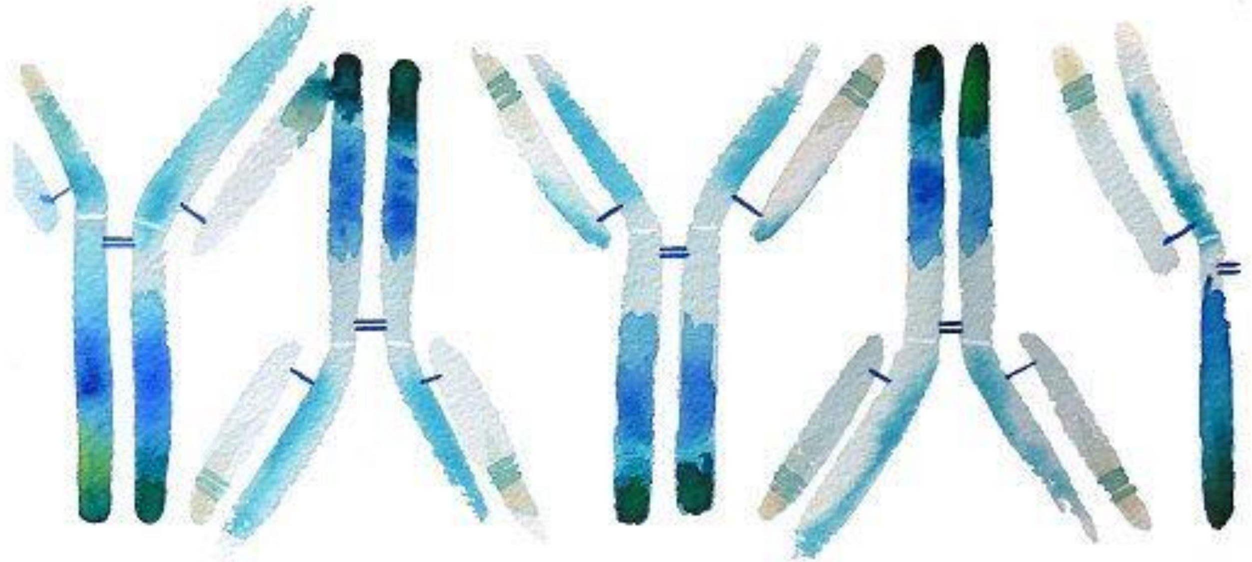
Medical Immunology



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

Lecture 14

Overview

In this lecture we will discuss:

- SIGNALS FOR T LYMPHOCYTE ACTIVATION
- MIGRATION OF EFFECTOR T LYMPHOCYTES TO SITES OF INFECTION
- EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS
- EFFECTOR FUNCTIONS OF CD8+ CYTOTOXIC T LYMPHOCYTES

Overview

- 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.

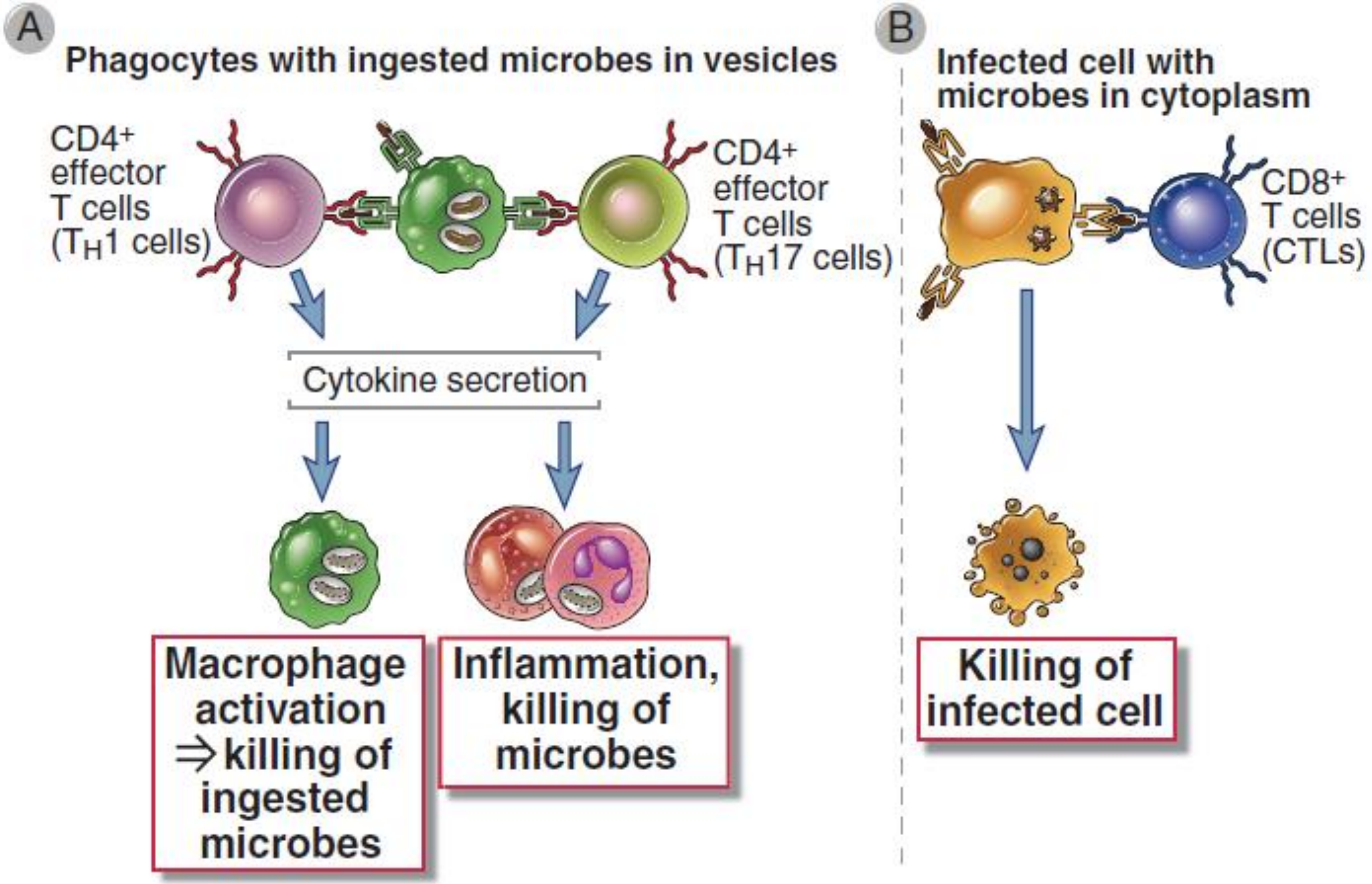
- The response to extracellular microbes, including many fungi and bacteria, is mediated by TH17 cells. While The response to helminthic parasites is mediated by TH2 cells,

Overview

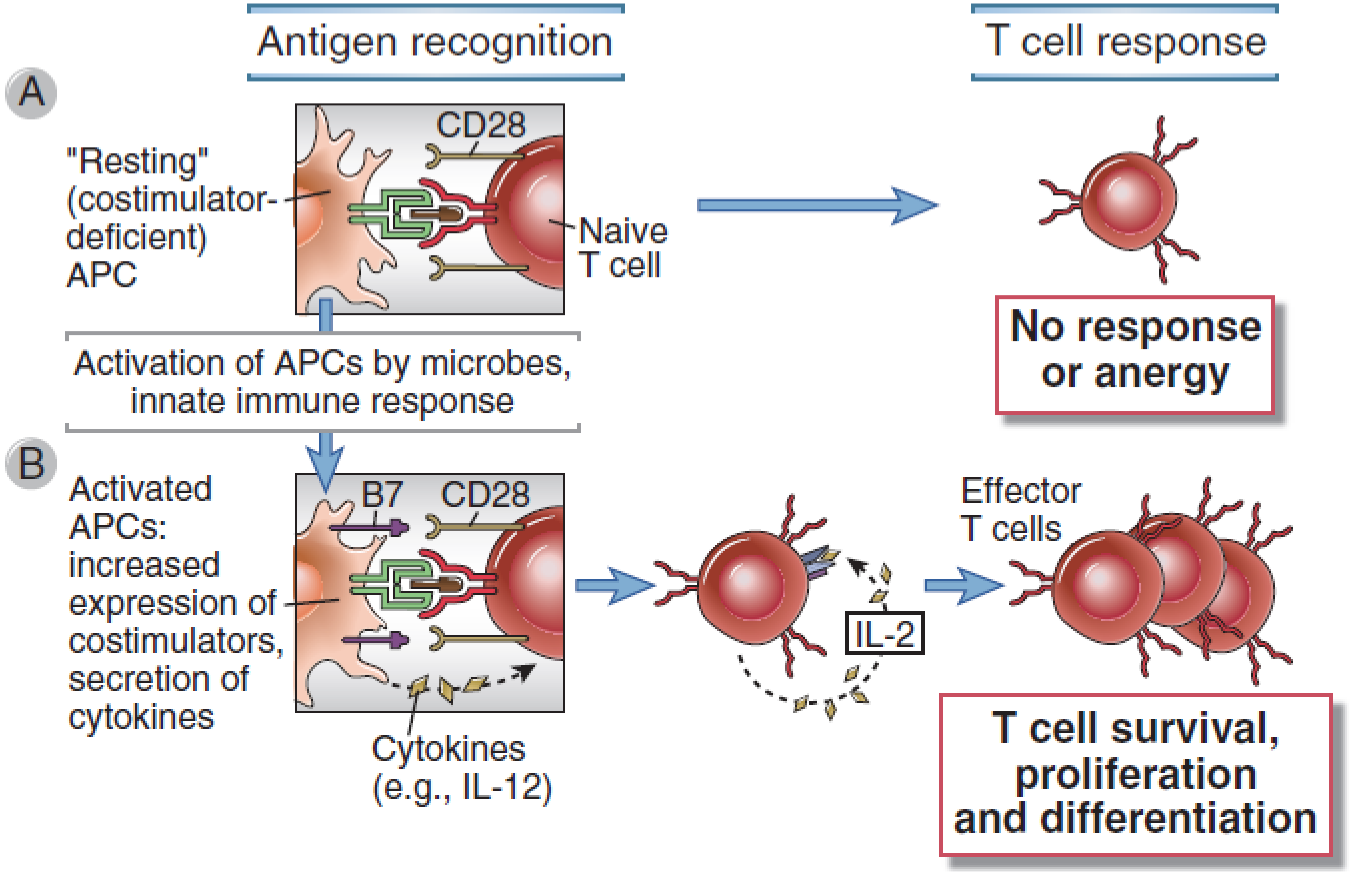
- The adaptive immune response to microbes that infect and replicate in the cytoplasm of various cell types, including nonphagocytic cells, is mediated by CD8+ cytotoxic T lymphocytes (CTLs), which kill infected cells and eliminate the reservoirs of infection.

- 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.

Overview

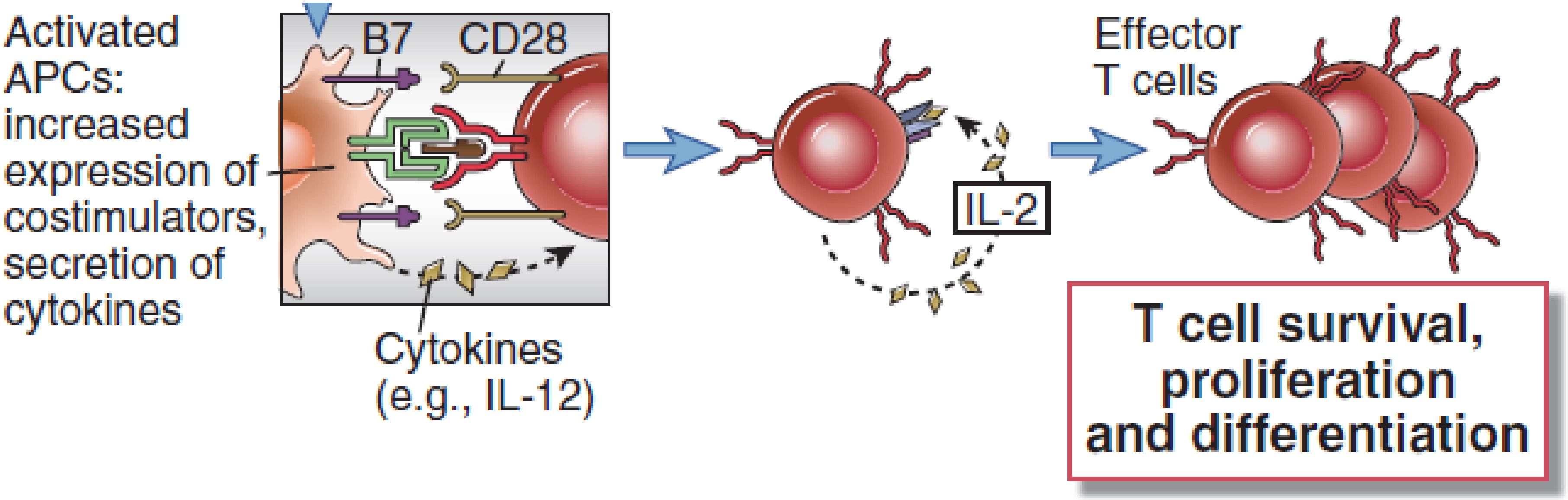

A
Phagocytes with ingested microbes in vesicles
CD4+ effector T cells (T_H1 cells)
CD4+ effector T cells (T_H17 cells)
Cytokine secretion
Macrophage activation ⇒ killing of ingested microbes
Inflammation, killing of microbes
B
Infected cell with microbes in cytoplasm
CD8+ T cells (CTLs)
Killing of infected cell

SIGNALS FOR T LYMPHOCYTE ACTIVATION



- 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.

SIGNALS FOR T LYMPHOCYTE ACTIVATION

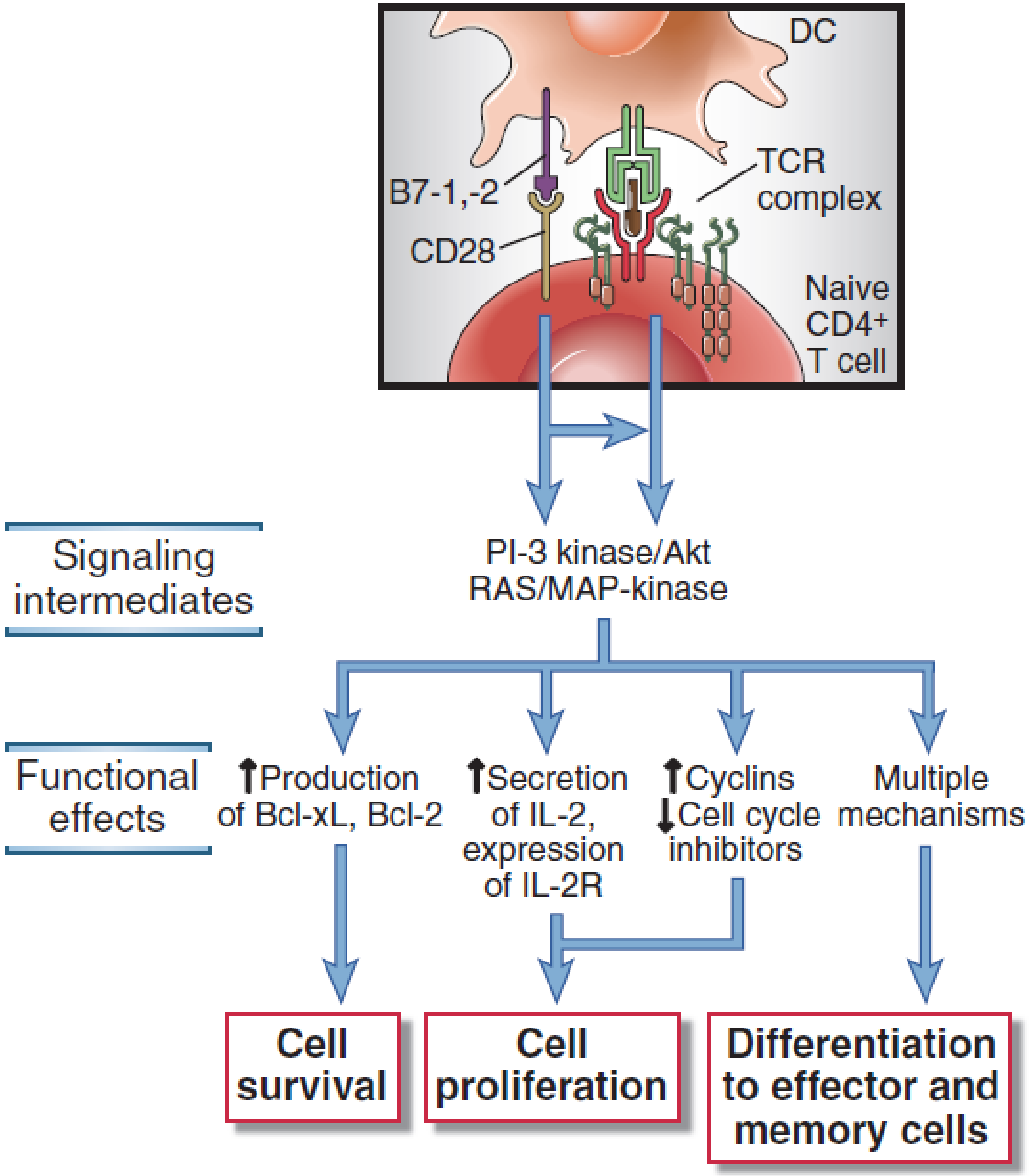


- The best characterized costimulatory pathway in T cell activation involves the T cell surface receptor **CD28**, which binds the costimulatory molecules **B7**-1 (CD80) and B7-2 (CD86) expressed on activated APCs.

- 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

- 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.

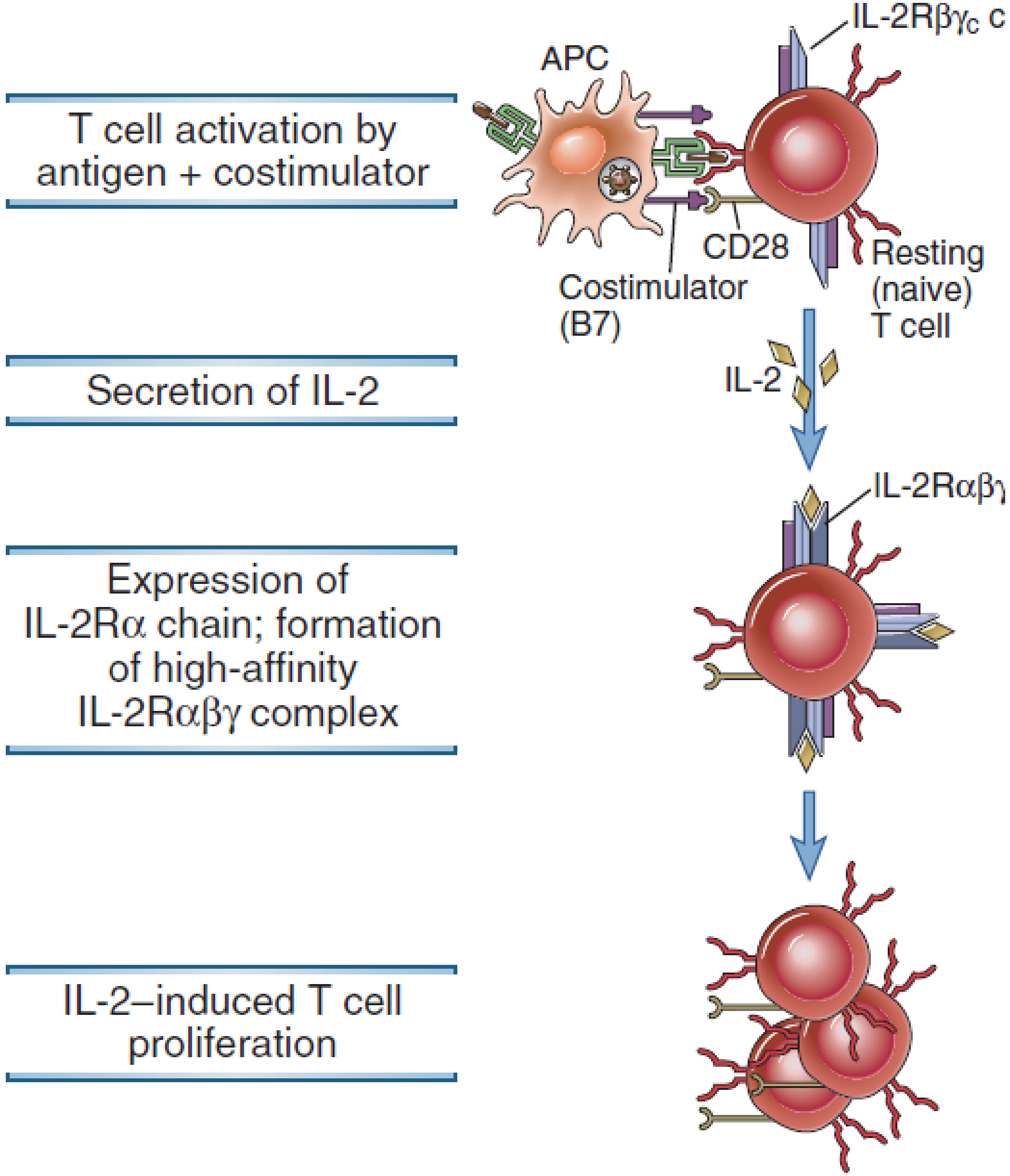


SIGNALS FOR T LYMPHOCYTE ACTIVATION

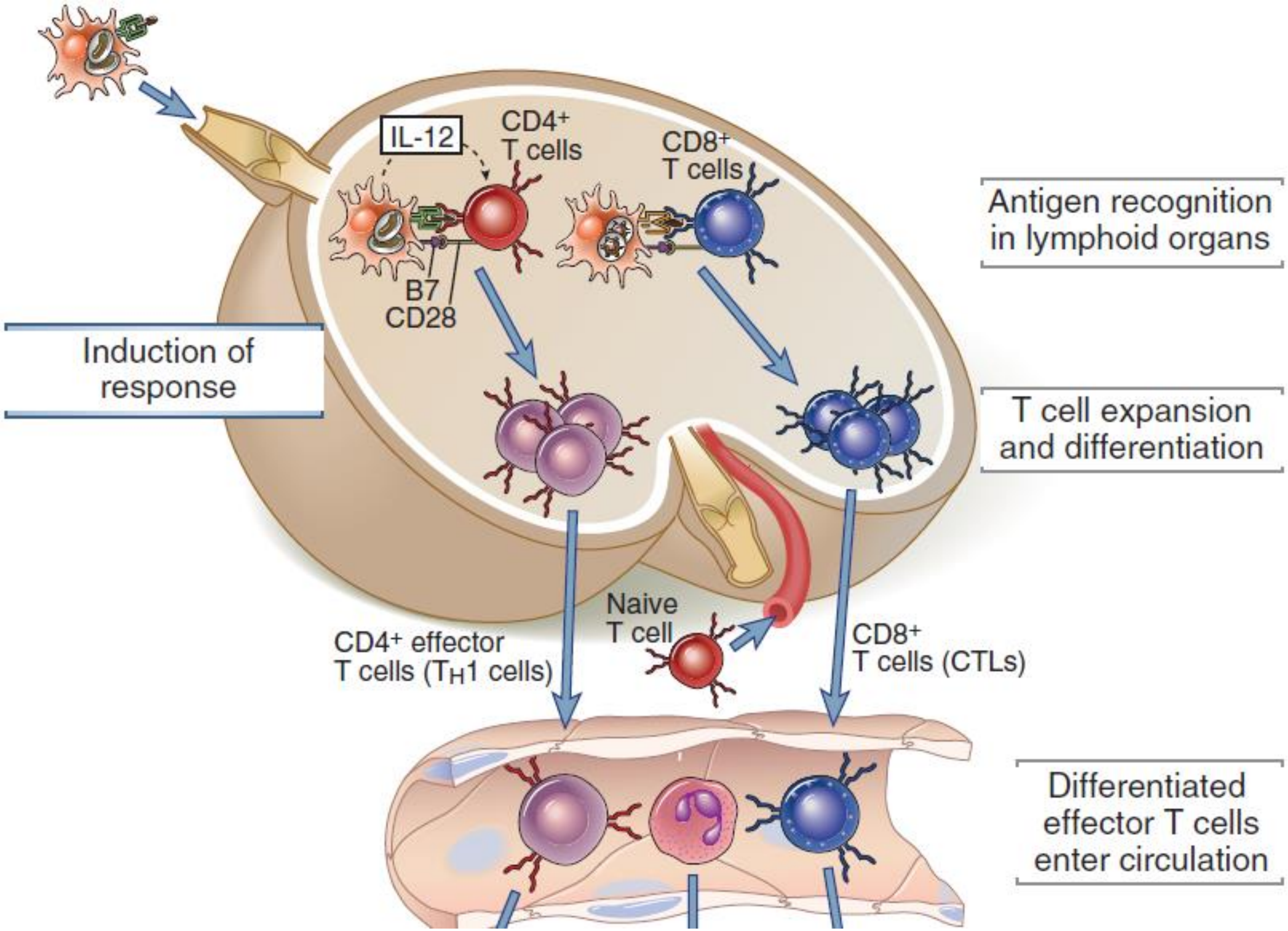
- The most important cytokine produced by T cells early after activation, often within 2 to 4 hours after recognition of antigen and costimulators, is **interleukin-2 (IL-2).**

- IL-2 stimulates the **survival, proliferation, and differentiation** of antigen-activated T cells.

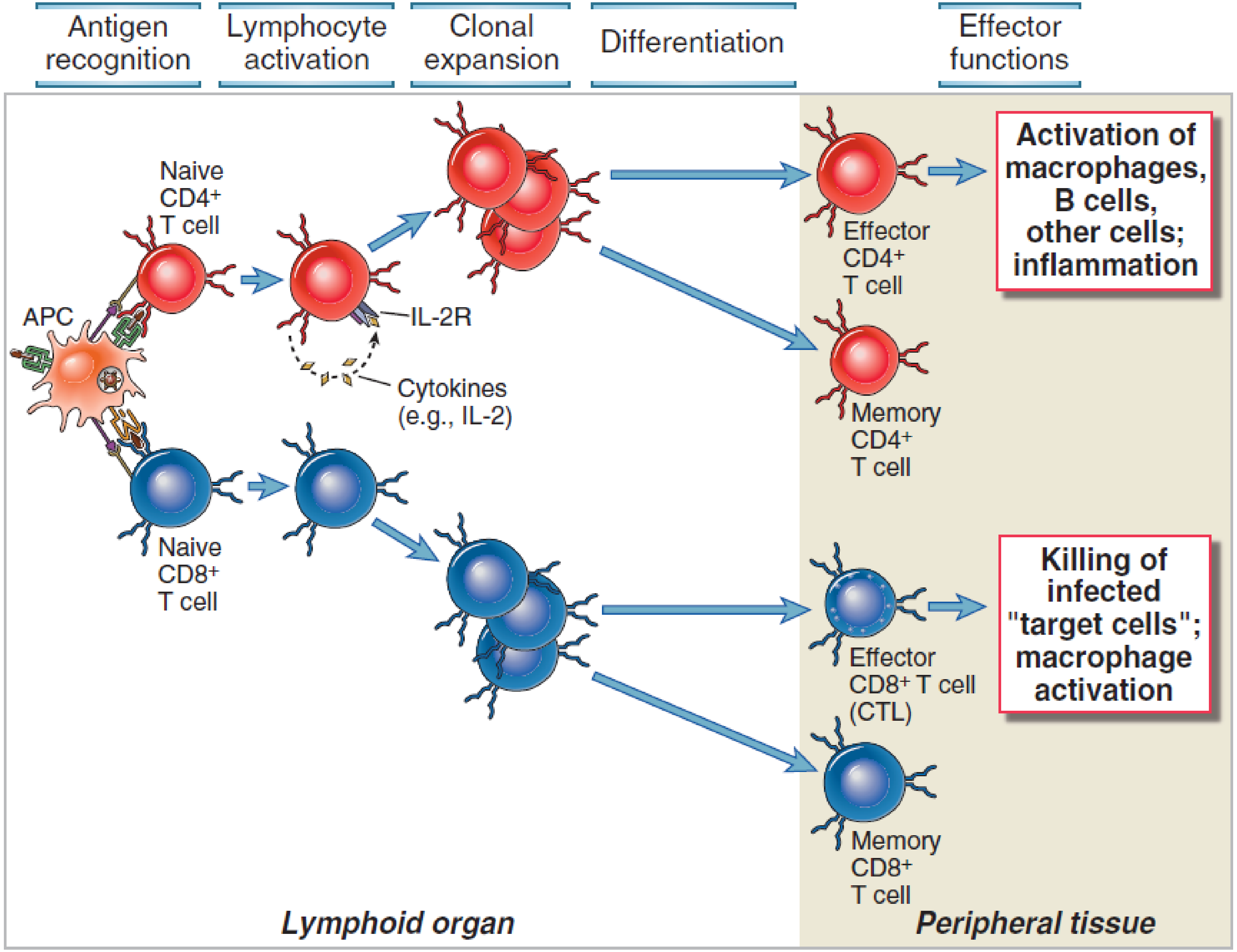
- T cell proliferation in response to antigen recognition is mediated primarily by a combination of signals from the antigen receptor, costimulators, and autocrine growth factors, **primarily IL-2**.



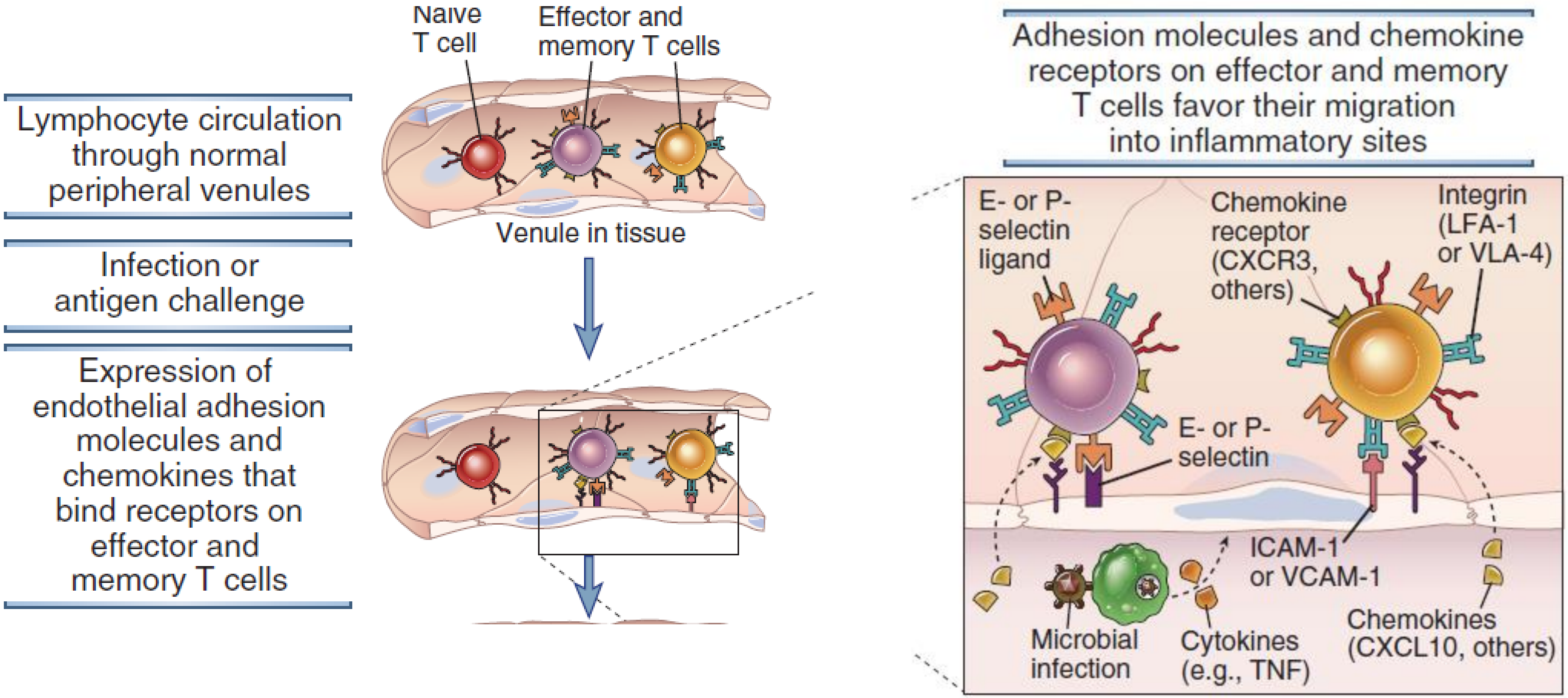
MIGRATION OF EFFECTOR T LYMPHOCYTES TO SITES OF INFECTION



MIGRATION OF EFFECTOR T LYMPHOCYTES TO SITES OF INFECTION



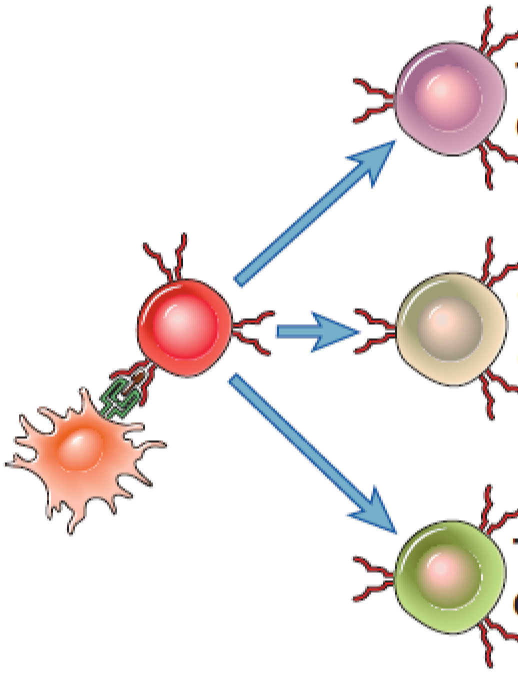
MIGRATION OF EFFECTOR T LYMPHOCYTES TO SITES OF INFECTION



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.

EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS

- 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



	Signature cytokines	Immune reactions	Host defense	Role in diseases
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

EFFECTOR FUNCTIONS OF CD4+ HELPER T CELLS/

- 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.

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

- 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.

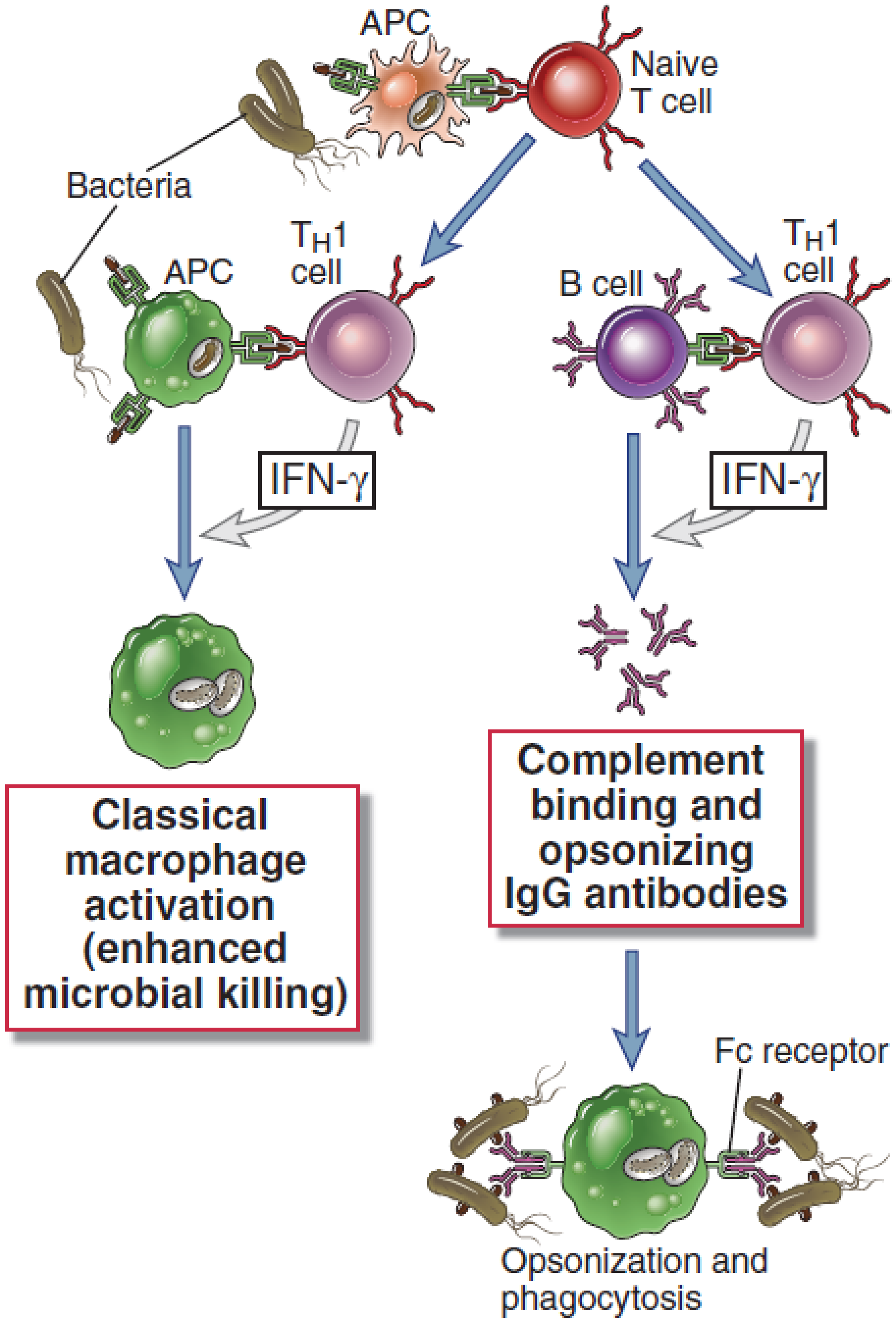
- IFN-γ is the principal **macrophage-activating cytokine** and serves critical functions in immunity against intracellular microbes.

- The actions of IFN-γ together result in **increased ingestion of microbes** and the **destruction of the ingested pathogens**.

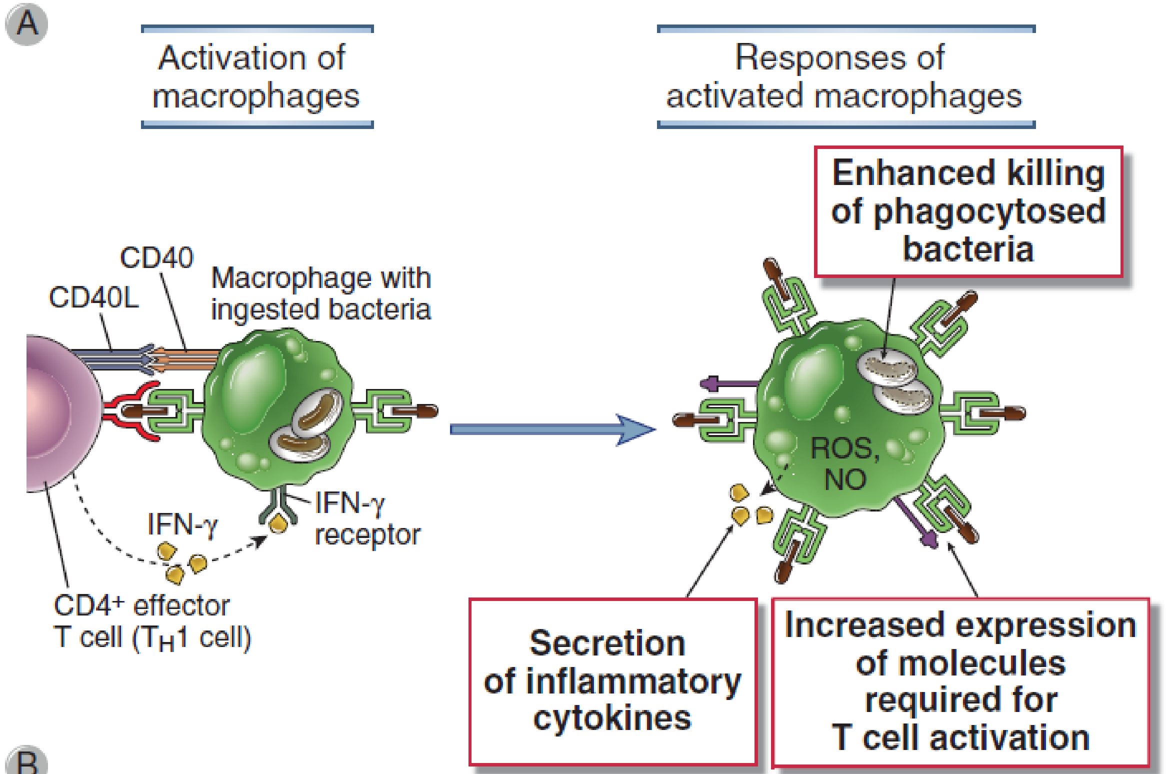
- CD4+ TH1 cells activate macrophages by contact-mediated signals delivered by **CD40L-CD40** interactions and by IFN-γ

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



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

- 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**.

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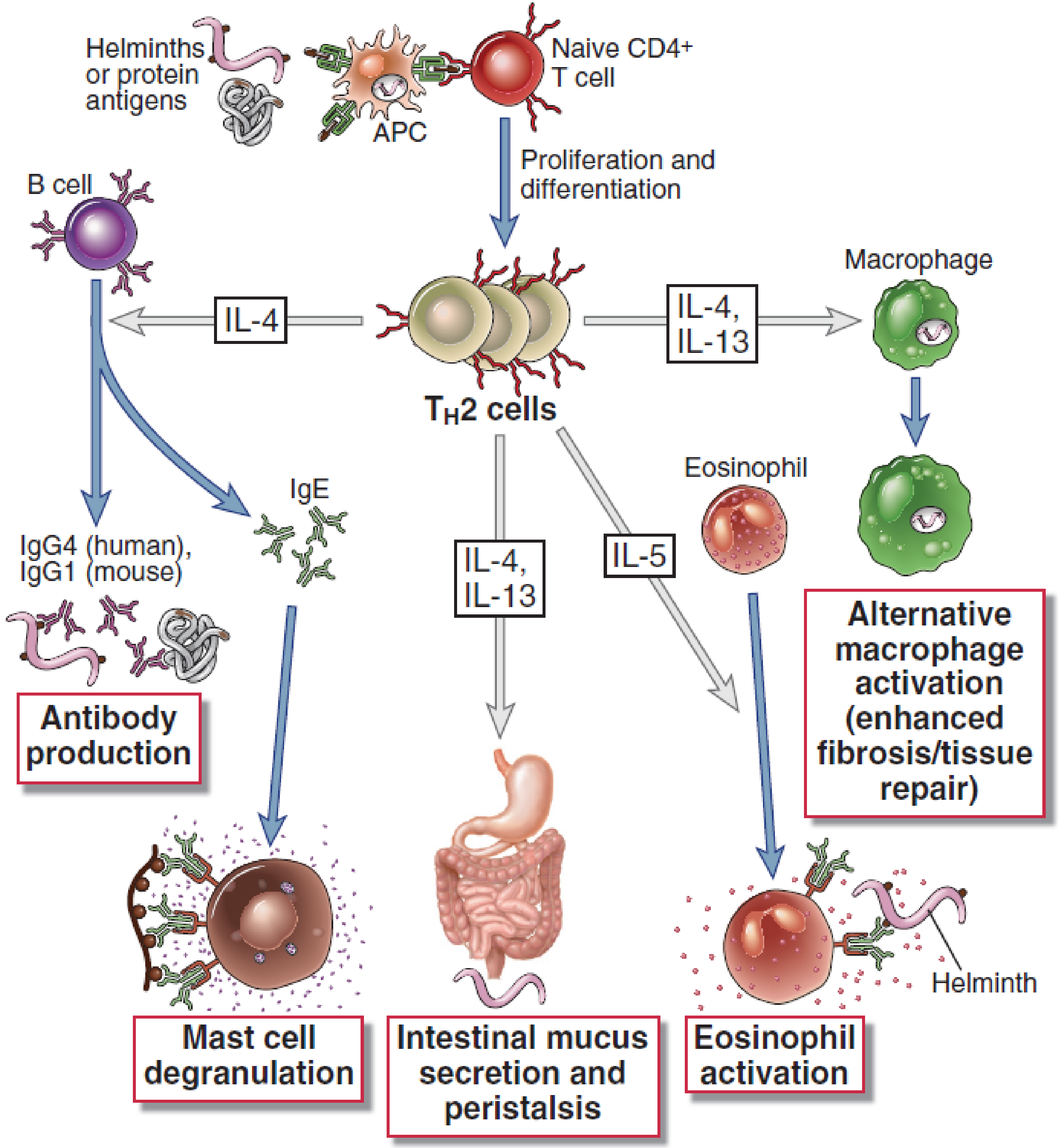
- IL-4 stimulates B cell Ig heavy chain **class switching to the IgE isotype**.

- 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**.**

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.



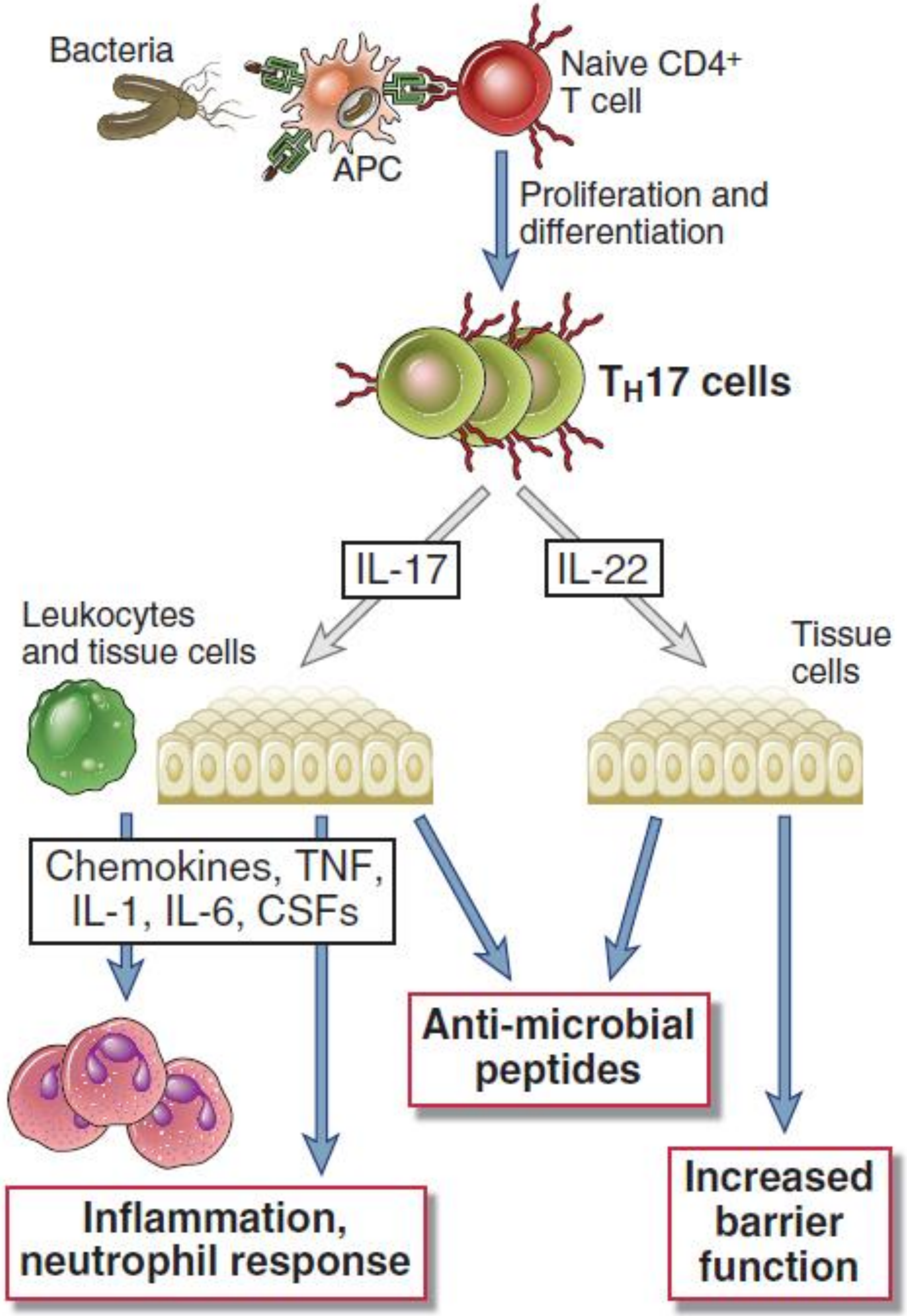
- **TH17 cells** secrete cytokines that **recruit leukocytes**, mainly **neutrophils**, to sites of infection.

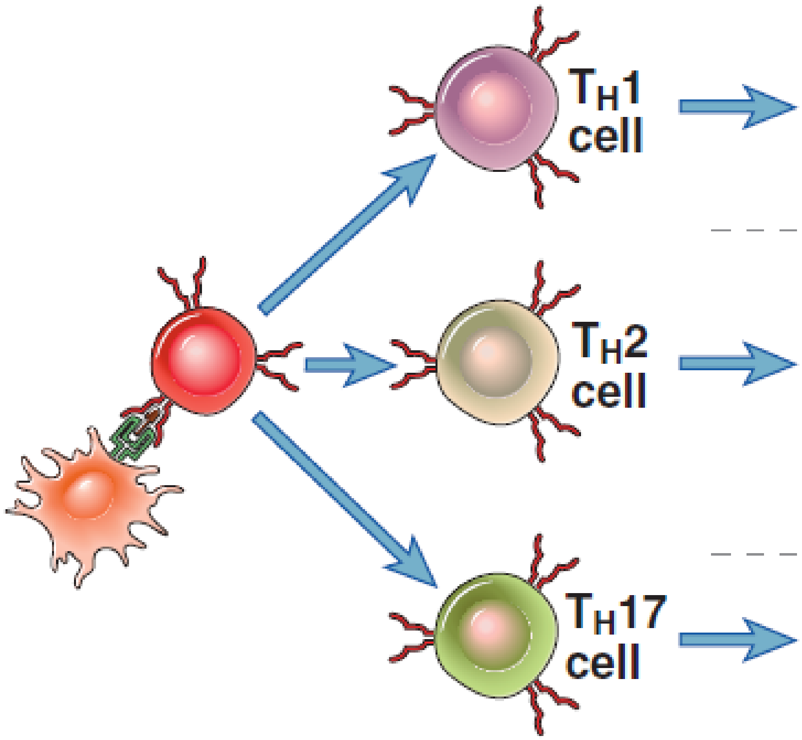
- Because neutrophils are a major defense mechanism **against extracellular bacteria** and fungi, **TH17 cells** play an especially important role in defense against these infections.

- TH17 cells produce several cytokines. Most of the inflammatory actions of these cells are mediated by **IL-17**.

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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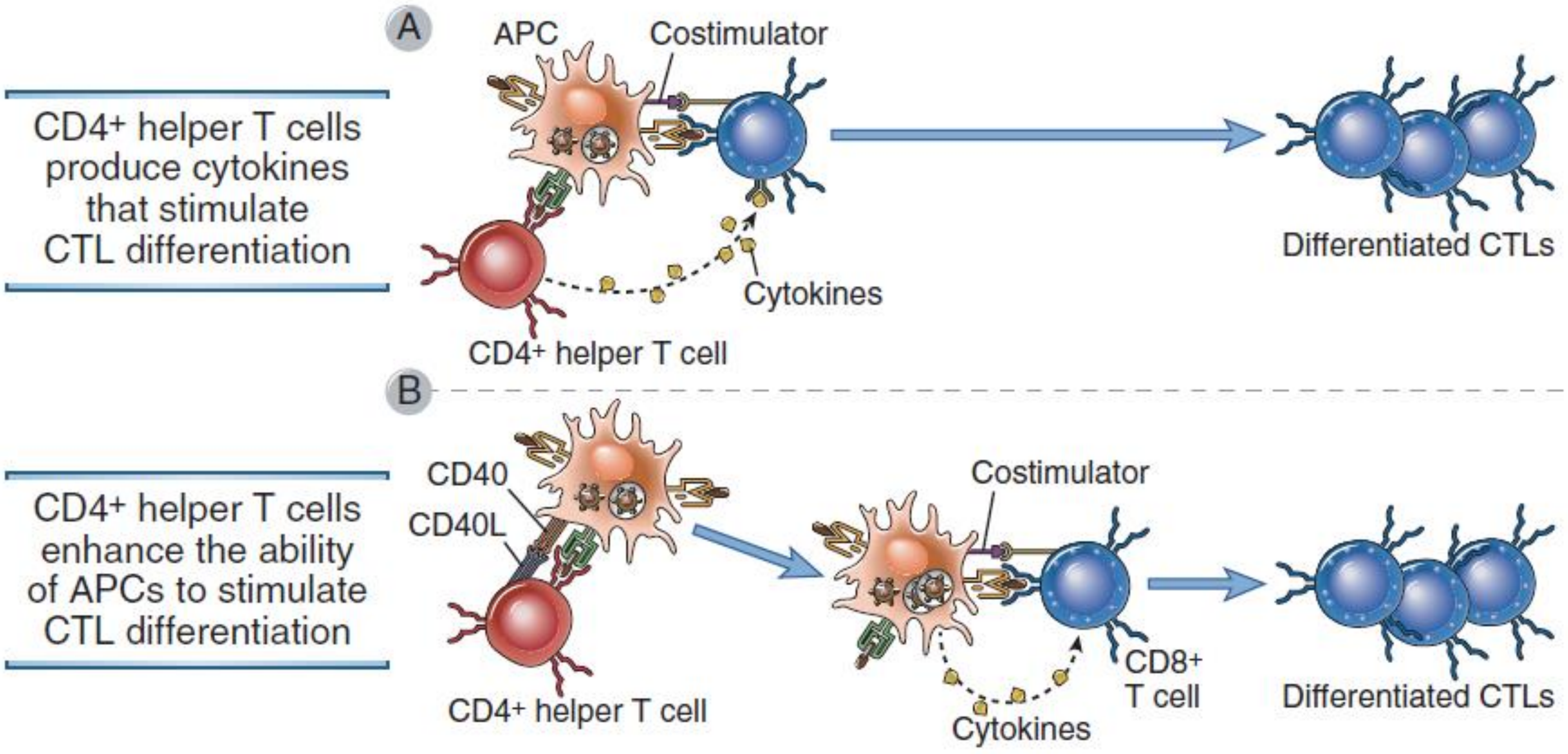
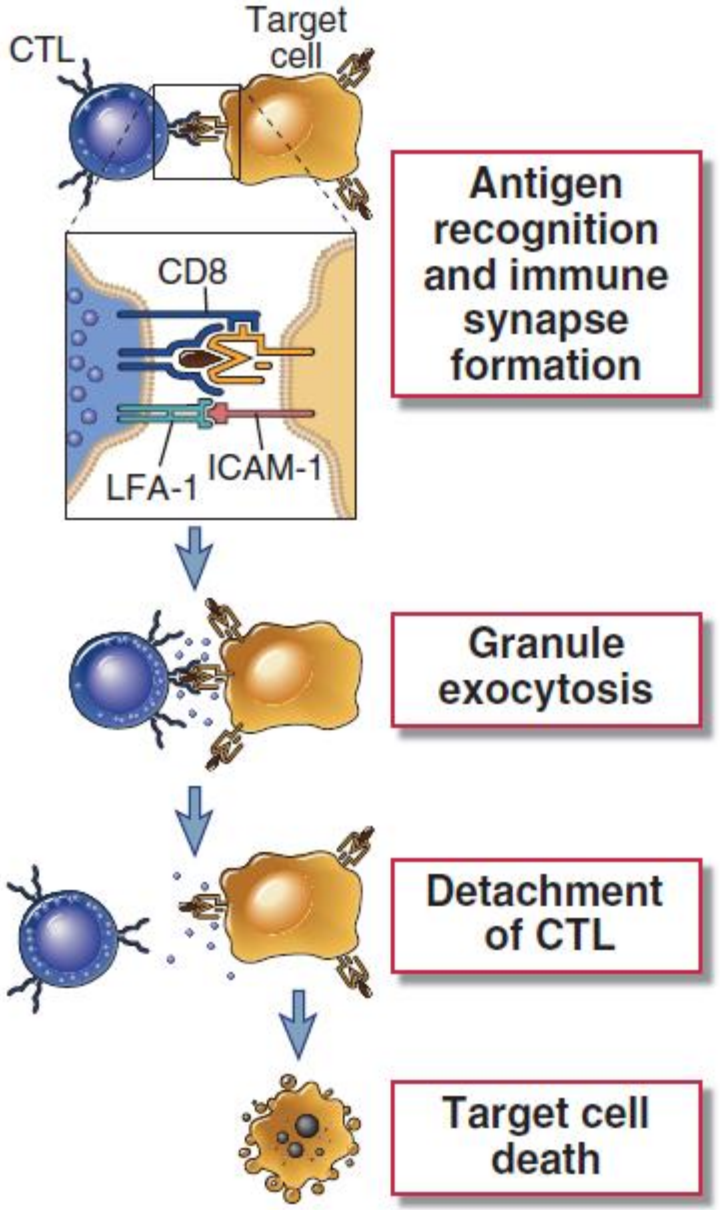
EFFECTOR FUNCTIONS OF CD8+ HELPER T CELLS

- 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**.



EFFECTOR FUNCTIONS OF CD8+ HELPER 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+ HELPER T CELLS

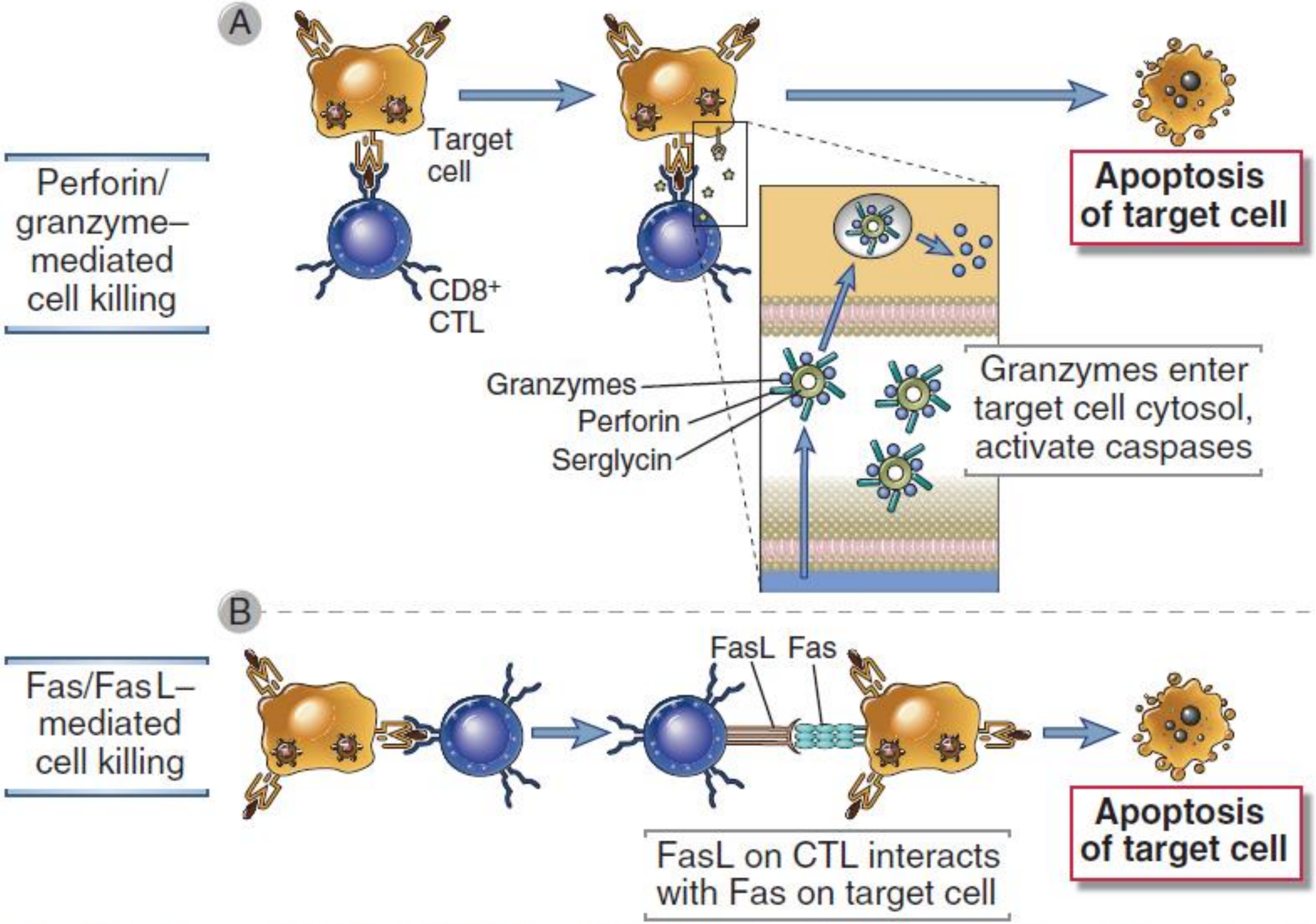


FIGURE 10–13 Mechanisms of CTL-mediated killing of target cells. CTLs kill target cells by two main mechanisms. **A,** Complexes of perforin and granzymes are released from the CTL by granule exocytosis and enter target cells. The granzymes are delivered into the cytoplasm of the target cells by a perforin-dependent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

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.

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 10. Effector Mechanisms of Cell-Mediated Immunity