Immunity; adaptive and innate immunity

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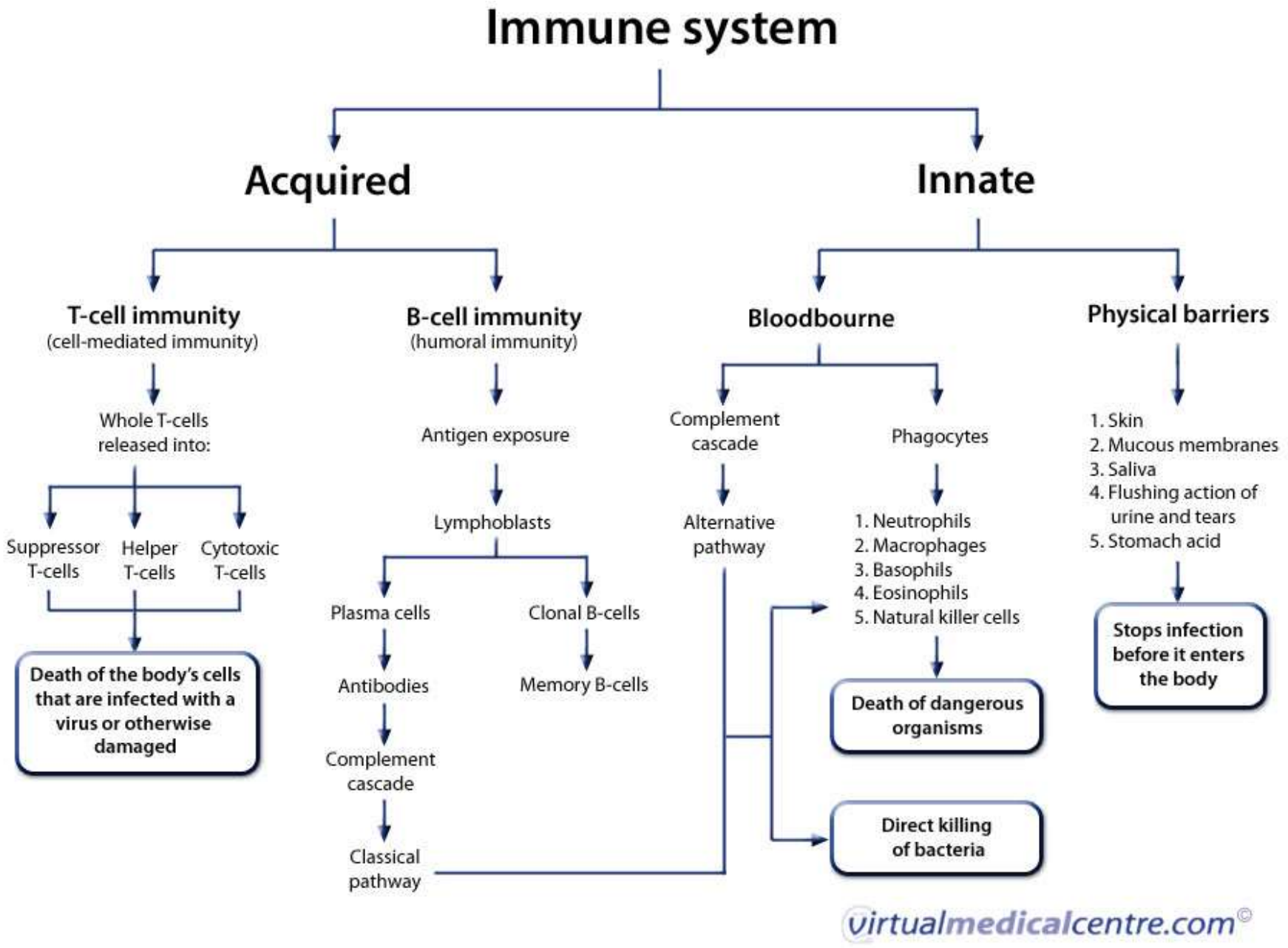
History

- Immunity: protection from infectious microbes or foreign macromolecules; proteins and polysaccharides
- Immune system constitutes of cells, tissues and small molecules
- The first application in immunology is done by edward jenner's vaccination against smallpox when he injected parts of cowpox microbe into small boy who is later became resistant to smallpox disease in 1798 (vaccine)

- This was crowned in 1980 when the WHO announce the smallpox have been eradicated worldwide.


Immune system
Acquired
Innate
T-cell immunity
(cell-mediated immunity)
B-cell immunity
(humoral immunity)
Bloodbourne
Physical barriers
Whole T-cells released into:
Antigen exposure
Complement cascade
Phagocytes
1. Skin
2. Mucous membranes
3. Saliva
4. Flushing action of urine and tears
5. Stomach acid
Suppressor T-cells
Helper T-cells
Cytotoxic T-cells
Lymphoblasts
Alternative pathway
1. Neutrophils
2. Macrophages
3. Basophils
4. Eosinophils
5. Natural killer cells
Plasma cells
Clonal B-cells
Stops infection before it enters the body
Death of the body's cells that are infected with a virus or otherwise damaged
Antibodies
Memory B-cells
Death of dangerous organisms
Complement cascade
Direct killing of bacteria
Classical pathway
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- The innate immune system (the first to act;),
  - barriers , Mechanical; skin, Chemical; acidic stomach,
  - Enzymes and anti-microbial peptides as defensins and surfactants
  - (Complements and cells) Cells are macrophages, neutrophils, basophils and eosinophils.
  - The complement system, also known as complement cascade, small proteins that are synthesized by the liver, and circulate in the blood as inactive precursors stimulated by one of several triggers, as microbes. It is a part of the immune system that enhances (complements) the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promote inflammation, and attack the pathogen's cell membrane present and act the same in all people against general antigens (not specific).
  - it is monotonic; the same magnitude and speed of response each time,
  - not specific, act against common microbial antigens..

- The second is adaptive immune system (T and B cells),
  - it is specific act against certain antigen,
  - increasing in magnitude and speed of response in re-exposure to the same antigen (memory)

Innate immunity

- Innate immunity is the initial response to microbes that
- Prevents, controls, or eliminates infection,
- Eliminate damaged cells
- Initiate the process of tissue repair.
- Innate immunity stimulates adaptive immune responses
- Innate immune system is started by inflammation in local tissue, innate cells activation, complements activation and production of cytokines.

Innate and Adaptive

- Innate immune response is better than adaptive in recognizing self from non-self.
- Innate immune responses to a foreign microbe are immediate and do not require prior exposure to the microbe
- Effective adaptive immune responses to a newly introduced microbe develop over several days as T and B lymphocytes are activated by some activated innate cells and they undergo expansion and differentiate into functional effector Th and Tc cells and antibody producing B cells.

IMMUNE SYSTEM

INNATE IMMUNE RESPONSE

* CELLS ARE NON-SPECIFIC
* RESPONSE = FAST
  (MINUTES - HOURS)
* NO MEMORY
  (ALWAYS THE SAME RESPONSE)

ADAPTIVE IMMUNE RESPONSE

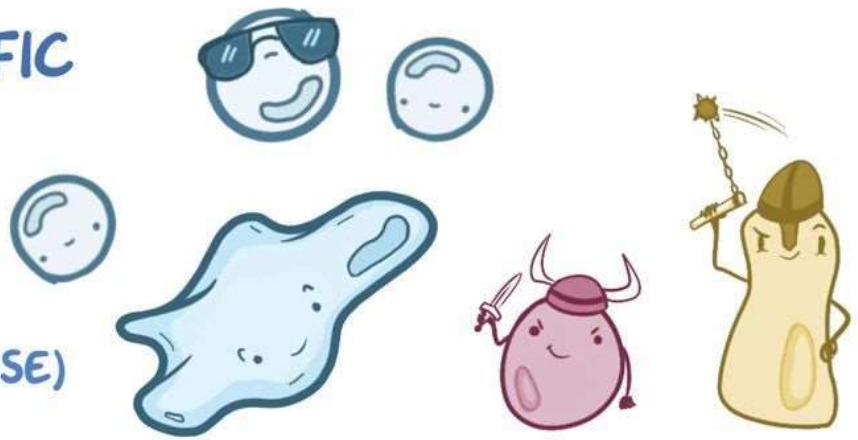


TABLE 1-3 Comparison of adaptive and innate immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse, improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response

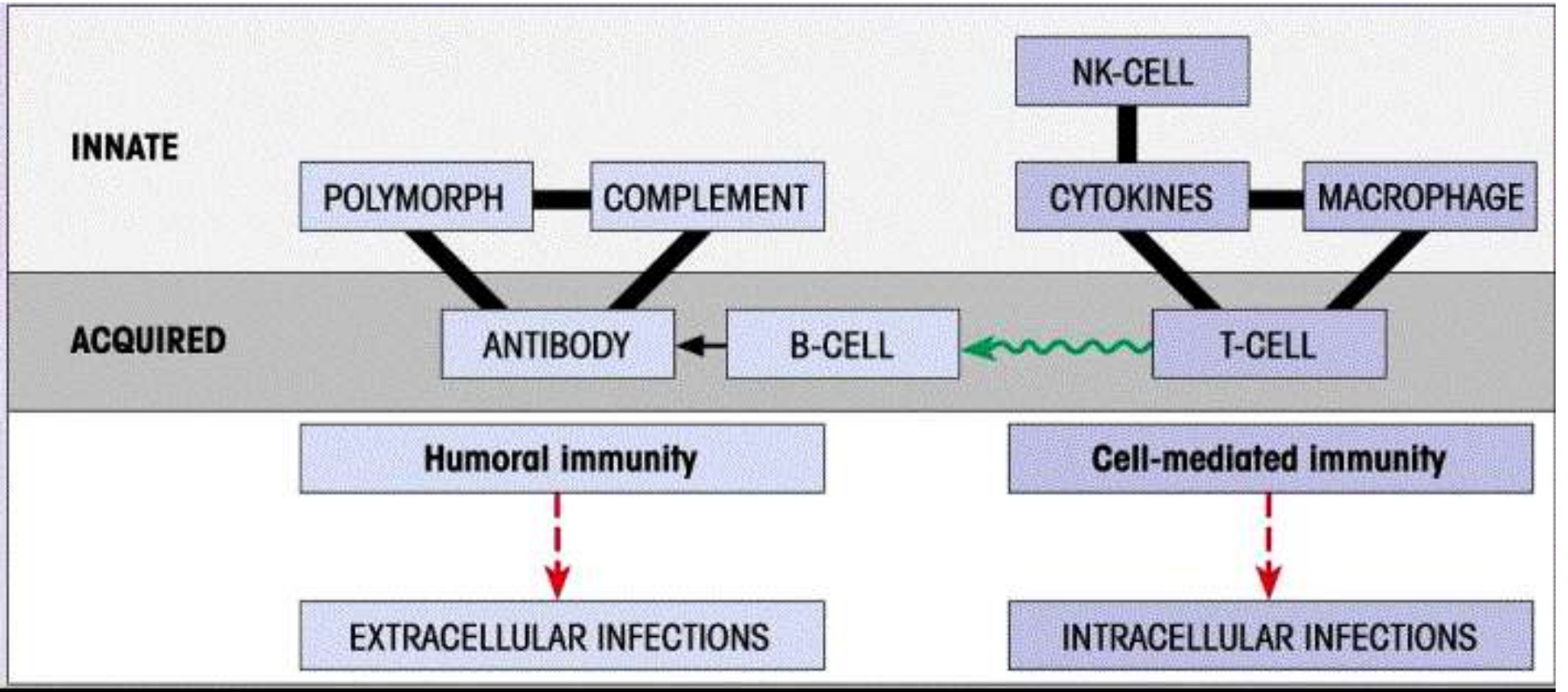
Antigen and immunogen

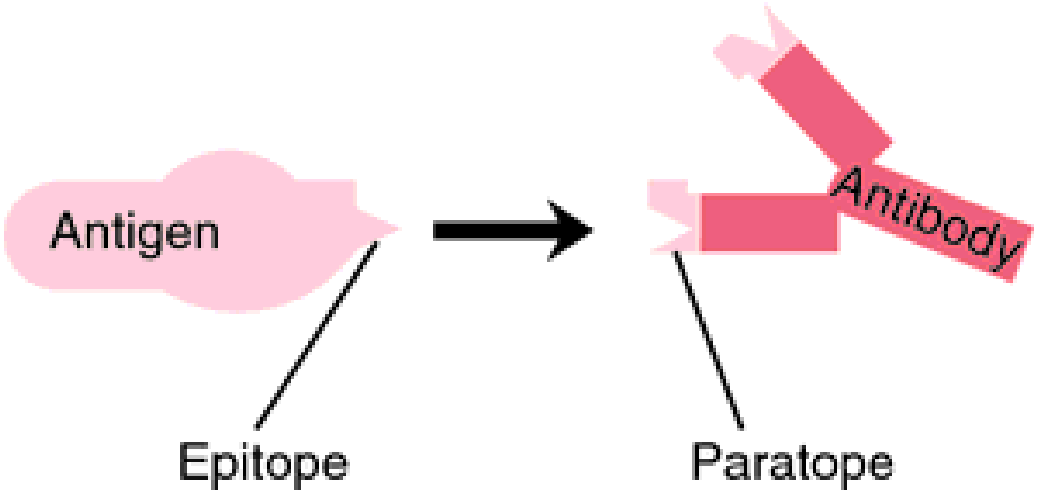
- Any particle (organism, molecule or part of molecule) that is recognized by the immune system called antigen
- Antigen that does not stimulate the immune response called (hapten, tolerogen)
- Antigen that stimulate the immune response called (immunigen)
- Each antigen contain one or more regions that are specific for binding to adaptive immune components (T and B cells and antibodies); called epitopes
- Epitopes are the smallest part of an antigen that is seen by antigen receptors on adaptive immune cells, or antibodies.

Haptens

- Very low molecular weight antigen need to conjugate to a carrier protein to induce the immune response, then the immune response will direct against both the carrier and the hapten
- Examples

1. Drugs as penicillin
2. Food additives, lipids, nucleic acids, small peptides and carbohydrates




Antigen
Antibody
Epitope
Paratope

Factors increase the antigenicity

1. More Foreignness more response
2. More Chemical complexity

Proteins are most potent, polysaccarides are both antigenic or non antigenic whereas nucleic acids and lipids are non antigenic but can be antigenic when bind protein carriers

3. High molecular weight antigen, whereas hapten have very low molecular weight
4. Higher Biodegradable
5. Mode of contact more response in Intra venous than subcutaneous or Intramuscular injections.
6. More different Host genetics like HLA type in organ transplant

Types of antigens

- Auto-antigen
- Iso-antigen; found in genetically identical twins, like HLA antigens
- Allo-antigens; found in members of the same species; blood groups in human
- Xeno-antigen; found in different species like animals and human

Receptors

- Are the key parts in activating innate and adaptive immune cells
- The receptors on the surface of the innate immune cells are fixed in all human being and encoded by inherited (germline) genes present from early life
- Whereas the genes encoding receptors of adaptive immune cells are variable and generated by a process called somatic recombination in response to specific antigen the lymphocytes throughout the life
- In Innate cells the receptors are present in nature, and are less in number (10^3) and less variety than adaptive cells receptors

Phases of innate immune cells response

- Antigen enter tissue cause **inflammation** which activate the local innate cells (mast cells, macrophages)
- Movement of the cells from all body toward the site of infection called **chemotaxis**, and mediated by molecules secreted from local innate cells.
- **Functional activities** of the immune cells
  - Recognition of the foreign antigen through cell receptors
  - Response
    - Effector or activated cells
    - Memory (only in adaptive response)

Inflammation

- Inflammation is the process by which local macrophages and Mast cells secret mediators (cytokines) or local complement activated and then help in chemotaxis of other innate cells and increase vascular permeability
- produced signals (cytokines and complements) recruit circulating immune cells to sites of infection in the tissues and are activated to destroy and eliminate the offending agents.
- Inflammation is also the major reaction to damaged or dead cells and to accumulations of abnormal substances in cells and tissues.
- It is the major way by which the innate immune system deals with infections and tissue injury

Changes in inflammation

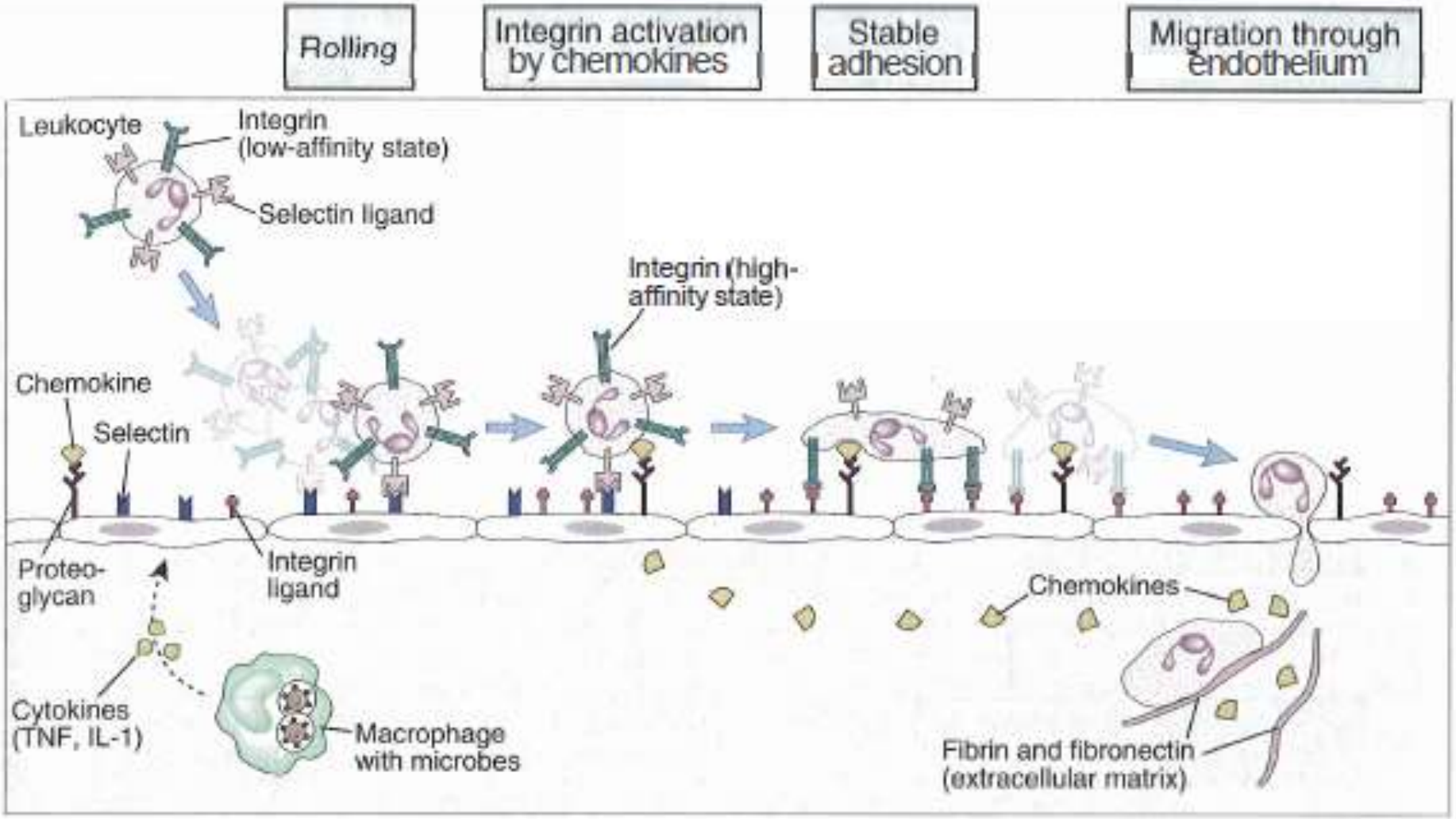
A. Increased blood supply to the area
B. expression of endothelial adhesion molecules on blood vessel lining
C. Increase capillary permeability
D. Activation of local innate cells to secret chemotactic factors that recruit leukocytes,

inflammation

- Signs of inflammation
  1. Swelling
  2. Pain
  3. Redness
  4. Loss of function
  5. Heat

Cell chemotaxis

- Recruitment of phagocytes to site of infection
  - Follow chemotactic factors gradient(cytokines) produced by resident macrophages and (complements) activated by peptides of bacteria, they migrate by
    - Capture and rolling; enhance adhesion molecules on both endothelial and innate immune cells
    - enhance the strength of binding of interacting molecules on both endothelium and leucocytes that make the leukocyte flatten
    - Extravasation to site of infection. First neutrophils then macrophages. activated T cells migrate in the same way


Rolling
Integrin activation by chemokines
Stable adhesion
Migration through endothelium
Leukocyte
Integrin (low-affinity state)
Selectin ligand
Integrin (high-affinity state)
Chemokine
Selectin
Proteo-glycan
Integrin ligand
Chemokines
Cytokines (TNF, IL-1)
Macrophage with microbes
Fibrin and fibronectin (extracellular matrix)

Receptors of innate immune cells

- Via Pattern recognition receptors (PRR).
  - They are proteins expressed by cells of the innate immune system to identify pathogen-associated molecular patterns (PAMPs), which are associated with microbial pathogens or cellular stress, as well as damage-associated molecular patterns (DAMPs), which are associated with cell components released during cell damage
  - PAMP is general conserved microbial molecules as sugar, protein, lipid and nucleic acids.
  - -The innate immune system also recognizes endogenous molecules that are produced by or released from damaged and dying cells. These substances are called damage-associated molecular patterns (DAMPs)
  - the receptors are similar in all humans,
  - And bind to the target :

1. directly through cell surface receptors binding to the antigen
2. indirectly by binding to soluble molecules that engage the microbe(opsonins as complements)

Types of receptors of innate immune cells (PRR)

PRR are 3 types

1. Toll like receptors (TLR), binding results; signaling; phagocyte activation and secretion of immune mediators called cytokines
2. Scavenger receptors they help in internalization of bacteria in the phagocytic cells

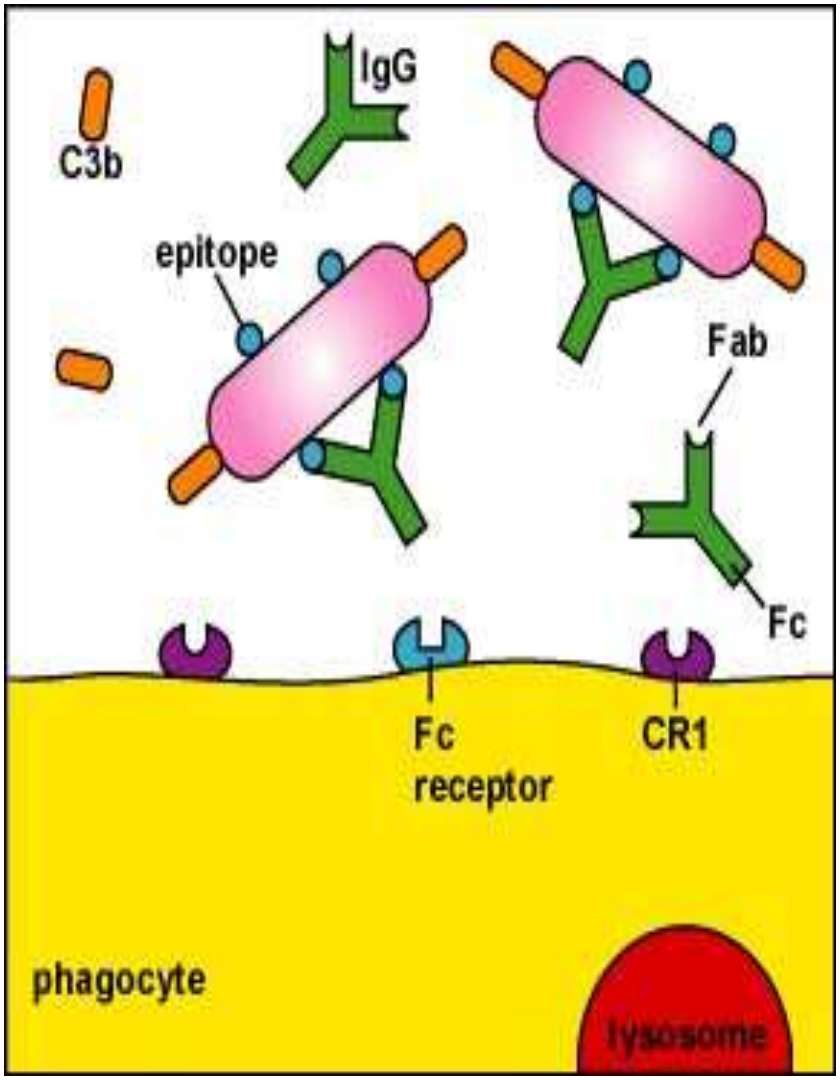
Types of receptors of innate immune cells (PRR)

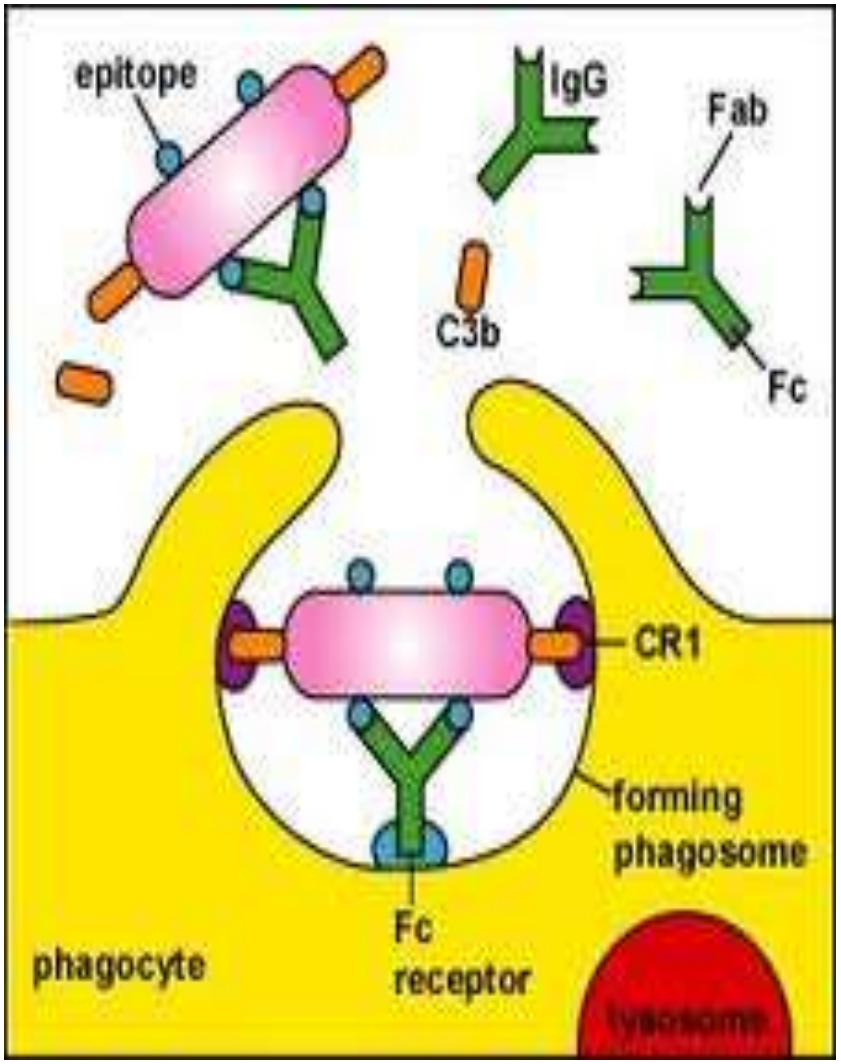
3. opsonin receptors, indirect binding to microbe (Opsonization of microbe :coating the microbe to make it obvious)

- Act indirectly by binding to soluble molecules that engage the microbe The result is microbe internalization to the cell.

1. complements receptors as receptors of C4b, C3b and C3bi
2. or antibodies receptors. using IGG or IGM. 2 types
    1. Direct opsonization by IGG, IGA on microbe
    2. Indirect opsonization by IGM + complement (IGM binds complement on microbe)

Opsonins


IgG
C3b
epitope
Fab
Fc
Fc
receptor
CR1
phagocyte
lysosome


epitope
IgG
Fab
C3b
Fc
CR1
forming
phagosome
Fc
receptor
phagocyte
lysosome

Innate immune cells

A. **phagocytic cells**
   - **Neutrophil polymorphs, main**
   - **Mononuclear phagocytes,**
   - **Dendritic cells**: macrophage origin and some are lymphoid origin

B. **Non phagocytic cells; Extracellular killing**
   - **Eosinophils and basophils**
   - **Natural killer cells,**

Functions of macrophages

1. **Phagocytosis of foreign particles the same as neutrophils**
   - **Scavenger receptors**
   - opsonin dependant phagocytosis; engulf antigen antibody complex as in viruses via **receptor for opsonizing IgG and complement C3b, No receptors for IGM**

2. **Secretion of enzymes and oxidative metabolites if antigen is big, cause tissue damage**
   (respiratory burst- oxygen radicals, NO, prostaglandins)

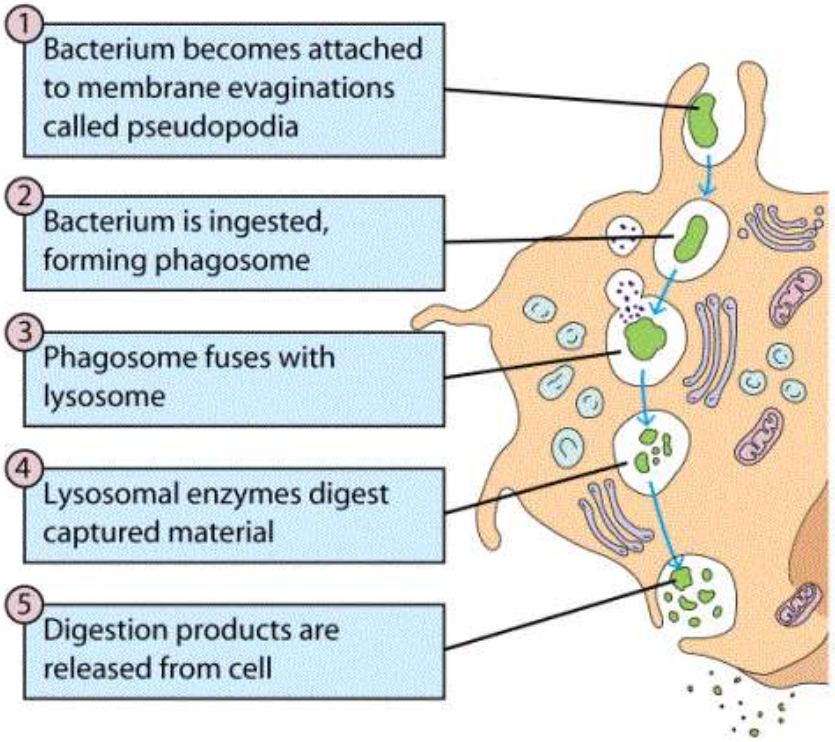
3. **Cytokine production which recruit other** inflammatory cells, as neutrophils

4. **Antigen-Presentation to T cells,**

phagocytosis (macrophages and neutrophils)

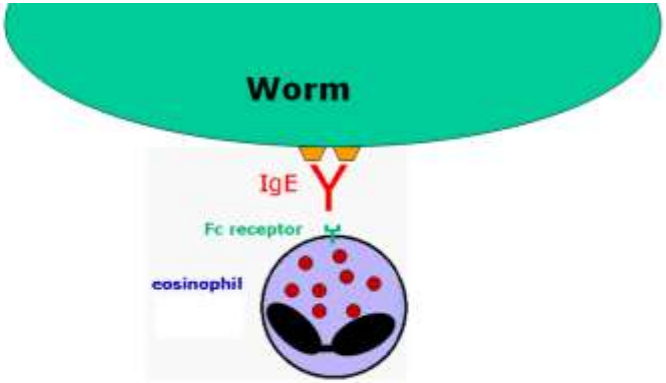
- Intracellular killing, mechanisms of lysosomal killing
  - O2 dependent; the process called respiratory burst. O2 metabolites are; hydrogen peroxide, singlet oxygen, hydroxyl radica, hypohalite (Ocl or OI) and nitric oxide
  - O2 independent; using granules contents as proteases, hydrolases and nucleases

phagocytosis



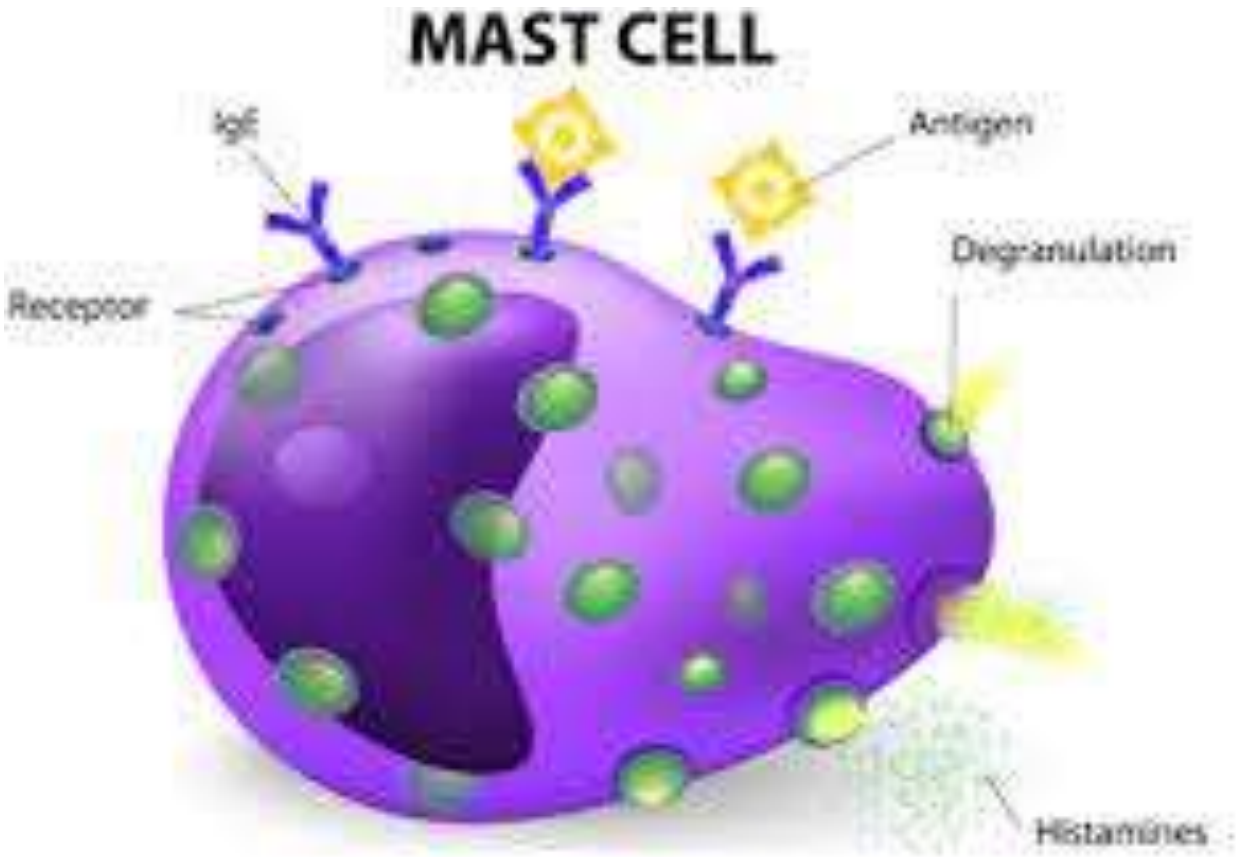
EOSINOPHILS

- Eosinophils kill extracellularly
- 2 functions
  - When eosinophils bind to IgE on the surface of a worm, the cell is triggered to degranulate. The contents of the granules cause damage to the worm.
  - Other function is in allergy.


Worm
IgE
Fc receptor
eosinophil

Basophils and mast cells

- 2 types of mast cells
  - Connective tissue
  - Mucosal mast cells, act in allergy and is T cell dependent to degranulat and produce histamine.
- Mast cells degranulation and release of the mediators the acidic granules, which help in Inflammatory cell response, allergy.
- 2 receptors on mast cells that mediate degranulation
  - High affinity IGE receptor. IGE dependent;
  - Receptors for anaphylatoxins. C3a and C5a. IGE in-dependent;


MAST CELL
IgE
Antigen
Degranulation
Receptor
Histamines

NK cells

- are a type of lymphocyte critical to the innate immune system. are defined as large granular lymphocytes (LGL) and constitute the third kind of cells differentiated from the common lymphoid progenitor-generating B and T lymphocytes.
- 10 % of mononuclear cells in blood and spleen and rare in lymphoid organs

NK

- Act very early against **viruses and intracellular microbes and tumor cells** or altered expression of surface MHC 1 molecule until T cells become activated.
- There activity increase by IFN alpha and beta (secreted by virally infected cells).
- activated cells secrete IFN gamma

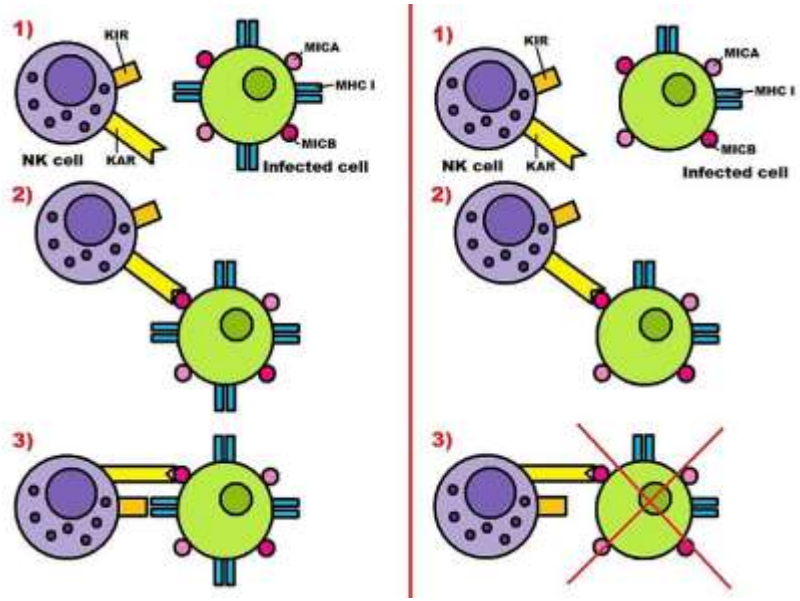
NK receptors

1. Killer inhibition receptors (KIR) of NK cells (most important), used to detect the presence of MHC 1 protein on host cells any binding means inhibition of killing
2. Killer activation receptors (KAR) of NK cells detect alteration in host cells as cancers. recognize stress related molecules as MICA, MICB

Other receptors:

1. Opsonin receptors for antibodies; and kill these opsonin- coated cells, this is called antibody dependent cell mediated cyto-toxicity (ADCC)

2. Expression fas ligands that bind fas on target cells and activation of caspases and cell apoptosis, this is a way in killing activated T cell (activation induced cell death)

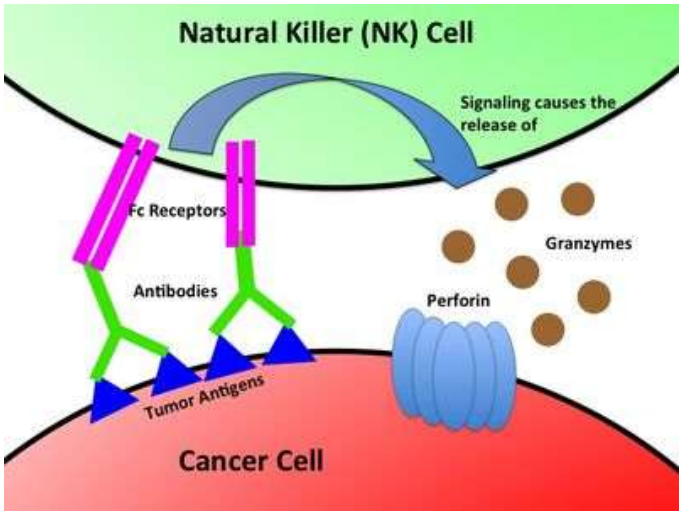


When a KAR binds to MICA and MICB molecules on the surface of an infected cell (or a tumor cell), a KIR examines the levels of MHC class I of this target cell. If the MHC class I levels are enough, killing of the cell doesn't proceed (left), but if they aren't, the killing signal proceeds and the cell is eliminated

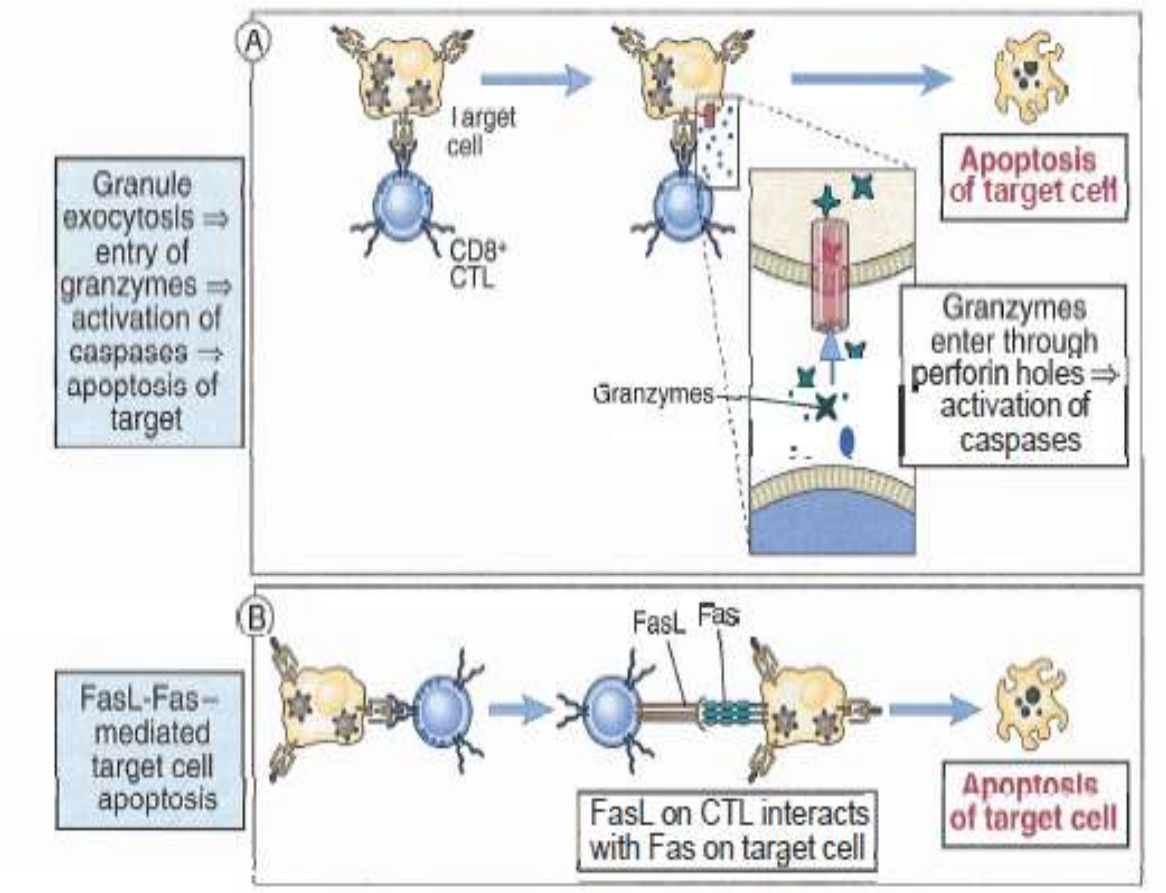
NK ways of killing

- Effecter functions of NK cells
  - Direct extracellular killing by secretion
    - Perforins and granzymes; perforins make pores then osmotic lysis. Granzymes, enzymes enter through perforin pores and activate caspases leading to cell death
    - FAS-FASL binding with target cell leads to direct cell apoptosis by activation the caspases
  - Indirect killing . increase macrophage phagocytosis and killing of microbe by secreting IFN gamma

Direct killing by NK cells



NK killing


A
Target cell
CD8+ CTL
Granule exocytosis ⇒ entry of granzymes ⇒ activation of caspases ⇒ apoptosis of target
Apoptosis of target cell
Granzymes enter through perforin holes ⇒ activation of caspases
Granzymes
B
FasL
Fas
FasL-Fas–mediated target cell apoptosis
FasL on CTL interacts with Fas on target cell
Apoptosis of target cell

- The link between innate and adaptive immunity

1. The innate stimulate the adaptive (macrophage secret IL-12 and/ or IL-4 that activate T cells. C3d complement activate B cell. Antigen presentation to T cell by macrophages.
2. The adaptive immune response use some innate cells to eliminate the antigen (T cells secret IFN gamma that activate macrophages)

Important definitions

- **The immune system** Cells in our bone marrow, thymus, and the lymphatic system of ducts and nodes, spleen, and blood that function to protect us.
- **Antigen** Anything causing an immune response, usually foreign material but may be our own tissues.
- **Pathogen** Any disease causing micro-organism.
- **Tolerance** Non-reactivity of the immune system, usually refers to "self" but may include foreign tissue in organ transplants.
- **Autoimmunity** A failure of tolerance, the immune system reacts to self.
- **Chemokines** Molecules released by pathogens and infected tissues to attract cells of the immune system.
- **Cytokines** Signaling molecules released by one cell to cause a response in another. Signaling is extremely important in our immune response.
- **Innate immunity** Protection that is always present. Includes phagocytic (cells that eat other cells) macrophages and dendritic cells.
- **Adaptive immunity** Protection that arises by an immune response, including humoral immunity producing antibodies and cellular immunity.

TABLE 1-1 Nobel Prizes for immunologic research

Year	Recipient	Country	Research
1901	Emil von Behring	Germany	Serum antitoxins
1905	Robert Koch	Germany	Cellular immunity to tuberculosis
1908	Elie Metchnikoff Paul Ehrlich	Russia Germany	Role of phagocytosis (Metchnikoff) and antitoxins (Ehrlich) in immunity
1913	Charles Richet	France	Anaphylaxis
1919	Jules Border	Belgium	Complement-mediated bacteriolysis
1930	Karl Landsteiner	United States	Discovery of human blood groups
1951	Max Theiler	South Africa	Development of yellow fever vaccine
1957	Daniel Bovet	Switzerland	Antihistamines
1960	F. Macfarlane Burnet Peter Medawar	Australia Great Britain	Discovery of acquired immunological tolerance
1972	Rodney R. Porter Gerald M. Edelman	Great Britain United States	Chemical structure of antibodies
1977	Rosalyn R. Yalow	United States	Development of radioimmunoassay
1980	George Snell Jean Dausset Baruj Benacerraf	United States France United States	Major histocompatibility complex
1984	Cesar Milstein Georges E. Köhler	Great Britain Germany	Monoclonal antibody
	Niels K. Jerne	Denmark	Immune regulatory theories
1987	Susumu Tonegawa	Japan	Gene rearrangement in antibody production
1991	E. Donnall Thomas Joseph Murray	United States United States	Transplantation immunology
1996	Peter C. Doherty Rolf M. Zinkernagel	Australia Switzerland	Role of major histocompatibility complex in antigen recognition by by T cells