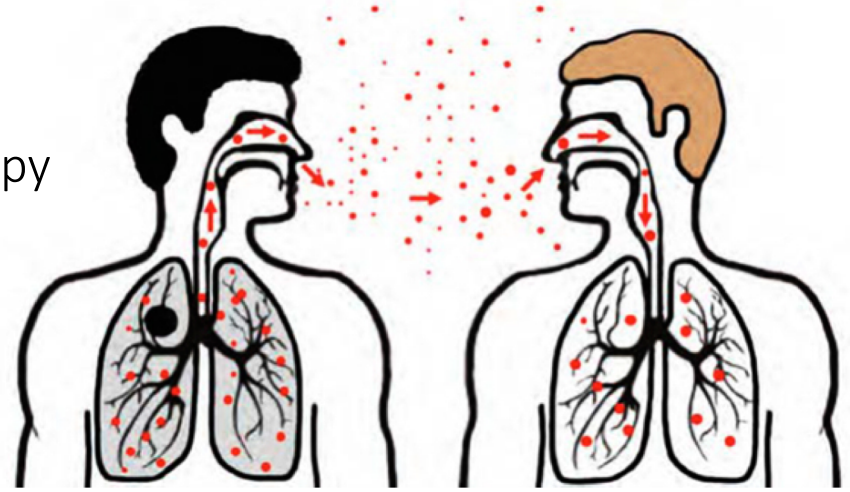


Example of a Th1-centric disease: Tuberculosis (Mtb)

- TB causes 1.5 million deaths per year (2015), second only to HIV
- Caused by Gram-positive bacterium: *Mycobacterium tuberculosis* (Mtb)
- Main host = humans; one third of human population carries Mtb
- Spread via aerosols
- 90% of carriers are asymptomatic; 10% develop disease progressively after infection or after long latency (relapse)
- Treated by long, complex antibiotic therapy



MtB, EPFL Scanning EM

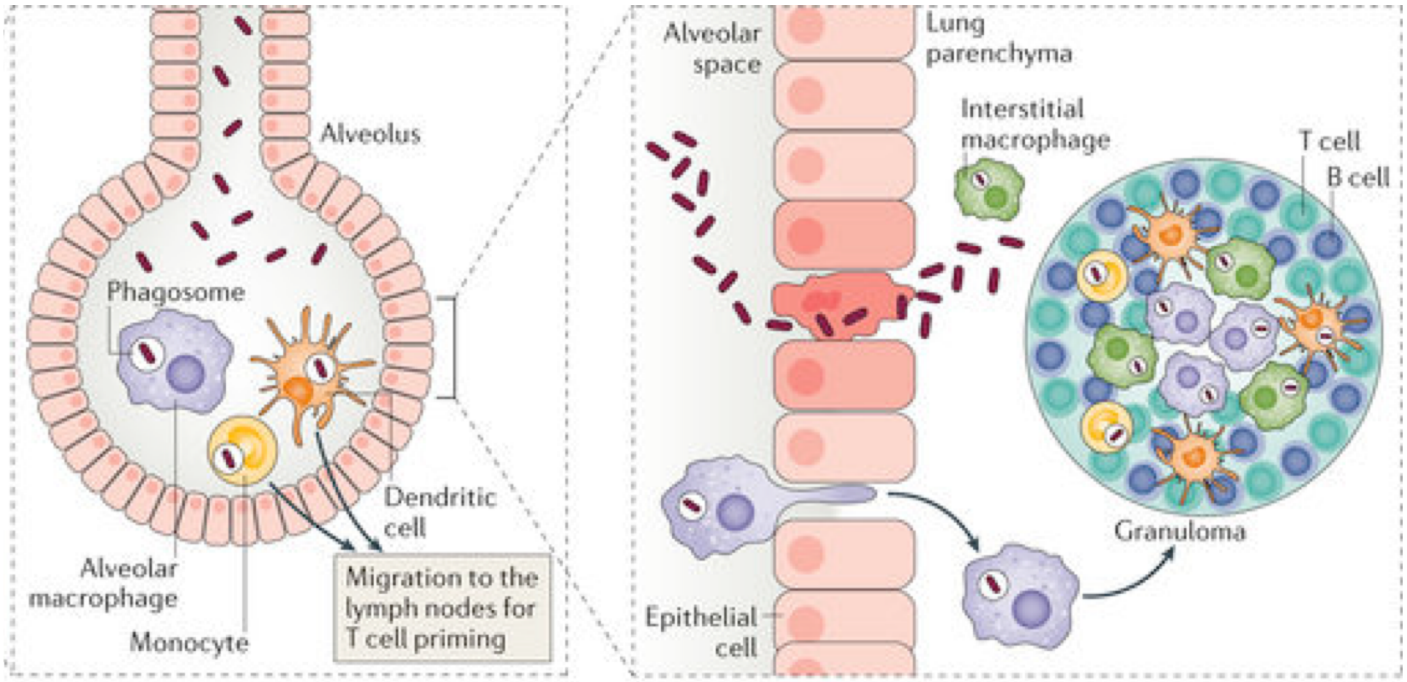


Source: Northern Inter-Tribal Health Authority

Example of a Th1-centric disease: Tuberculosis (Mtb)

Latent infection:

- Infection of monocytes, alveolar macrophages and DCs by Mtb
- Activation of a Th1 response (driven by Il-12 released by DCs)
- Th1 T cells produce IFN-γ to activate macrophages, leading to the killing of bacteria

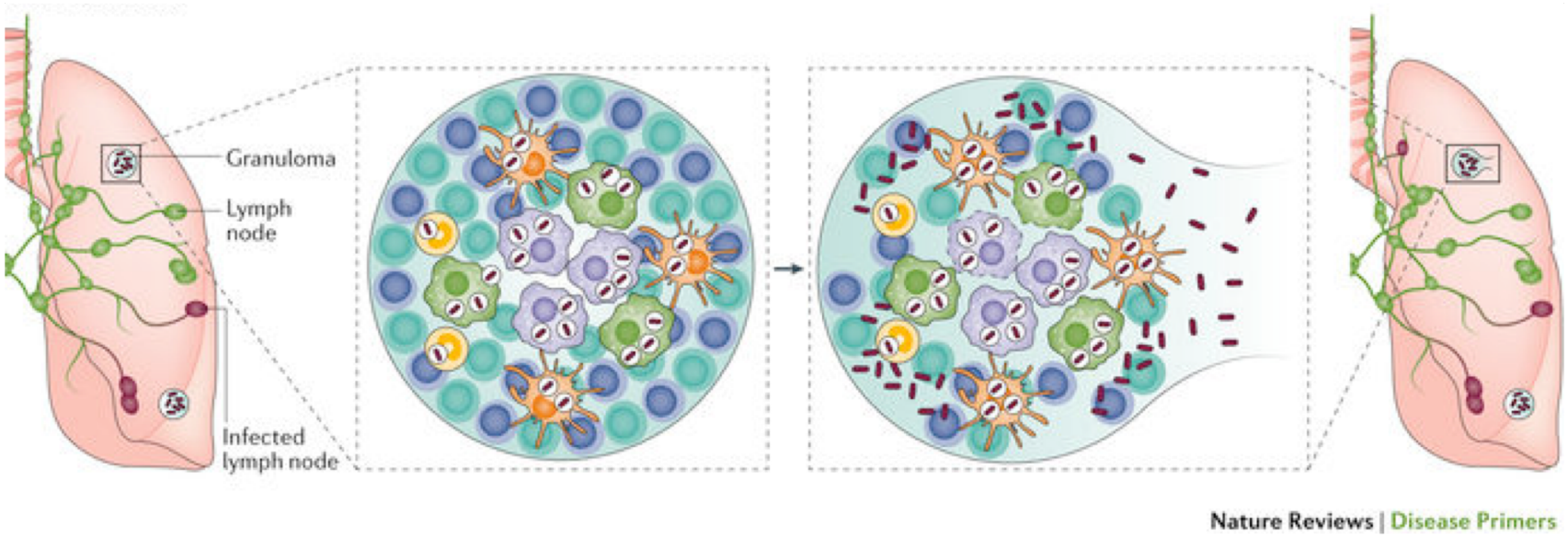


Pai *et al.,* 2016 Nature Review Disease primers

Example of a Th1-centric disease: Tuberculosis (Mtb)

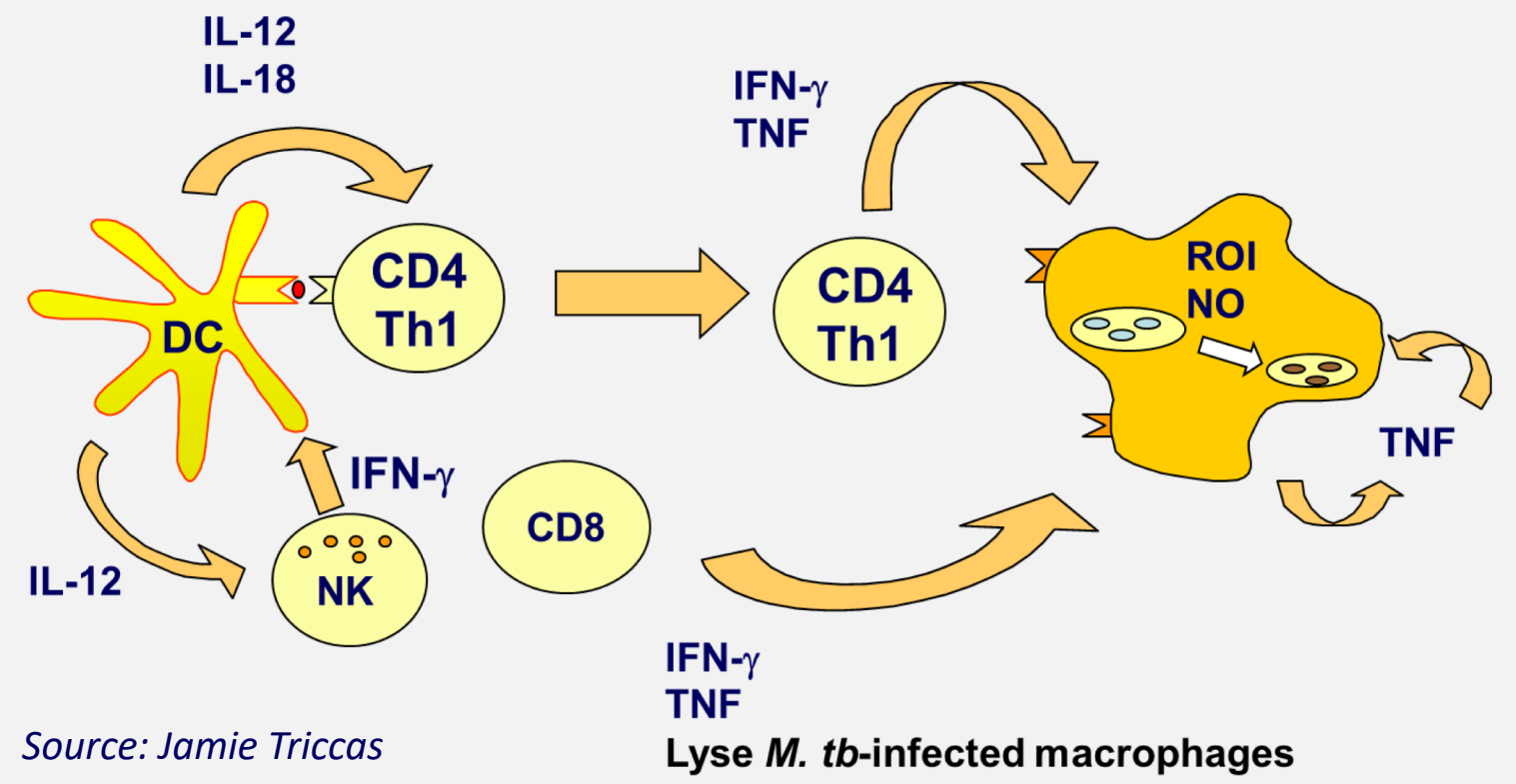
Active disease:

- If bacterial killing fails, new monocytes are recruited and activated by IFN-γ: formation of granulomas
- Important role of TNFα (synergizes with IFN- γ in macrophage activation)



Pai et al, 2016 Nature review primers

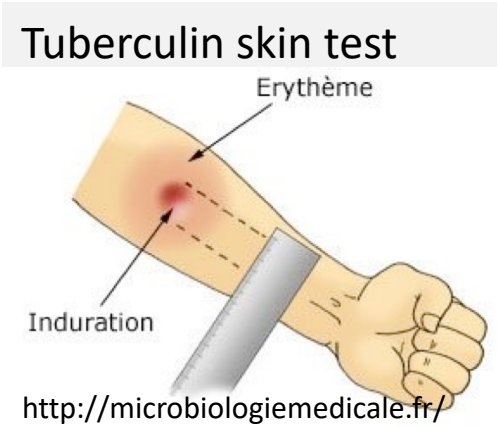
Overview of immune response to *M. tuberculosis*

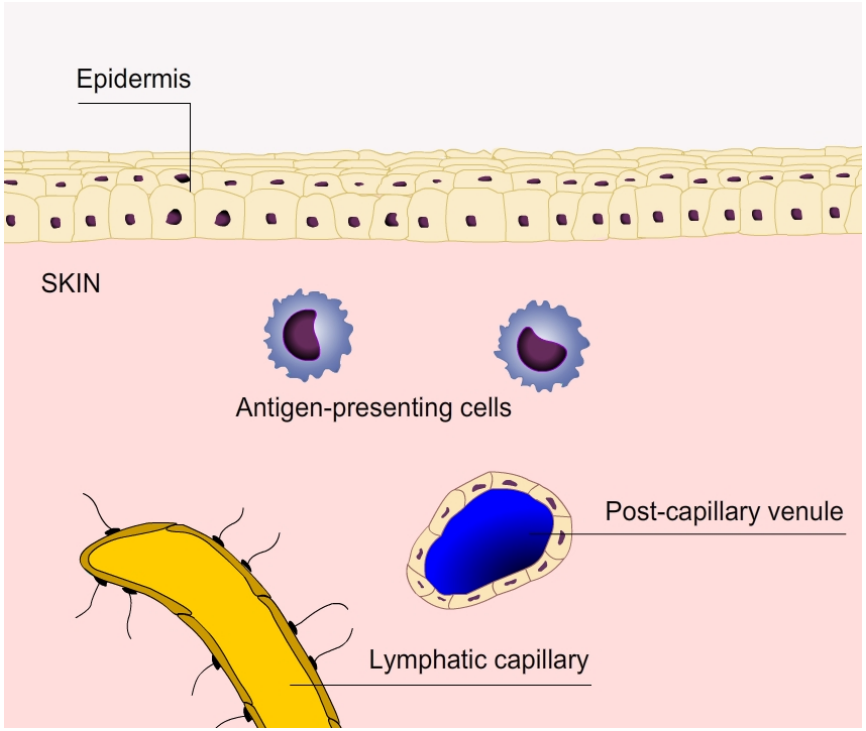


- Innate immune recognition of MtB by pattern recognition (TLR6/2)
- Mice deficient for IL-12, CD4, CD8 , IFN-γ, or TNF show increased susceptibility to Mtb infection

Example of a Th1 T cell response: the Delayed-Type Hypersensitivity (DTH) reaction

- Activation of macrophages by CD4 T cells can be elicited by injecting a protein into the skin of an individual who has been immunized against the microbe by prior infection or vaccination.
- This reaction is called delayed-type hypersensitivity (DTH), because it occurs 24 to 48 hours after an immunized individual is challenged with a microbial protein (i.e., the reaction is delayed). The delay occurs because it takes 24 to 48 hours for circulating effector T lymphocytes to home to the site of antigen challenge, respond to the antigen at this site, and induce a detectable reaction.
- DTH reactions are manifested by infiltrates of T cells and blood monocytes into the tissues, edema and fibrin deposition caused by increased vascular permeability in response to cytokines produced by CD4+ T cells, and tissue damage induced by the products of macrophages activated by T cells.
- DTH reactions are often used to determine if people have been previously exposed to and have responded to an antigen (e.g. response to a mycobacterial antigen, tuberculin PPD, is an indicator of a T cell response to the mycobacteria).





Th2 T cell effector functions

Th2 effector function is primarily mediated through the cytokines (IL-4, IL-5) T cells secrete

B cell modulation

- Th2 cytokines (IL4, IL5):
  - regulate B cell proliferation
  - isotype switching
  - hematopoiesis
  - recruitment of eosinophils & mast cells
  - stimulate mucus production

Anti-parasite defense

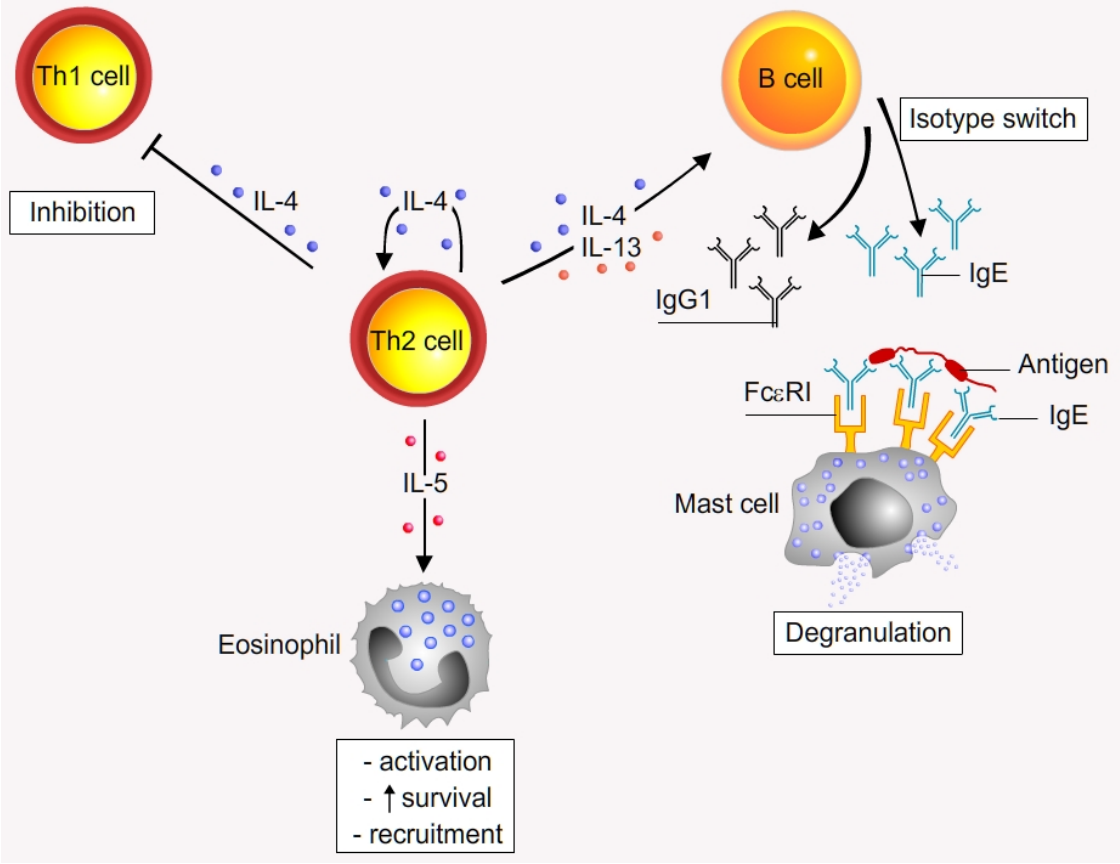
- Defense against extracellular parasites
  - gastrointestinal worms
  - amoebae

Repair

- Th2 induce M2 macrophages involved in repair

Th1 antagonism

- Th2 response inhibits Th1 response



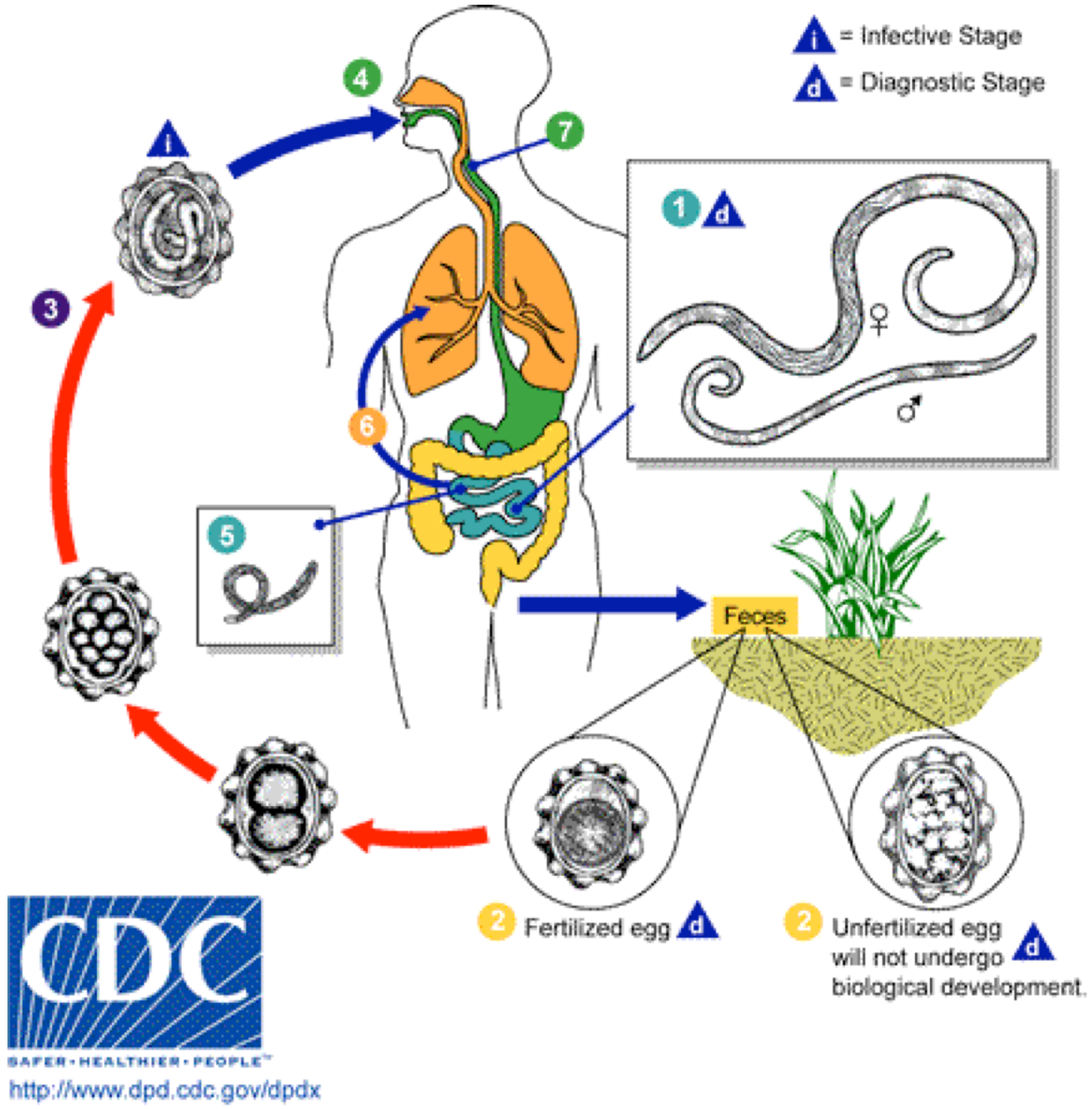
Example of a Th2-centric disease: worm infestation

- Helminths (nematodes or platyhelminths) are large multicellular organisms
- Ubiquitous exposure, important health burden in developing countries
- Humans co-evolved with worms
- Various routes of transmission (mosquito, snail, soil…)
- Th2 response orchestrates immune response to the worm

Figure 3: **Girl from Paraguay with heavy ascaris infection before deworming and worms extracted**

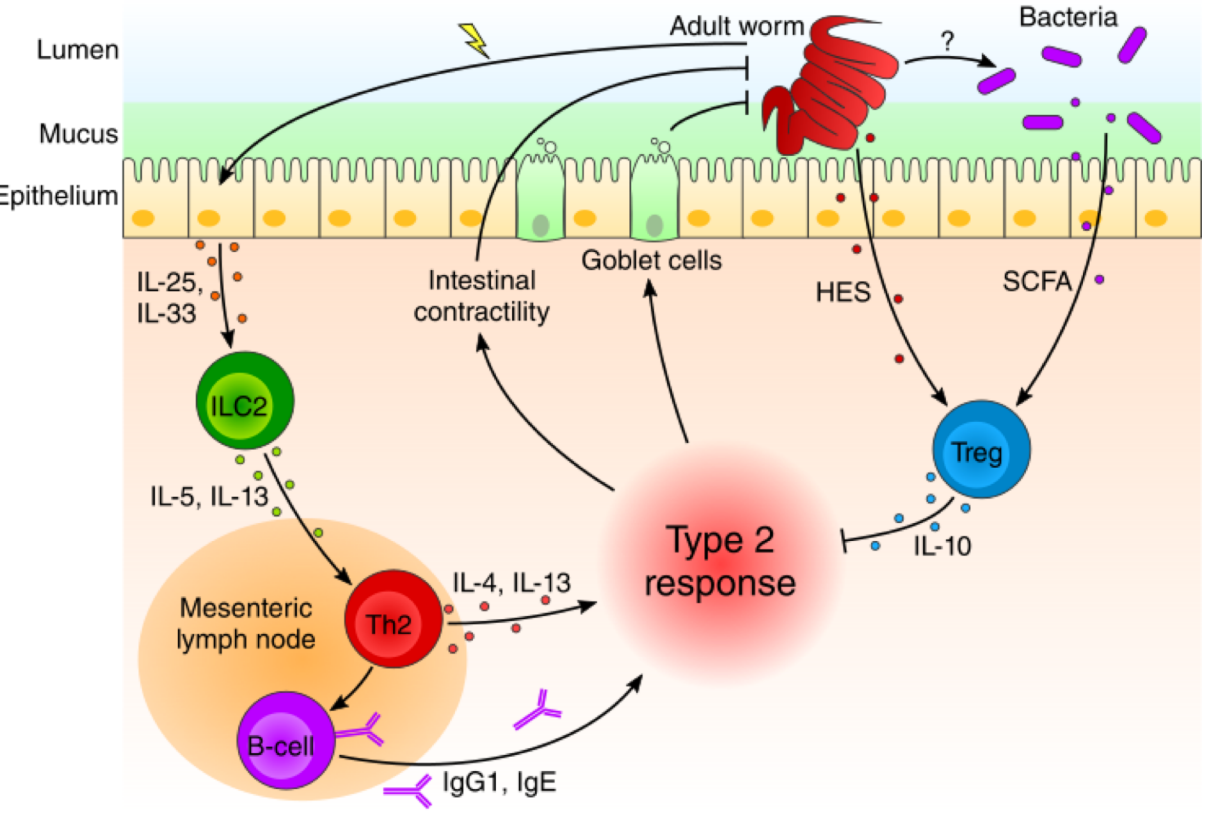
Despommier D et al. Parasitic disease, 5th edn, NY, Apple tree Production 2005

Example of a Th2-centric disease: worm infestation



Life cycle of *Ascaris lumbricoides*, the largest nematode (roundworm) parasitizing the human intestine

Example of a Th2-centric disease: worm infestation



Th2 response also includes

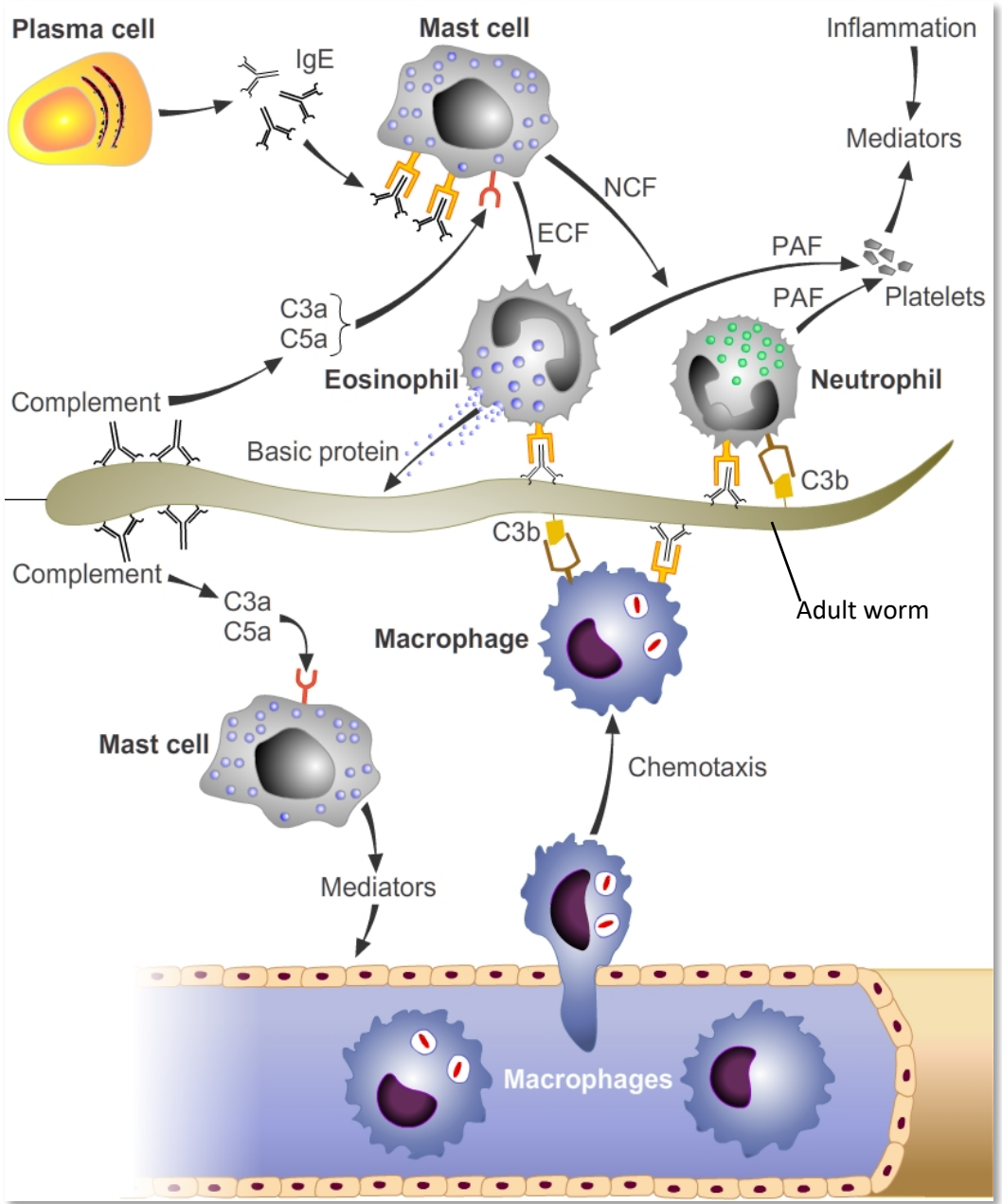
- activation of M2 macrophages involved in tissue repair
- production of mucus and smooth muscle contraction to induce worm ejection

ILC2: innate lymphoid cells 2

HES: secreted factors [HES] which induces Treg

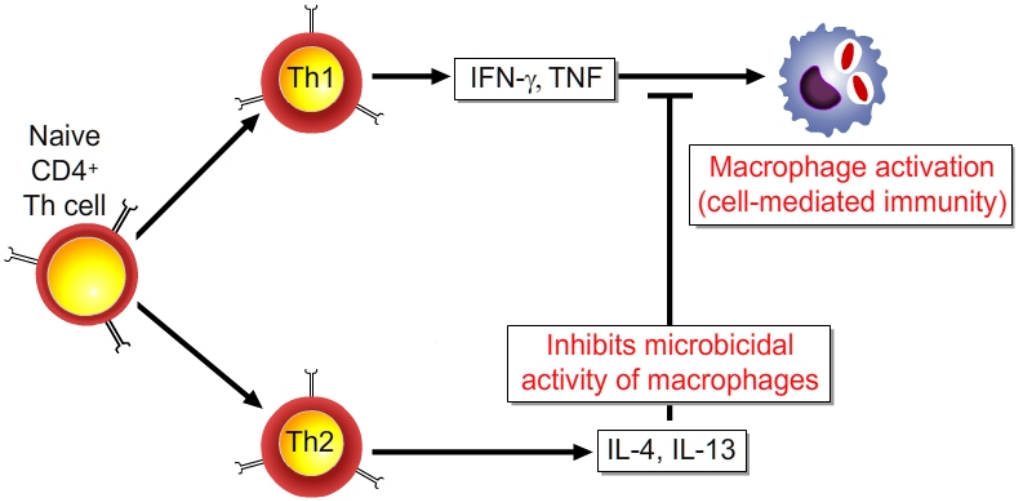
SCFA: Short chain fatty acid

Example of a Th2-centric disease: worm infestation



Allergic responses are Th2 like (IgE, mast cells)

Th1 / Th2 antagonism



Infectious agent	Type of T cell response	Result
Leishmania major	• Th1 (most mouse strains) • Th2 (BALB/c mice)	• Host recovers • Disseminated infection
Mycobacterium leprae	• Th1 (some patients) • Th2 dominant or Th1 defective (some patients)	• Tuberculoid leprosy • Lepromatous leprosy (high bacterial count)

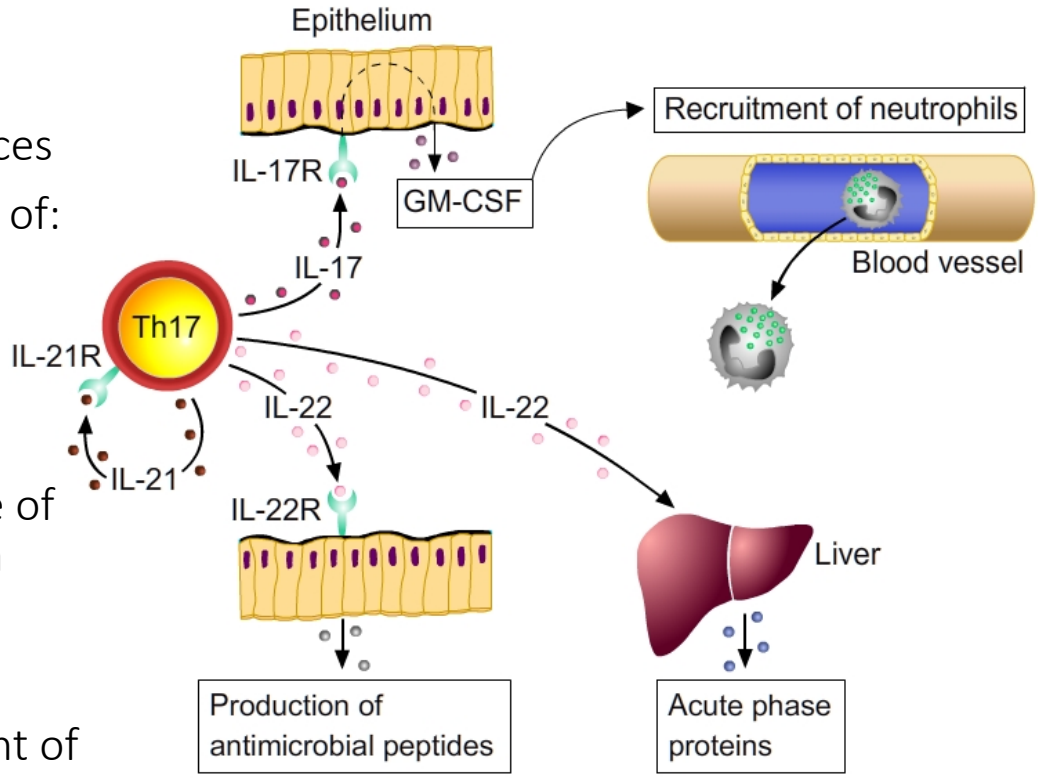
The balance between Th1 and Th2 responses may influence the outcome of infections, as illustrated by Leishmania infection in mice and leprosy in humans.

IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Adapted from Abbas, Cellular and Molecular Immunology

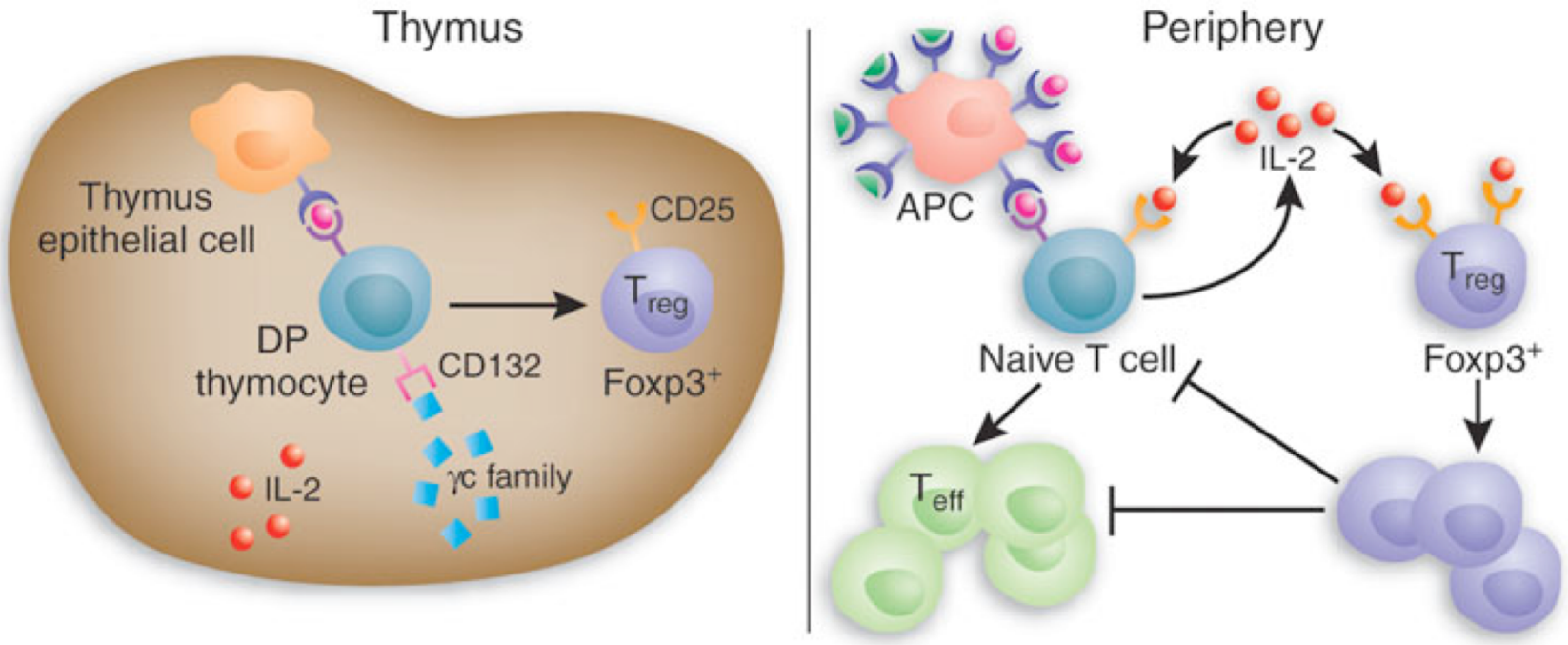
Th17 T cell response

- Th17 cells play an important role in the protection of the host at mucosal surfaces
- Th17 is associated with the production of:
  - IL-17, which increases GM-CSF production to stimulate haematopoiesis and neutrophil recruitment
  - IL-22, which stimulates the release of antimicrobial peptides by epithelia
  - IL-21
- Th17 cells coordinate defense against pathogens by enhancing the recruitment of neutrophils, and by stimulating the production of defensins by epithelial cells.



Treg (regulatory T cells)

- Foxp3 positive
- generated in the thymus or in secondary lymphoid organs
- Participate in peripheral tolerance by inhibiting immune responses
  - compete for IL-2
  - produce inhibitory cytokines IL-10 and TGFβ



VI-3
CD8+ T cell (CTL) response

- Effector functions
- Killing Mechanisms

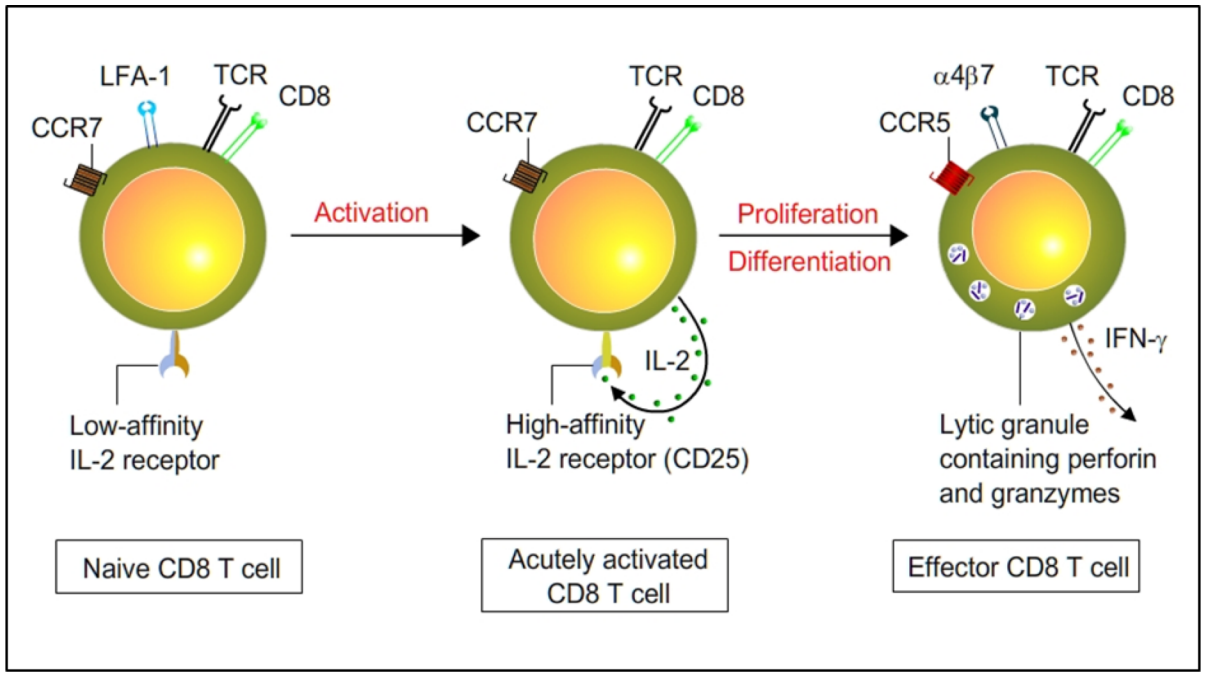
CD8 T cell effector functions

Naïve CD8 T cells express receptors required for migration through HEV

Activated CD8 T cells produce IL-2 and express the IL-2 receptor

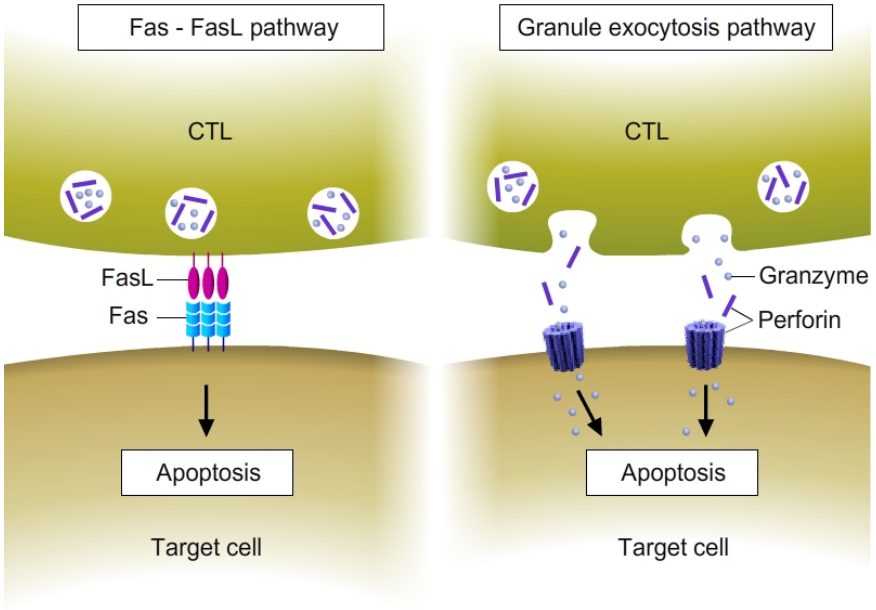
After several rounds of proliferation, **effector CD8 T cells**

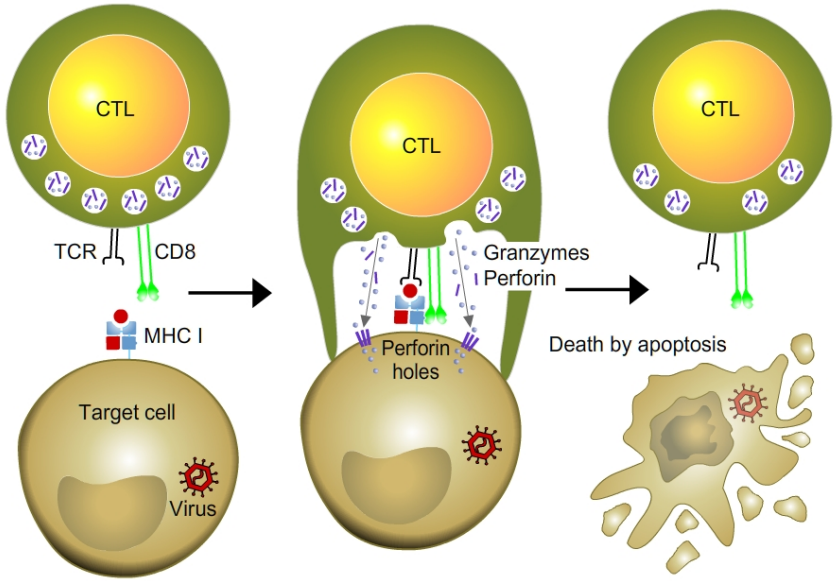
- Lose IL-2 production
- Start IFN-γ production
- Contain lytic granules (perforin & granzymes)
- Express homing CCR5 for migration to non-lymphoid tissues
- Express integrins for interaction with target cells



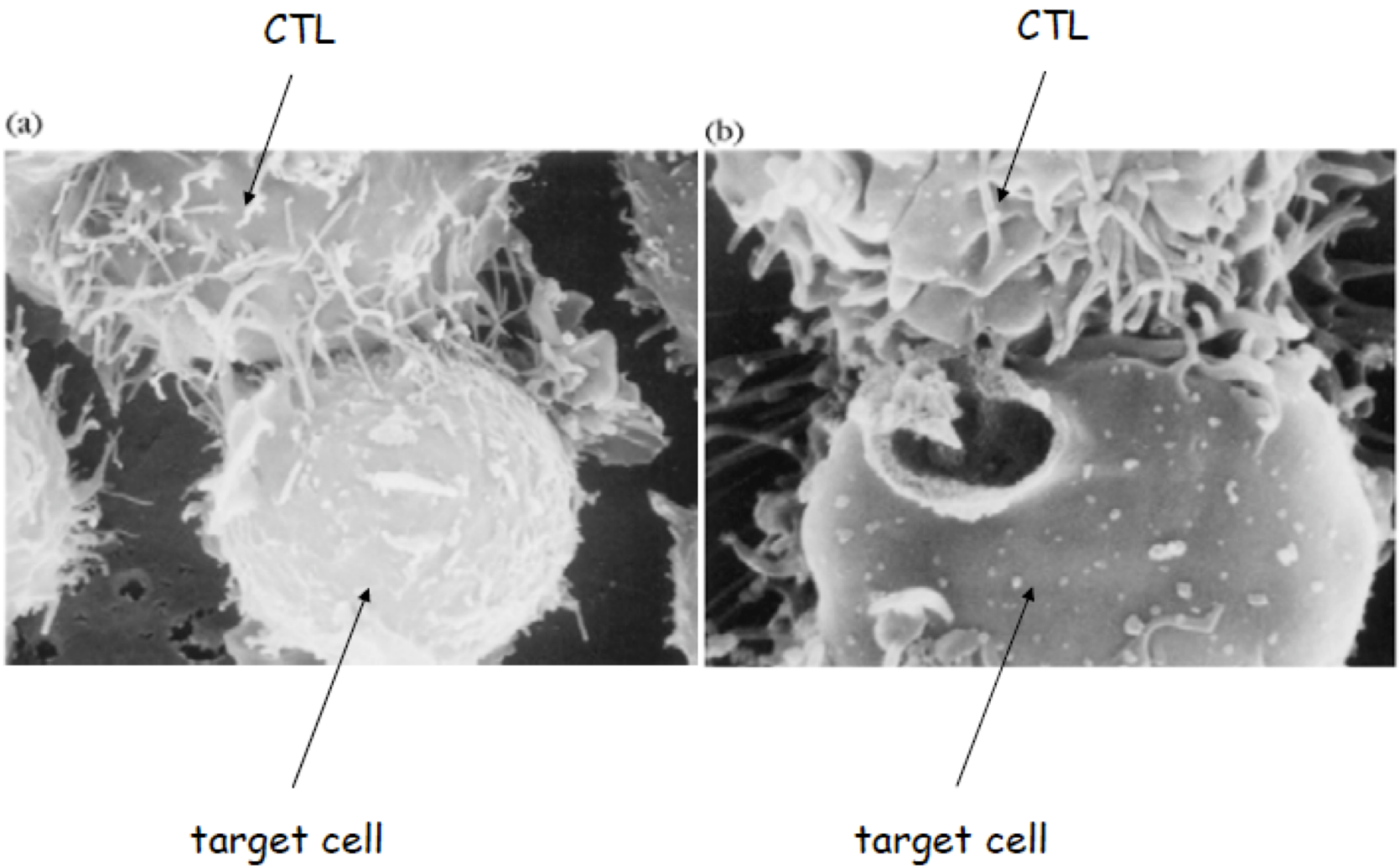
CD8 T cell killing mechanisms

- Effector CTLs induce apoptosis of infected cells through:
  - granule exocytosis pathway: calcium-dependent release of specialized lytic granules
  - Fas-FasL pathway (minor pathway)
- A CTL is able to serially kill multiple infected target cells
- CTLs produce IFNγ to activate macrophages.
- Note: Th1 CD4+ T cells and CD8+ CTLs synergize in the elimination of intracellular pathogens.



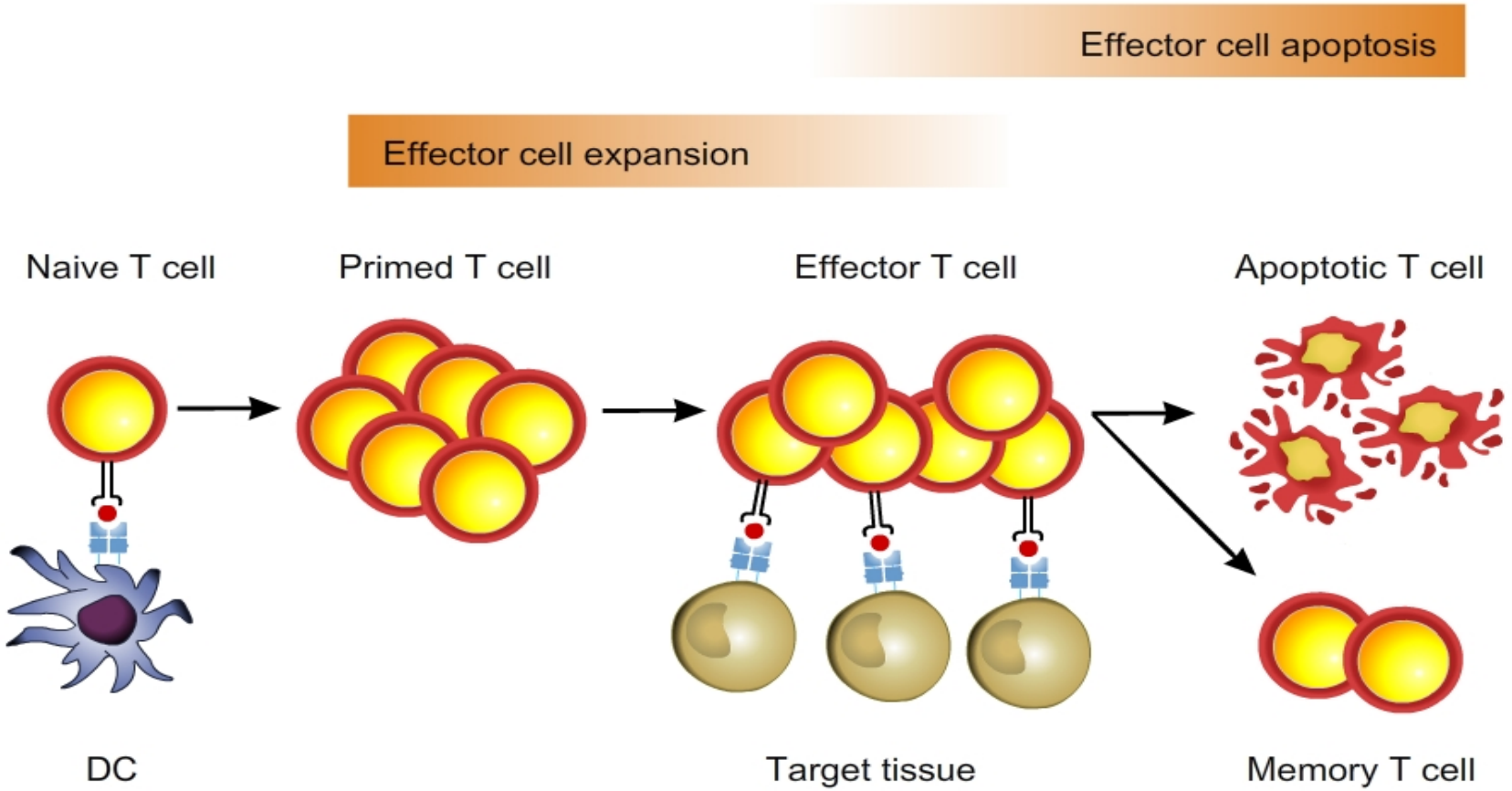


CD8 T cell killing mechanisms



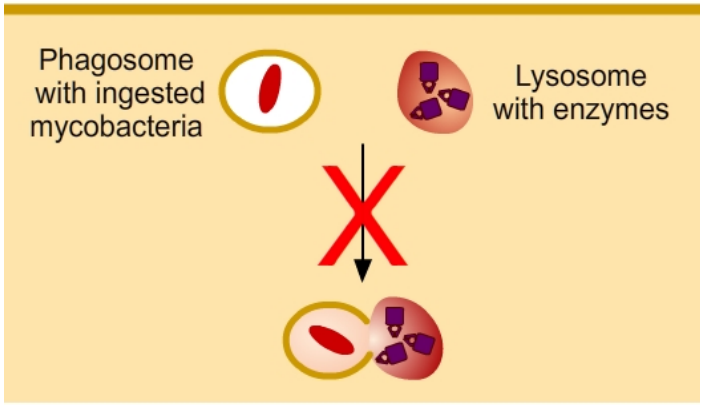
How killer cells kill. *Young JD, Cohn ZA. Sci Am. 1988 Jan*

VI-4 End of T cell response

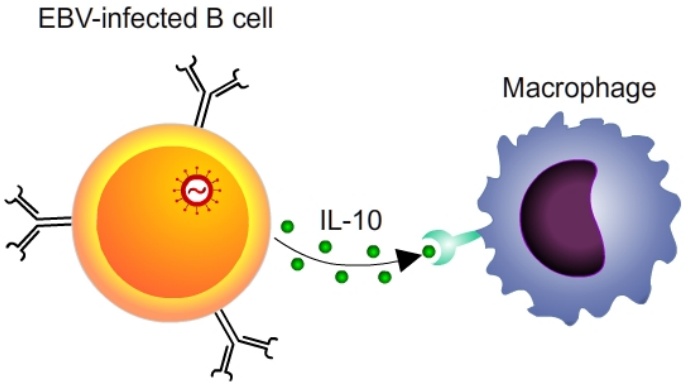


VI-5 Evasion of T cell-mediated immunity (1)

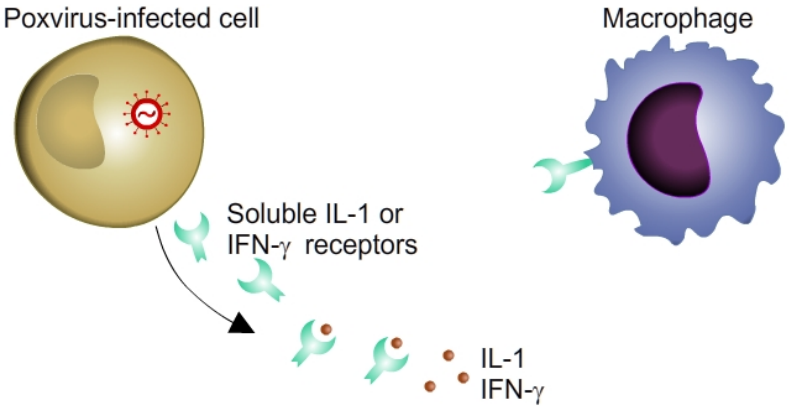
- **Mycobacteria** inhibit phagolysosome fusion and survive within phagosomes



- **Epstein-Barr virus (EBV):** infected cells produce IL-10 to inhibit macrophage and DC activation



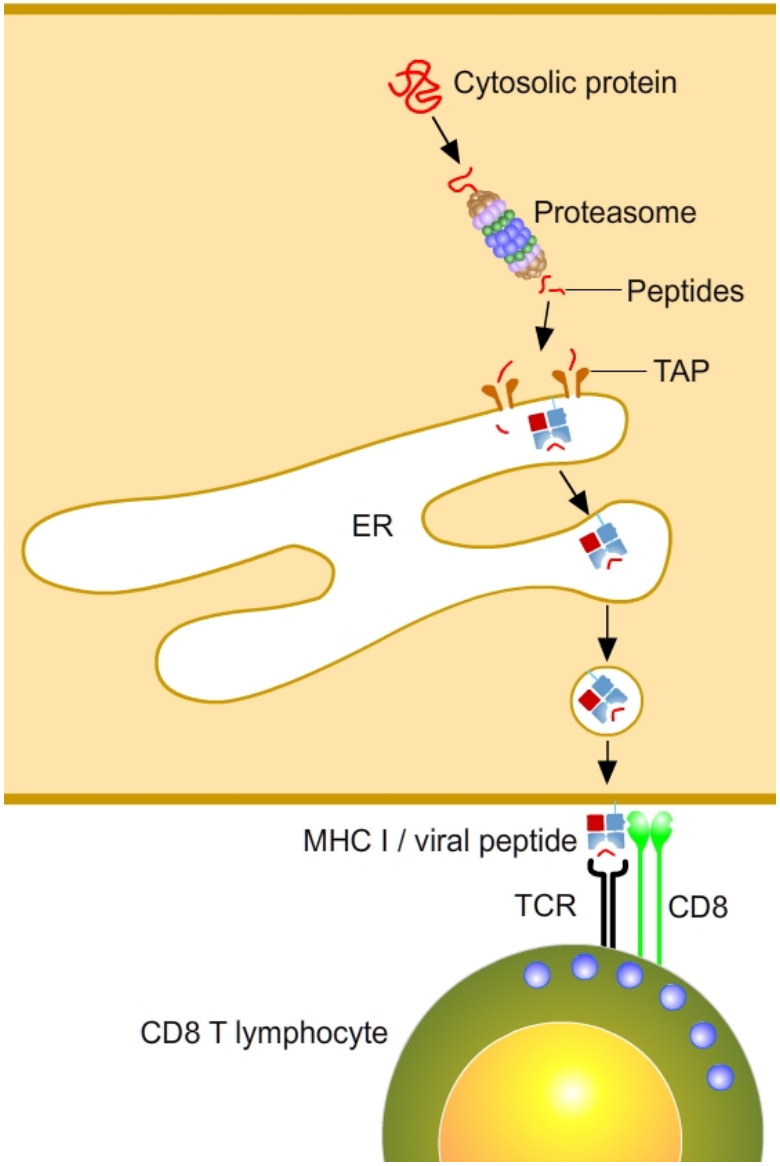
- **Pox Virus:** infected cells inhibit effector cell activation an by producing soluble cytokine receptors



VI-5 Evasion of T cell-mediated immunity (2)

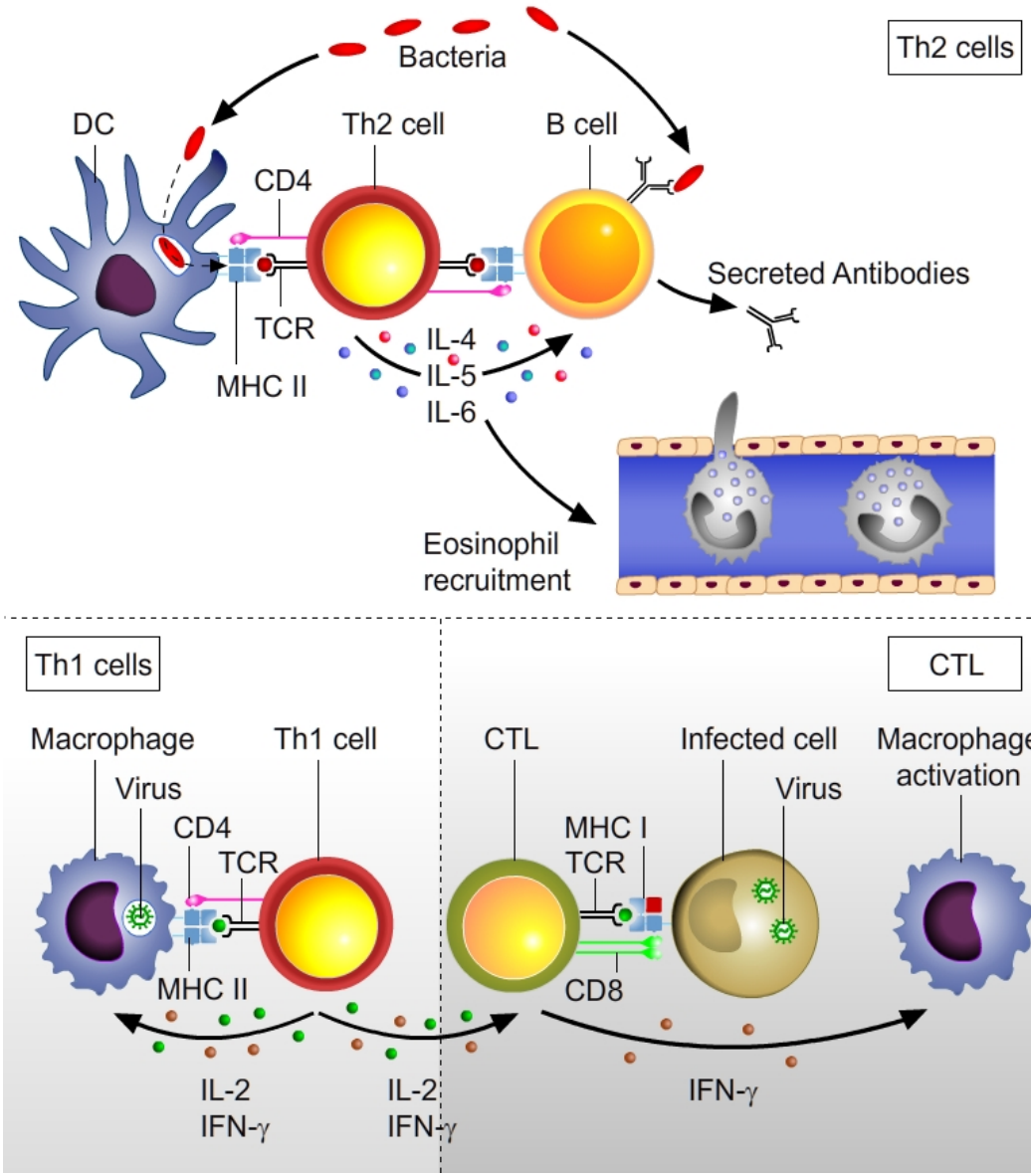
Inhibition of antigen presentation:

- **Herpes simplex virus (HSV)** viral peptide blocks TAP transporter
- **Cytomegalovirus (CMV)** inhibits proteasomal activity and removes class I MHC molecules from ER
- **Epstein-Barr virus (EBV)** inhibits proteasomal activity



Conclusions | Effector T cells

- Effector T cells express specific cytokines, chemokine receptors, adhesion proteins and effector molecules to interact with target cells.
- Th1 T cells play a key role against intracellular pathogens (intracellular bacteria, viruses).
- Th2 T cells play a key role against extracellular pathogens (worms, amoebae).
- Th17 T cells play a key role in mucosal infection.
- Tregs contribute to peripheral tolerance.
- CTLs eliminate virus-infected cells and tumor cells.
- Th1 T cells and CTLs cooperate in the elimination of intracellular pathogens.



Summary | Effector T cells

- Cell-mediated immunity is the arm of adaptive immunity that eradicates infections by intra-cellular microbes. Cell-mediated immune reactions are of two types: CD4+ T cells activate macrophages to kill ingested microbes that are able to survive in the vesicles of phagocytes, and CD8+ CTLs kill cells harbouring microbes in their cytoplasm, thereby eliminating reservoirs of infection.
- Effector T cells are generated in peripheral lymphoid organs, mainly lymph nodes draining sites of microbe entry, by the activation of naive T lymphocytes. Effector T cells are able to migrate to any site of infection.
- The migration of effector T cells is controlled by adhesion molecules and chemokines. Various adhesion molecules are induced on the T cells after activation and bind to their ligands, which themselves are induced on endothelial cells by microbes and by cytokines produced during innate immune responses to microbes. The migration of T cells is independent of antigen, but cells that recognize microbial antigens in tissues are retained at these sites.
- Effector cells of the Th1 subset of CD4+ T cells recognize the antigens of microbes that have been ingested by macrophages. These T cells express CD40 ligand and secrete IFN-γ, which function cooperatively to activate macrophages. Th17 cells may enhance leukocyte recruitment and inflammation.
- Activated macrophages produce substances, including reactive oxygen species, nitric oxide, and lysosomal enzymes, that kill ingested microbes. Macrophages also produce cytokines that induce inflammation and other cytokines that promote fibrosis and tissue repair.
- Effector CD4+ T cells of the Th2 subset stimulate eosinophilic inflammation and inhibit the microbicidal functions of activated macrophages. Eosinophils are important in host defence against helminthic parasites. The balance between activation of Th1 and Th2 cells determines the outcome of many infections, with Th1 cells promoting and Th2 cells suppressing defence against intracellular microbes.
- CD8+ T cells differentiate into CTLs that kill infected cells, mainly by inducing DNA fragmentation and apoptosis. CD4+ and CD8+ T cells often function cooperatively to eradicate intracellular infections.
- Many pathogenic microbes have evolved mechanisms to resist cell-mediated immunity. These mechanisms include inhibiting phagolysosome fusion, escaping from the vesicles of phagocytes, inhibiting the assembly of class I MHC-peptide complexes, and producing inhibitory cytokines or decoy cytokine receptors.

Learning objectives

1. Describe the different categories of T cells and their sub-types
    - Describe the migration of T cells in homeostasis and upon antigen recognition
2. Describe how T cells are activated by Dendritic cells
    - What are the steps involved in the activation of T cells?
    - What mediates the interaction between an APC and a T cell?
    - What is an immunological synapse?
    - How do superantigens activate the immune response? Why are they dangerous?
    - What are the consequences of T cell activation?
    - How do T cells differentiate into Th1 and Th2 subtypes?
    - How are CD8 T cells activated?
3. Describe the functions of helper T cells and CTLs
    - What is the respective function of Th1 and Th2 cells?
    - How do CTLs recognize and kill target cells?
    - Why are CD4 T cells called helper T cells?