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Andrew H. Lichtman, M.D., Ph.D.

Cell Mediated Immunity

Recommended reading

Abbas and Lichtman. Cellular and Molecular Immunology, 5th edition. W.B. Saunders, 2005 (Chapter 13, Chapter 12--NK cells)

Janeway, Travers, Walport and Carpa. Immunobiology: The immune system in health and disease. 6th ed. Current Biology: Garland, 2005 (Chapter 8)

Overview

Cell-mediated immunity (CMI) is the type of immunity mediated by T lymphocytes, and is the defense mechanism against microbes that survive within phagocytes or infect non-phagocytic cells. Microbes in these locations are inaccessible to antibodies. In CMI, the effector phase is initiated by the recognition of peptide-MHC antigens by T cells. Defects in CMI result in increased susceptibility to infections by viruses and intracellular bacteria. Cell-mediated immune reactions are also important in graft rejection and tumor immunity. In this lecture, we will discuss the induction and effector mechanisms of cell-mediated immune reactions. We will also briefly cover Natural Killer (NK) cells, which are effector cells of the innate immune system that share many properties with a one type of effector T cell.

- Types of cell mediated immunity:
  - **$CD4^+$ helper T cell** responses to microbes residing within the **phagosomes** of phagocytes
    - T cell **cytokine and CD40-ligand expression, which activate the phagocytes** to kill the microbes and stimulate inflammation.
  - **$CD8^+$ cytolytic T lymphocyte** (CTL) responses to microbes (e.g. viruses) that infect and replicate in the cytosol of various cell types, including non-phagocytic cells
    - CTL killing of the infected cells.
    - CTL secretion of cytokines

- **$CD4^+$ T cell mediated macrophage activation**: In CMI against phagocytosed microbes, the specificity of the response is due to T cells, the effector functions are provided by phagocytes, and the communications between lymphocytes and phagocytes are mediated mainly by cytokines and CD40 ligand:CD40 interactions. The steps in the process of $CD4^+$ T cell and macrophage-mediated CMI include:

  - **Induction of cell-mediated immunity**: Activation of CD4+ TH1 cells by microbes and protein antigens
    - Antigen recognition by naïve T cells in lymph nodes.
    - Requires costimulation by professional APCs.
    - Clonal Expansion: driven by activated T cell IL-2 and IL-2 receptor production, leading to increase in numbers of T cells of a particular specificity, as much as 100-fold.
    - Differentiation of CD4+ T Lymphocytes into effector cells
    - **Th1** and **Th2** subsets of effector CD4+ T cells are defined by cytokines they produce.
      - Th1 differentiation is stimulated by IL-12 produced by microbe-activated phagocytes
      - Th2 differentiation stimulated by IL-4
    - Th1 cells produce IFN-γ and are the effectors that activate macrophages in CMI.

- Th2 cells produce IL-4 and IL-5, which promote IgE and eosinophil-mediated anti-helminthic responses. Th2 responses may also down regulate Th1 responses.
- TH1 differentiation is stimulated by IL-12 produced by APCs.

- **Migration of differentiated effector T cells and other leukocytes to site of antigen**.
  - The migration of leukocytes to sites of infection is stimulated by cytokines, which induce the expression of adhesion molecules on endothelial cells and the chemotaxis of leukocytes.
  - Effector and memory T lymphocytes express adhesion molecules (intergrins, selectin ligands) that promote their migration to sites of infection and inflammation.
  - The migration of effector and memory T cells from the circulation to peripheral sites of infection is largely independent of antigen, but cells that recognize antigen in extravascular tissues are preferentially retained there.
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- **Activation of macrophages:** Activated macrophages are the effector cells of cell-mediated immunity that function to eliminate microbes and other sources of antigen.
  - T cell stimuli for macrophage activation include **CD40 ligand** and **IFN-γ**

- **Functions of activated macrophages:**
  - Killing phagocytosed and extracellular microbes, mainly by producing microbicidal reactive oxygen intermediates, nitric oxide, and lysosomal enzymes.
  - Stimulate acute inflammation through secretion of cytokines, mainly TNF, IL-1 and chemokines, and short-lived lipid mediators, such as platelet-activating factor (PAF), prostaglandins, and leukotrienes.
  - Remove dead tissues, facilitating repair after the infection is controlled.
  - In addition to their effector functions, activated macrophages become more efficient APCs.

- **Delayed type hypersensitivity (DTH)** is injury (rather than protection) caused by a helper T cell mediated immune response. This happens if the activated macrophages fail to eradicate the infection; T cells and macrophages continue to produce cytokines and growth factors, and this leads to progressive modification of the local tissue environment, including fibrosis.

  - **Granulomatous inflammation** is a form of chronic DTH with epithelioid macrophages, sometimes giant cells, and tissue fibrosis. Infection with Mycobacterium tuberculosis often leads to granuloma formation.

- **$CD8^+$ T cells and cytolytic T lymphocyte (CTL) responses.** Cytolytic T lymphocytes (CTLs) are effector T cells that recognize and kill target cells expressing foreign peptide antigens in association with class I MHC molecules.

  - Most cell types may be infected with viruses, but most cell types also express class I MHC and can process proteins by the class I MHC pathway. Therefore most cells can be targets of CTL killing.
  - Activation of naïve CD8+ T cells and development of effector CTLs
    - Problem: The differentiation of naive CD8+ T cells to functional CTLs requires the recognition of class I MHC-associated peptides (“signal 1”) and costimulators and/or cytokines (“signal 2”) normally only present on professional antigen presenting cells.
    - Solution: **cross priming**- a mechanism to ensure that naïve CD8+ T cells specific for the virus can be activated even when the primary infection is in cells that do not express costimulators, e.g. epithelial cells.

- Infected cells, debris form dying infected cells, or microbes released from the cells, are ingested by professional APCs.
- Microbial proteins leave the phagosomes/endosomes (not known how) and enter the cytoplasm.
- The microbial proteins are processed and presented by the class I MHC pathway.
- Naïve $CD8^+$ T cells specific for the peptide-MHC are activated by the professional APCs.

- Clonal expansion of CD8+ T cells in lymphoid tissues in response to viral infections often leads to as much as 50,000 to 100,000 fold increase in numbers of viral-specific CD8+ T cells.
- Peptide-MHC tetramers can be used as probes for expansion of viral peptide-specific T cells; this has been done with EBV and HIV infected patients.
- Differentiation of CD8+ T cells into effector T cells capable of cytolytic functions.
- Development of membrane-bound cytoplasmic granules that contain perforin and granzymes.
- Acquisition of the capacity to transcribe and secrete cytokines, mostly IFN-γ, LT, and TNF.

- Mechanisms of CTL-mediated cytolysis: Cell killing by CTLs is antigen-specific and contact-dependent. CTLs kill targets that express the same class I-associated antigen that triggered the proliferation and differentiation of naïve CD8+ precursor of the CTL.
  - Recognition of antigen on the target cell and activation of CTLs (does not require costimualtion)
  - Accessory molecule interactions, including CD2:LFA3 and LFA-1: ICAM-1 strengthen conjugate formation between CTL and target.
  - Delivery of a "**lethal hit**" by the activated CTL to its target.
  - Granule exocytosis releases:
    - **Perforin** that forms pores in membrane of target cells.
    - **Granzymes** (serine proteases) that enter the target cell through the perforin pore and activate cellular enzymes called caspases, which lead to target cell apoptosis.
    - **Fas ligand** expressed on activated CTL may bind Fas on target cells and induce apoptosis.
  - Cytokines (Th1-like) such as IFN-γ and TNF secreted by CTL promote inflammation.
  - Release of the CTL: The CTL is not killed in the process, and can detach and find another target cell to kill.

- **Role of Th2 cells in cell mediated immunity**

  - Suppression of Th1 mediated CMI by action of cytokines IL-4, IL-10, IL-13 which inhibit macrophage activation.
  - Promote inflammatory reactions, by secretion of IL-4 and IL-5, that are dominated by eosinophils and mast cells for protection against helminthic infections.
    - IL-4 stimulates the production of helminth-specific IgE antibodies, which opsonize the helminthes and bind to mast cells.
    - IL-5 activates eosinophils, which bind to the IgE-coated helminths by virtue of Fc receptors specific for the ε heavy chain. Activated eosinophils release their granule contents, including major basic protein and major cationic protein, which are capable of destroying even the tough integuments of helminths.

- **Natural Killer (NK) cells.** NK cells are effector cells of the innate immune system that recognize and kill host cells which fail express some class I MHC molecules or kill host cells that express certain molecules indicative of intracellular infection or stress.

- Many viruses may interfere with class I MHC expression and class-I pathway antigen processing, thereby rendering their host cells invisible to CTL. NK cells, however, "recognize" the absence of class I MHC and/or recognize cell surface molecules only expressed on stressed (e.g. infected) cells infection.
- NK cells recognize" their target cells using both activating and inhibitory receptors.
  - Activating receptors include CD16 (FcγR receptor), natural cytotoxicity receptors (unknown ligands), NKG2 (binds stress induced ligands)
  - Inhibitory receptors include: CD94, ILT2, and Killer Inhibitory Receptors (KIRs), which bind class I or class I-like molecules.
  - Inhibitory receptor signals suppress signals from activating receptors.
- NK cells perform two major effector functions:
  - Cytotoxicity: kill targets by same perforin/granzyme based mechanisms that CTLs use
  - IFN-γ secretion-promote inflammation, and perhaps Th1 differentiation
- NK cells play important protective roles against viruses (e.g. EBV), and perhaps other intracellular microbes.
- Diseases characterized by lack of NK cells or NK function , such as X-linked lymphoproliferative disease (XLP) are associated with severe EBV infections and B cell neoplasm.
  - XLP due to mutation sin gene encoding an adaptor protein in a signaling pathway involving the T-cell co-stimulatory molecule SLAM, and the NK-cell-activating receptor2B4.

- **Natural Killer T (NKT) cells**. NKT T cell are numerically small subset of immune effector cells which develop as a separate lineage from, but share properties of both T cells and NK cells.
  - NKT cell recognize glycolipids presented by CD1d.
  - NKT cells recognize glycolipid/CD1 complexes via a TCR with an invariant T cell alpha chain.
  - NKT cells can secrete many different cytokines, rapidly after stimulation.
  - NKT cells can activate dendritic cells.
  - NKT cell activation may either suppress or stimulate immune responses.
  - Mouse models have indicated that NKT cell are involved in many different protective and pathological immune responses.