

# Medical immunology

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MEDICAL IMMUNOLOGY & SEROLOGY Terence L. Eday, RMT, MT(ASCPi), MPH  
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Perpetual Help System DALTA Historical Perspective • 1773, Voltaire  
reported on an ancient Chinese custom where dried and powdered small pox  
scabs were inhaled • 1798, Edward Anthony Jenner, Smallpox vaccination •  
1862, Ernst Haeckel, Recognition of phagocytosis 1877, Paul Ehrlich,  
recognition of mast cells Historical Perspective • 1879, Louis Pasteur,  
Attenuated chicken cholera vaccine development • 1883, Ellie Metchnikoff  
developed the cellular theory of immunity through phagocytosis; phagocytic  
theory; cellular theory of vaccination • 1885, Pasteur discovered therapeutic  
vaccination; first report of live “attenuated” vaccine for rabies Historical  
Perspective 1888, Pierre Roux & Alexander Yersin, Bacterial toxins (*Yersinia  
pestis*) • 1888, George Nuttall, Bactericidal action of blood • 1890, Emil von  
Behring and Kitasato introduced passive immunization into modern  
medicine; humoral theory of immunity • 1891, Robert Koch demonstrated  
the cutaneous (delayed-type) hypersensitivity • 1894, Richard Pfeiffer,  
Bacteriolysis Historical Perspective (1 of 6 ) 1895, Jules Bordet, Complement  
and antibody activity in bacteriolysis • 1900, Paul Ehrlich, responsible for the  
antibody formation theory • 1901, Karl Landsteiner, A, B, and O • 1901-8,  
Carl Jensen & Leo Loeb, Transplantable tumors • 1902, Paul Portier & Charles  
Richet, Anaphylaxis Historical Perspective (1 of 6 ) • 1903, Nicolas Maurice  
Arthus, discovered the Arthus reaction of intermediate hypersensitivity •  
1903, Almroth Wright and Stewart Douglas observed the humoral  
component, opsonin • 1906, Clemens von Pirquet, coined the word allergy •  
1907, Svante Arrhenius, coined the term immunochemistry

Historical Perspective • 1910, Emil von Dungern, & Ludwik Hirszfeld, Inheritance of ABO blood groups • 1910, Peyton Rous, Viral immunology theory • 1914, Clarence Little, Genetics theory of tumor transplantation • 1915-20, Leonll Strong & Clarence Little, Inbred mouse strains Historical Perspective • 1917, Karl Landsteiner, Haptens • 1921, Carl Prausnitz & Heinz Kustner, Cutaneous reactions • 1924, L. Aschoff, Reticuloendothelial system • 1926, Loyd Felton & GH Bailey, Isolation of pure antibody preparation • 1938, John Marrack, Antigen-antibody binding hypothesis Historical Perspective 1936, Peter Gorer, Identification of the H2 antigen in mice • 1940, Karl Landsteiner & Alexander Weiner, Identification of the Rh Antigens • 1941, Albert Coons, Immunofluorescence technique • 1942, Jules Freund & Katherine McDermott, Adjuvants • 1942, Karl Landsteiner & Merrill Chase, Cellular transfer of sensitivity in guinea pigs (anaphylaxis) Historical Perspective • 1944, Peter Medwar, Immunological hypothesis of allograft rejection • 1948, Astrid Fagraeus, Demonstration of antibody production in plasma B cells • 1948, George Snell, Congenic mouse lines • 1949, Macfarlane Burnet & Frank Fenner, Immunological tolerance hypothesis

Historical Perspective • 1950, Richard Gershon and K Kondo, Discovery of suppressor T cells • 1952, Ogden and Bruton, discovery of agammaglobulinemia (antibody immunodeficiency) • 1953, Morton Simonsen and WJ Dempster, Graft-versus-host reaction • 1953, James Riley & Geoffrey West, Discovery of histamine in mast cells Historical Perspective • 1953, Rupert Billingham, Leslie Brent, Peter Medwar, & Milan Hasek, Immunological tolerance hypothesis • 1955-1959, Niels Jerne, David Talmage, Macfarlane Burnet, Clonal Selection Theory • 1957, Ernest

Witebsky et al. Induction of autoimmunity in animals • 1957, Alik Isaacs & Jean Lindemann, Discovery of interferon (cytokine) Historical Perspective • 1958-62, Jean Dausset et al. , Human leukocyte antigens • 1959-62, Rodney Porter et al. , Discovery of antibody structure • 1959, James Gowans, Lymphocyte circulation • 1961-62, Jacques Miller et al. , Discovery of thymus involvement in cellular immunity • 1961-62, Noel Warner et al. , Distinction of cellular and humoral immune response Historical Perspective • 1963, Jacques Oudin et al. Antibody isotypes • 1964-68, Anthony Davis et al. , T and B cell cooperation in immune response • 1965, Thomas Tomasi et al. , Secretory immunoglobulin antibodies • 1967, Kimishige Ishizaka et al. , Identification of IgE as the reaginic antibody Historical Perspective • 1971, Donald Bailey, Recombinant inbred mouse strains • 1972, Gerald M. Edelman & Rodney Porter, Identification of antibody molecule • 1974, Rolf Zinkernagel & Peter Doherty, MHC restriction • 1975, Kohler and Milstein, First monoclonal antibodies used in genetic analysis

Historical Perspective • 1984, Robert Good, Failed treatment of severe combined immunodeficiency (SCID, David the bubble boy) by bone marrow grafting • 1985, Tonegawa, Hood et al. , Identification of immunoglobulin genes • 1985-1987, Leroy Hood et al. , Identification of genes for the T cell receptor • 1986, Monoclonal hepatitis B vaccine Historical Perspective • 1986, Mosmann, Th1 versus Th2 model of T-helper-cell function • 1990, Yamamoto et al. Molecular differences between the genes for blood groups O and A and between those for A and B • 1990, NIH team, Gene therapy for SCID using cultured T cells • 1993, NIH team, Treatment of SCID using genetically altered umbilical cord cells Historical Perspective • 1996-1998,

Identification of toll-like receptors • 2001, FOXP3, the gene directing regulatory-T-cell development • 2005, Frazer, Development of human papilloma-virus vaccine

### The IMMUNE SYSTEM What is Immunology?

- Study of the molecules, cells, organs, and systems responsible for the recognition and disposal of foreign (nonself) material
- ... how body components respond and interact
- ...desirable and undesirable consequences of immune interactions
- ...ways in which the immune system can be advantageously manipulated to protect against or treat disease

### What is Immunity?

- Latin word “immunitas”, freedom from
- It refers to all mechanisms used by the body as protection against environmental agents that are foreign to the body.
- Can be either natural (innate or inborn) or acquired (adaptive)

### Function of the Immune System

- Recognize “ self” from “ nonself”
- Defend the body against nonself

### Physiologic function is to prevent infection and to eradicate established infections (sterilizing immunity)

### Key Characteristics of the Immune System

- Innate immunity
- Primary response
- Secondary response and immunologic memory
- Immune response is highly specific
- Immune system is tolerant of self-antigens
- Immune responses against self-antigens can result in autoimmune diseases
- Immune responses against infectious agents do not always lead to elimination of the pathogen (HIV/AIDS)

### Major Principles of Immunity (immune response):

Elimination of many microbial agents through the nonspecific protective mechanisms of the innate immune system.

- Cues from the innate immune system inform the cells of the adaptive immune system as to whether it is appropriate to make a response and what type of response to make.

### Major Principles of Immunity (immune response):

- Cells of the adaptive immune system display exquisitely specific recognition of foreign antigens and mobilize potent

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mechanisms for elimination of microbes bearing such antigens. The immune system displays memory of its previous responses.

- Tolerance of self-antigens.

Cells of the Immune System

- Lymphocytes – occupy the central stage; determines the specificity of immunity
- Dendritic cells (DCs) & Langerhan cells
- Monocyte/macrophages
- Natural killer (NK) cells
- Neutrophils
- Mast cells & Basophils
- Eosinophils
- Epithelial and stromal cells – provides anatomic environment (secretion of critical factors that regulate migration, growth and homeostasis)

Lymphoid Tissues and Organs

Primary Lymphoid Organs Sites where pre-B and pre-T lymphocytes mature into naive T and B cells in the absence of foreign antigen;

- Fetal Liver, Adult bone marrow, and thymus

The INNATE IMMUNE SYTEM INNATE IMMUNE SYSTEM

- relies on germ line-encoded receptors to detect a limited set of microbial structures that are uniquely associated with microbial infection
- not a function of a single defined physiologic system; rather, it is a product of multiple and diverse defense mechanisms

Modules of the Innate Immune System

- Surface epithelium

The phagocyte system - critical for the defense against both intracellular and extracellular bacteria as well as fungal pathogens; aided by opsonins

- Acute phase response and complement - variety of secreted proteins that function in the circulation and in tissue fluids; secreted by the hepatocytes in response to the inflammatory cytokines IL1 and IL-6

Modules of the Innate Immune System

- Natural killer (NK) cells are specialized in the elimination of infected host cells and in aiding defense against viral and other intracellular infections through production of cytokines (IFN- $\gamma$  ; regulated by type I interferons (IFN- $\alpha$  /  $\beta$  )
- Mast cells, eosinophils, and basophils are specialized in defense against multicellular parasites, such as helminthes; regulated by several cytokines,

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including IL-4, IL-5, IL-9, and IL-13 Strategies of Innate Immune Recognition

1. Recognition of microbial nonself - referred to as pattern recognition, based on the recognition of molecular structures that are unique to microorganisms and not produced by the host 2.

Recognition of missing self - based on the recognition of molecules expressed only on normal, uninfected cells of the host Targets of Innate

Immune Recognition • PAMPs (pathogen-associated molecular patterns) - molecular structures produced by microbial pathogens, but not by the host organism • PRRs (pattern recognition receptors) - receptors of the innate

immune system and represents targets of the innate immune system

Targets of Innate Immune Recognition Examples of PAMPs include: (1) LPS of

gram-negative bacteria (2) LTA of gram-positive bacteria (3) Peptidoglycans

(4) Lipoproteins of bacteria (cell wall) (5) Lipoarabinomannan of

mycobacteria (6) dsRNA produced by virus during the infection cycle (7) ? -

glucans and mannans found in fungal cell wall Receptors of the Innate

Immune System • Broad categories of PRRs: (1) PRRs that signal the

presence of infection; expressed on the cell surface or intracellularly

Categories of gene products: a. proteins and peptides that have direct

antimicrobial effector functions (antimicrobial peptides and lysozyme) b.

inflammatory cytokines and chemokines (TNF, IL-1, IL-8) c. gene products

that control activation of the adaptive immune response (MHC, CD80/CD86,

IL-12) Receptors of the Innate Immune System • Broad categories of PRRs:

(2) Phagocytic (or endocytic) PRRs; expressed on the surface of

macrophages, neutrophils, and dendritic cells(DCs) (3) Secreted PRRs

(mannan-binding lectin and peptidoglycan-recognition proteins Function: a.

activate complement b. opsonize microbial cells to facilitate their phagocytosis c. accessory proteins for PAMP recognition by transmembrane receptors (TLR) Receptors of the Innate Immune System • Toll-like Receptors – comprise a family of type 1 transmembrane receptors characterized by leucine rich repeats (LRRs) in the extracellular portion and an intracellular TIR (Toll/IL-1 receptor) domain; grouped into two classes: (1) TLRs 1, 2, 4, 5, and 6 are expressed on the plasma membrane and detect bacterial and fungal cell wall components; (2) TLRs 3, 7, and 9 are expressed in endosomal compartments and recognize viral nucleic acids

Toll-like receptor 4 (TLR4) • expressed predominantly in the cells of the immune system, including macrophages, DC, neutrophils, mast cells, and B cells • also expressed on endothelial cells, fibroblasts, surface epithelial cells, and muscle cell • Signal transducing receptor for LPS, heat sensitive protein associated with the cell walls of MTB • Together with CD14 shown to mediate responsiveness to the fusion (F) protein of RSV

Toll-like receptor 2 (TLR2) • Involved in recognition of LTA and peptidoglycan from gram-positive bacteria, bacterial lipoproteins, mycoplasma lipoprotein, mycobacterial lipoarabinomannan, a phenol-soluble modulin from *S. epidermidis*, zymosan of yeast cell walls, and lipoglycosylphosphatidylinositol T. cruzi • Also shown to recognize two kinds of atypical LPS: *L. interrogans* and *Porphyromonas gingivitis* Toll-like receptor 3 (TLR3) Receptor for dsRNA • Can mediate responses to poly(IC) • Expressed on DCs, macrophages, and surface epithelial cells, including intestinal epithelium • Also expressed in CD8+ DCs Toll-like receptor 7 (TLR7) • Involved in viral recognition and both detect nucleic acids together with TLR9 • Recognizes viral ssRNA (derived

from RNA viruses); TLR9 (unmethylated DNA derived from DNA viruses) • Expressed primarily on plasmacytoid dendritic cells • Activated by small antiviral compounds, e. g. imiquinoid •

TLR7-mediated recognition takes place inside the late lysosomes Toll-like receptor 9 (TLR9) • Involved in the antiviral host defense; especially on recognition of DNA viruses (HSV) • Expressed in type-I INF-producing plasmacytoid DCs Phagocytic Receptors • Scavenger receptors – cell-surface glycoproteins that are defined by their ability to bind to modified LDL • Macrophage Mannose Receptor (MR) – type I transmembrane protein expressed primarily in macrophages; involved in phagocytosis of bacterial (MTB, *P. aeruginosa*, *K. pneumoniae*), fungal (*S. cerevisiae*, *C. albicans*), and protozoan pathogens (*P. carinii*) Cells of the Innate Immune System • Macrophages – most central and essential functions and have multiple roles in host defense (e. i. “housekeeping functions”); in red pulp of the spleen, it phagocytose and remove from circulation senescent RBCs • Neutrophils • Mast Cells – best known effectors of allergic response; protective role is by rapid production of TNF- $\alpha$  and leukotriene B<sub>4</sub> (neutrophil recruitment) Cells of the Innate Immune System • Eosinophils – found primarily in the respiratory, intestinal, and genitourinary tracts; contains cationic effector proteins toxic to parasitic worms; poor phagocytes • Dendritic Cells – immature DCs reside in peripheral tissues and are highly active in macropinocytosis and receptor-mediated endocytosis; expresses PRRs and TLRs; have roles in the initiation of adaptive immune response Cells of the Innate Immune System Surface Epithelium – lines the mucosal surfaces of the intestinal, respiratory, and genitourinary tracts provide an important physical barrier The Effector

Mechanisms of the Innate Immune System The Major Categories of Antimicrobial Effector Enzymes that hydrolyze components of microbial cell walls Antimicrobial proteins and peptides that disrupt the integrity of microbial cell walls • Lysozyme • Chitinases • Phospholipase A2 • • • • BPI Defensins Cathelicidins Complement Eosinophil cationic protein Microbicidal serine proteases

Proteins that sequester iron and zinc Enzymes that generate toxic oxygen and nitrogen derivatives • Sepsocidins • Lactoferrin • NRAMP • calprotectin • Phagocytic oxidase • Nitric oxide synthase • myeloperoxidase The Effector Mechanisms of the Innate Immune System • Lysozyme - a. k. a. muramidase; degrades the peptidoglycan of some gram(+) bacteria; highly concentrated in secretions such as tears and saliva • Chitinases - enzymes that degrade chitin; secreted by activated macrophages and presumably play a role in antifungal defense

The Effector Mechanisms of the Innate Immune System • Defensins - cationic peptides with a broad spectrum of antimicrobial activities against gram(+) and gram(-) bacteria, fungi, parasites, and some envelope viruses; kill microorganisms by forming pores in the membranes; divided into ? - and ? defensins • ? -defensins - presynthesized and stored in granules of neutrophils and Paneth cells of the small intestine • ? -defensins - produced by epithelial cells and not stored in cytoplasmic granules

The Effector Mechanisms of the Innate Immune System • Cathelicidins - active against gram(+) and gram(-) bacteria and fungi; produced in neutrophils and stored as inactive proproteins in the secondary granules • Serprocedins - comprise a family of cationic serine proteases with

antimicrobial activity (neutrophil elastase, proteinase 3, cathepsin G, and azurocidin); exert its antimicrobial activity by either perturbation of microbial membranes or by proteolysis

The Effector Mechanisms of the Innate Immune System • Lactoferrin, NRAMP, and Calprotectin - antimicrobial activities are due to the ability to sequester iron and zinc • Lactoferrin - found in the secondary granules of neutrophils, in epithelial secretions (e. i. breast milk), in the intestinal epithelium of infants, and in airway fluids; bacteriostatic (iron sequestration) and bacteriocidal (perturbation of microbial membranes) The Effector Mechanisms of the Innate Immune System NRAMP (natural resistance-associated macrophage protein) - integral membrane protein that functions as an ion pump in the phagocytic vacuoles of macrophage and neutrophils • Calprotectin - member of the family of calciumbinding proteins; microbial activity is by chelation and sequestration of zinc ion ACUTE PHASE REACTANTS • Soluble factors which are normal constituents that increase or decrease rapidly as produ • Not a function of a single defined physiologic system; rather, it is a product of multiple and diverse defense mechanisms