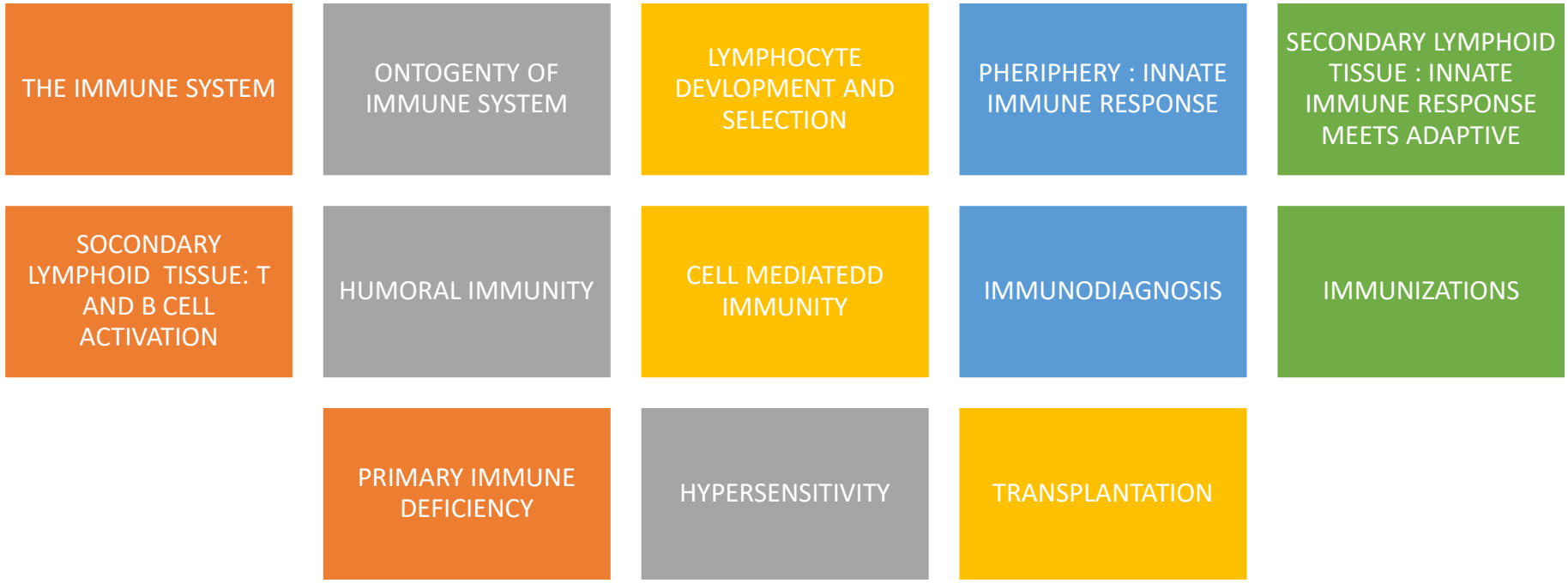
IMMUNOLOGY


THE IMMUNE SYSTEM
ONTOGENTY OF IMMUNE SYSTEM
LYMPHOCYTE DEVLOPMENT AND SELECTION
PHERIPHERY : INNATE IMMUNE RESPONSE
SECONDARY LYMPHOID TISSUE : INNATE IMMUNE RESPONSE MEETS ADAPTIVE
SOCONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION
HUMORAL IMMUNITY
CELL MEDIATEDD IMMUNITY
IMMUNODIAGNOSIS
IMMUNIZATIONS
PRIMARY IMMUNE DEFICIENCY
HYPERSENSITIVITY
TRANSPLANTATION

Immunology

IMMUNOLOGY

CELL MEDIATED IMMUNITY

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Learning Objective

- Describe the role of macrophages, B cells, cytotoxic T lymphocytes, and NK cells
- Demonstrate understanding of antibody dependent cell-mediated cytotoxicity
- Demonstrate understanding of agglutination
- Answer questions about ABO testing
- Demonstrate understanding of lab tests, including labelled antibodysystems, fluorescent antibody tests, enzyme-linked immunosorbent assay, and fluorescence activated cell sorting

CELL MEDIATED IMMUNITY

Contents

CELL MEDIATED IMMUNITY

CELL-MEDIATED IMMUNITY

Cell-mediated immunity has evolved to battle 2 different types of pathogens:

- **Facultative intracellular pathogens**, which have adapted to living inside of phagocytic cells that are designed to kill them
- **Obligate intracellular pathogens**, which can't replicate outside of host cells

Cell-mediated immunity is dictated by the Th1 response and is mediated primarily via Macrophages and CD8+ T cells.

While the Th1 response is geared toward eliminating intracellular pathogens, Th cells—in general—direct all aspects of the immune system. The primary mechanism by which Th cells direct all aspects of immunity is the secretion of cytokines.

NK cells also have a role in this type of immunity;

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Facultative intracellular Parasite

Legionella pneumophila It prefers intracellular environment of macrophages for growth. Legionella induce its own uptake and blocks lysosomal fusion by undefined mechanism.

R. Rickettsii destroys the phagosomal membrane with which the lysosomes fuse.

Mycobacterium tuberculosis: M.tuberculosis survives intracellularly by inhibiting phagosome-lysosome fusion.

Listeria Monocyotogenes: Listeria quickly escapes the phagosome into the cytoplasm **before** phagosome-lysosome fusion.

Salmonella Spp: Very resistant to intracellular killing by phagocytic cells.

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Obligate intracellular Parasite

All viruses

Pneumocystis Jeroveci

Mycobacterium Lprae cannot be cultured in vitro; it is an obligate intracellular parasite.

Coxiella Burnetti: The metabolic activity of Coxiella Burnettii is greatly increased in the acidic environment of the phagolysosome.

Rickettsia Spp

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MACROPHAGES/B CELLS

The Th1 response activates both macrophages and B cells via the cytokine IFN-γ.

IFN-γ activates classical M1 macrophages to eradicate intracellular pathogens and induces B cells to class switch to produce opsonizing IgG antibodies that can assist the macrophages with phagocytosis.

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Cell Medicate Immunity

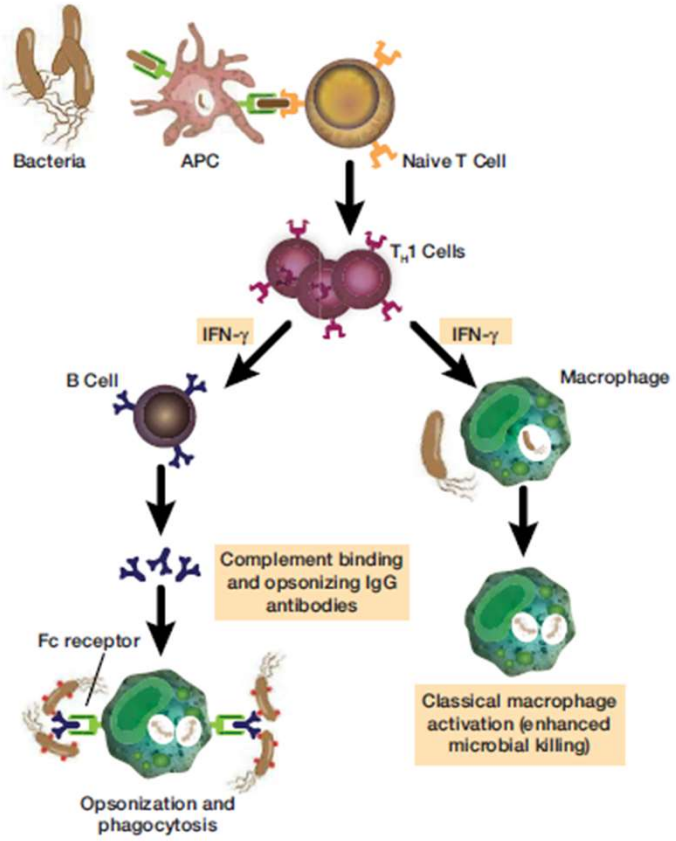

Figure I-8-1. Cell-Mediated Immunity

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Macrophage-Th Cell Interaction

The binding of the TCR of the naive Th cell to the MHC class II–peptide complex of the macrophage provides the first signal to the T cell to begin its activation. This provides the antigenic specificity of the response. Co-stimulatory molecules on macrophage provide the second signal, and cytokines secreted by the macrophage and the activating T cells themselves induce the proliferation (clonal expansion) and differentiation of the T cells into effector cells and memory cells. Effector cells leave the secondary lymphoid tissue, enter into circulation, and travel to the site of the infection.

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Microphases Molecule and Function

Cell	CD Markers	MHC class I	Effector Mechanisms
Macrophage	CD14 (LPS receptor)	yes	Nitric oxide, oxygen radicals, TNF-α

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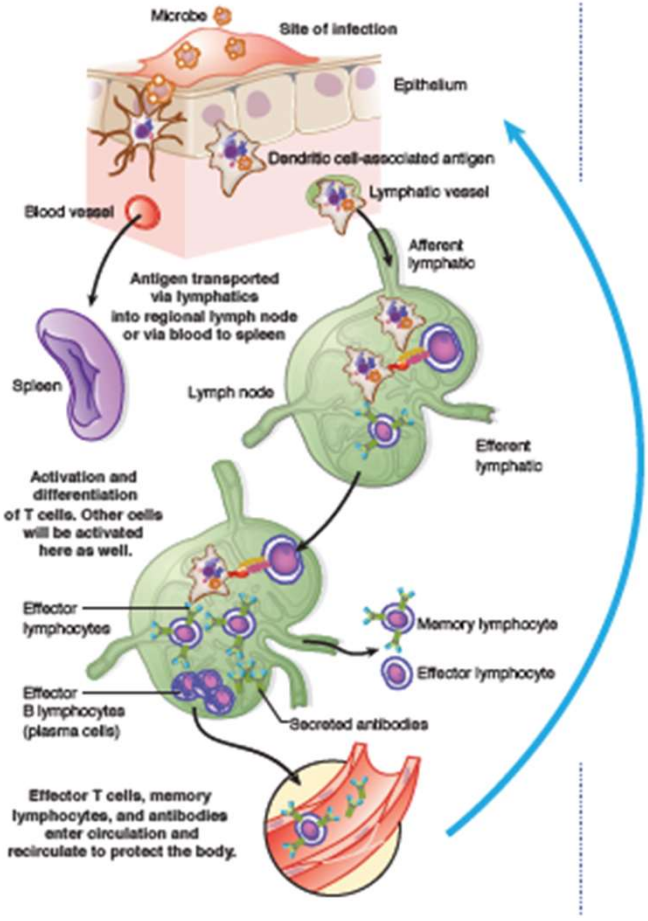
Migration of effector cell at the site of infection



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The proliferation of naive T cells in response to antigen recognition is mediated principally by an autocrine growth pathway, in which the responding T cell secretes its own growth-promoting cytokines and also expresses receptor molecules for these factors.

IL-2 is the most important growth factor for T cells and stimulates the proliferation of clones of T cells specific to that antigen.

Additionally, the T cells provide IFN-γ, which promotes macrophage activation that also helps to activate Th cells.

The production of IL-12 by the macrophage also helps to activate the Th cells. Together, IL-12 and IFN-γ also help to promote the differentiation of the naïve Th cell into a Th1 cell.

The reaction mediated by the Th1 cell via macrophage and CD8+ T cell activation is often referred to as the delayed-type hypersensitivity (DTH) reaction. Although this is the normal response of the body to intracellular pathogens, it is the exact same mechanism of cellular interactions and cytokine production as a hypersensitivity to poison ivy or nickel.

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CYTOTOXIC T LYMPHOCYTES (CTLS)

CTLs recognize the cell they will ultimately kill by interaction between their TCR and the MHC class I peptide complex on the surface of the target cell.

- If the cell in question is performing **normal functions** and therefore producing normal “self ” peptides, there should be no CD8+ T cells that have a complementary TCR structure.
- If the cell is **infected with an intracellular pathogen or is expressing neoantigens reflective of Tumor transformation**, some small proportion of those CD8+ T cells generated from the thymus should be capable of binding their TCRs to this MHC class I/non-self-peptide complex.

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Unfortunately, because of the extreme polymorphism of the HLA (MHC) system in humans, when tissues are transplanted between nonidentical individuals, cells of the transplant are often targeted by CTLs as abnormal. In spite of the fact that they may only be presenting normal cellular peptides, in these cases the HLA molecules themselves are different enough to elicit an immune response(*see* chapter 13). CTLs are capable of differentiation and cloning by themselves in the presence of the appropriate MHC class I non-self peptide complex stimulus, but are much more effective in so doing if they are assisted by signals from Th1 cells. The Th1 cell secretes IL-2, which acts on CD8+ cells to enhance their differentiation and cloning. Th s occurs via cross priming as discussed in chapter 5. Additionally, interferons produced in the area will increase the expression of MHC molecules to make target cells more susceptible to killing. CTLs kill their target cells by the delivery of toxic granule contents that induce the apoptosis of the cell to which they attach. This process occurs in 4 phases:

- Attachment to the target cell (mediated by TCR, CD8, and LFA-1 integrin)
- Activation (cytoskeletal rearrangement to concentrate granules against attached target cell)
- Exocytosis of granule contents (perforin and granzymes)
- Detachment from the target cell

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The death of the target cell may be mediated in distinct fashions.

1. Perforin present in the CTL granules creates pores in the membrane of the target cell through which Granzymes (serine proteases) enter the cell, inducing the activation of caspases, which activate the “death domain.”
2. Cytokines such as IFN-γ with TNF-α or TNF-β can induce apoptosis.
3. Activated CTLs express a membrane protein called Fas ligand (FasL), which may bind to its complementary structure, Fas, on the target cell. When this occurs, caspases are induced and death results.

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Cytotoxic T Cell- Markers and Functions

Cell	CD Markers	MHC class I	Effector Mechanisms
CTL	CD8, CD3, TCR, CD2	Yes	Perforin, granzymes, cytokines

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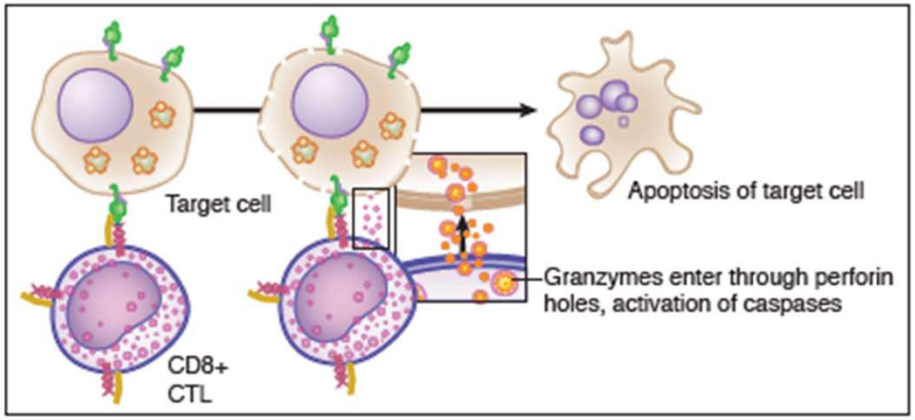
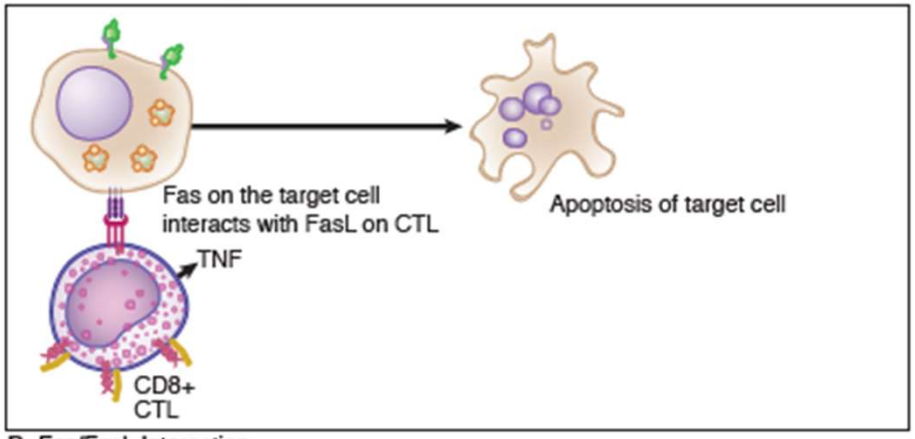
Cytotoxic T Cell Killing



A: Perforin and Granzymes



B: Fas/FasL Interaction

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NK CELLS

Another cell-mediated effector mechanism enhanced by the action of Th1 cells is NK cell-killing. Since the innate function of NK cells was discussed in chapter 4, the table below summarizes that information.

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NK Cell Marker and Function

Cell	CD Markers	MHC class I	Effector Mechanisms
NK	CD16 (FcR)* CD56 (CAM)	Inhibited by the normal expression of class I MHC via HLA-E.	Perforin, granzymes, cytokines (identical to CTL)**

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ADCC

A final mechanism of cytotoxicity which bridges humoral and cell-mediated effector systems in the body is antibody-dependent cell-mediated cytotoxicity(ADCC). A number of cells with cytotoxic potential (NK cells, macrophages, neutrophils, and eosinophils) have membrane receptors for the Fc region of IgG (aka CD16). When IgG is specifically bound to a target cell, the cytotoxic cells can bind to the free Fc “tail” and subsequently cause lysis of the target cell. Although these effectors are not specific for antigen, the specificity of the idiotype of the antibody directs their cytotoxicity. The mechanism of target cell killing in these cases may involve the following:

- Lytic enzymes
- Tumor necrosis factor
- Perforin/granzymes

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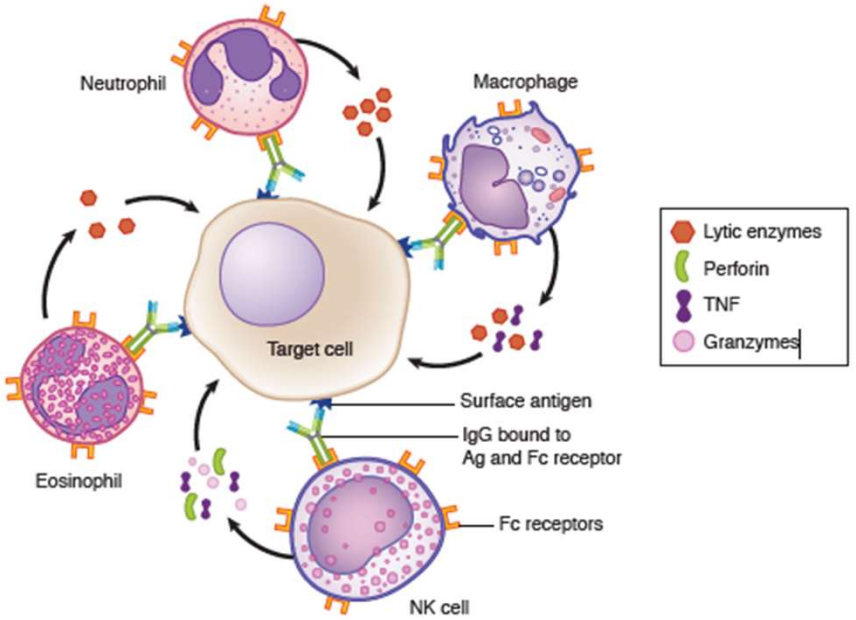
ADCC



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Chapter Summary

- The cell-mediated immune response protects against intracellular pathogens.
- TH1 cells activate macrophages, B cells, CTLs, and NK cells.
- Macrophages kill intracellularly in response to TNF-α, TNF-β, and IFN-γ activation; the DTH skin test measures Th1 function.
- CTLs kill targets expressing MHC class I/altered-self peptides, using perforin, cytokines, granzymes, and Fas ligand.
- CTLs are stimulated by IL-2 from Th1 cells. IFNs increase MHC expression on targets.