Lecturer : ***Karama T.Al-Taee*** ***six lecture for third year***

MSc. Medical microbiology

The immune system and the oral cavity

Immunology is the branch of biology concerned with the body defense

There are two kind of immunological defense:

1- Natural or innate immunity comprising mainly pre-existing antigen –non specific defenses.

2-Adaptive or acquired immunity ,during which the immune system responds in an antigen –specific manner to neutralize the threat efficiency and retains a memory of the threat so that any future encounter with the same threat will result in an accelerated and heightened protective response .

During its development the immune system must be educated specifically to avoid reacting against all normal components of the body (tolerance). Immunology can be considered, the science of self-non –self discrimination.

The vital importance of the immune system is evident in the life threatening infections suffered by patients with immune defects (immunodeficiency) .Deficiencies of immune-regulation may be the root causes of hypersensitivity diseases such as autoimmunity and allergy .

1- The innate immunity system:-

These intrinsic mechanisms are present at birth prior to exposure to pathogens or pathogenic macromolecules .They are not enhanced such exposures and are not specific to a particular pathogens.

1-Mechanical and chemical barriers

Intact skin is usually impenetrable to microorganisms. Membranous linings of the body tracts are protected by mucus, acid secretions and enzymes such as lysozyme, which breaks down bacterial cell wall proteoglycan . In the lower respiratory tract mucous membrane is cover by hair -like protrusions of the epithelial cell membrane called cilia. The movement of cilia can propel mucus-entrapped microorganism from the tract(mucociliary escalator) .Although most pathogens enter the body by binding to and penetrating mucous membranes several defense mechanisms including saliva tears and mucous secretions are involved in

preventing this entry .A part from acting to wash away potential invaders these secretions also contain antibacterial or antiviral substances .

Defensins and Cathelicidins

Defensins and cathelidins are

_Two major families of mammalian antimicrobial proteins .They contribute to host innate antimicrobial defenses by disrupting the integrity of the bacterial cell membrane .

_Defensins and cathelidins have chemotactic effects on host cells mobilize the phagocytic leukocyte ,immature dendritic cells and lymphocytes together with their other effects ,such as stimulating interleukin-8 production and mast cell degranulation

In brief upon microbial invasion ,epithelial cells keratinocyte and tissue macrophages are induced to produced beta – Defensins and cathelidins .

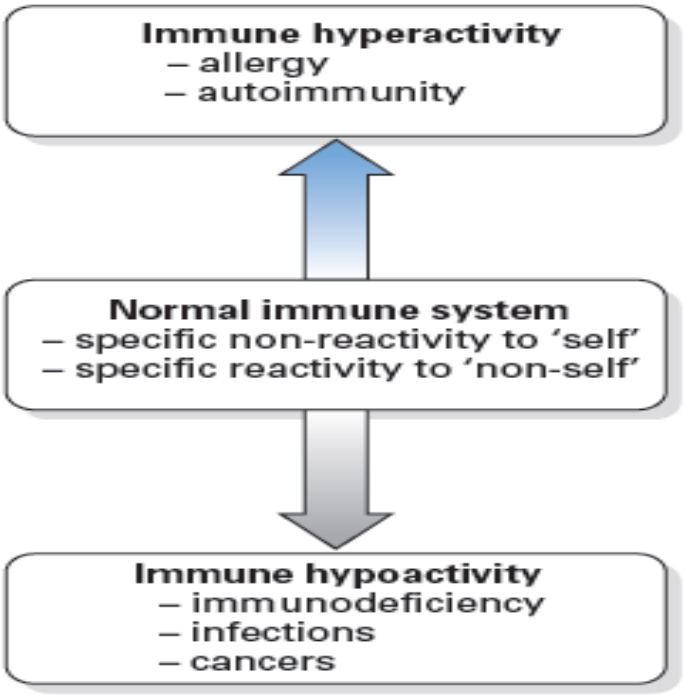

Fig. 8.1 Normal and aberrant immunity.

Table 8.1 Antigen-non-specific defence chemicals in oral secretions

Chemical	Antimicrobial function(s)	Major cell source(s)
Calprotectin	Divalent cation chelator, restricts microbe nutrition	Oral epithelial cells and neutrophils
Defensins (α and β types)	Membrane pore-forming peptides, cause osmotic lysis	Leukocytes and epithelial cells
Cathelicidins	Lysosomal antimicrobial polypeptides	Macrophages and neutrophils
Saliva	Ig, lysozyme, lactoferrin, peroxidases and GCF	Salivary acinar cells
Lysozyme	Muramidase activity, aggregates microbes and amphipathic sequences	Macrophages, epithelial cells and neutrophils
Peroxidase	Oxidizes bacterial enzymes in glycolytic pathways	Salivary acinar cells, neutrophils, eosinophils
His-, Cis- statins	Various effects	Salivary acinar cells
SLPI, PRP	Antiviral activities	Various cell types
GCF	Provides blood components	Various cell types
Mucins	Aggregates bacteria, various effects, homotypic and heterotypic complexes	Salivary acinar cells

SLPI, secretory leukocyte protease inhibitor; PRP, proline-rich proteins; GCF, gingival crevicular fluid; Ig, immunoglobulin.

2-Phagocytosis

Phagocytosis is a process by which phagocytic cells ingest extracellular particular materials including whole pathogenic microorganisms .If the mechanical defenses are breached ,the phagocytic cells become the next barrier .These include polymorph nuclear leukocyte (polymorphs short-lived circulating cells can invade the tissue) and macrophage are the mature ,tissue –resident stage of circulating monocyte .
Macrophage are found in* areas of blood filtration where they are most likely * encountered foreign particles e.g. liver sinusoids kidney mesangium alveoli lymph nods and spleen .* phagocytes attach to microorganisms by non specific cell membrane , threat , receptors after which *pseudopodia extend around the particle and *neutralize in to a phagosome .* Lysosomal vesicles containing proteolytic enzymes

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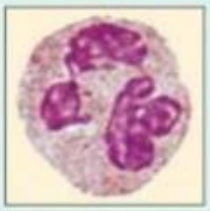
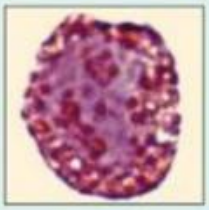
Leukocytes (White Blood Cells)

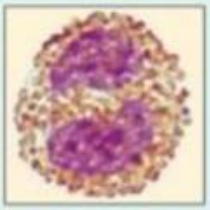
A. Granulocytes (stained)
1. Neutrophils (PMNs) (60–70% of leukocytes)



2. Basophils (0.5–1%)



3. Eosinophils (2–4%)

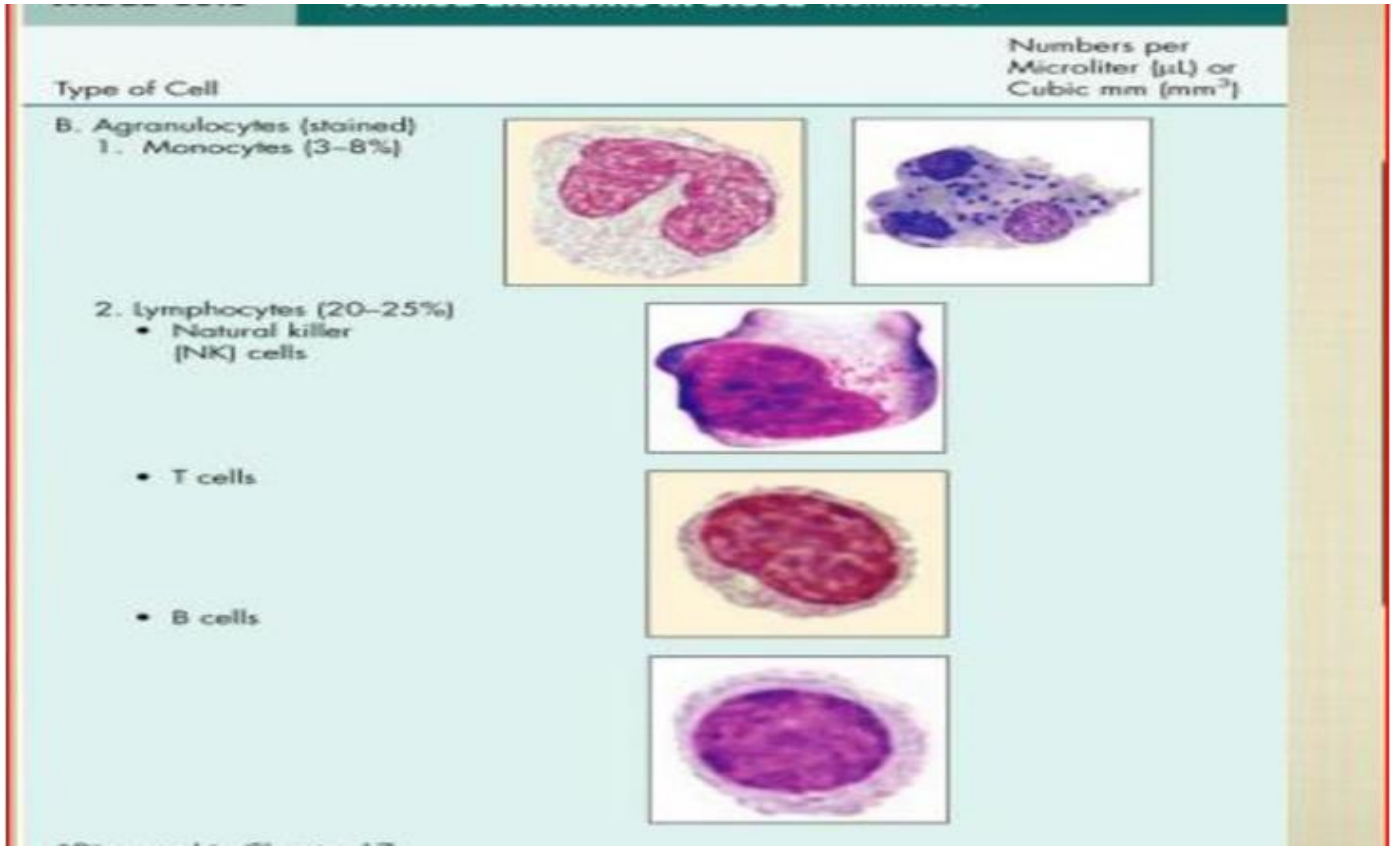


4. Dendritic cells

Differential White Cell Count

Neutrophils	60-70%
Basophils	0.5-1%
Eosinophils	2-4%
Monocytes	3-8%
Lymphocytes	20-25%

1. Neutrophils: Phagocytic
2. Basophils: Produce histamine
3. Eosinophils: Toxic to parasites and some phagocytosis
4. Dendritic cells: Initiate adaptive immune response
5. Monocytes: Phagocytic as mature macrophages
   a. Fixed macrophages in lungs, liver, and bronchi
   b. Wandering macrophages roam tissues
6. Lymphocytes: Involved in specific immunity



Pathogen associated molecular patterns , Patterns recognition receptors and Toll-like receptors

Unlike adaptive immunity ,innate immunity dose not recognize every possible antigen .The cells involved in innate immunity responses like phagocytes (neutrophil ,macrophage, monocyte) and cells that release inflammatory mediators (basophil, mast cell and eosinophil) are designed to recognize only a few highly conserved structures present in many different microorganisms. These cells recognize microbial structures called pathogen associated molecular patterns (PAMPs) in order to activate the innate immunity response . PAMPs are molecular component s common to a Varity microorganisms but not found as a part of eukaryotic cells and include :

* Lipopolysaccharide (LPS) from the Gram negative bacteria cell wall .

*peptidoglycan and lipotechoic acid from gram positive bacteria .

*mannose (common in microbial glycolipids and glycoprotein but rare in human).

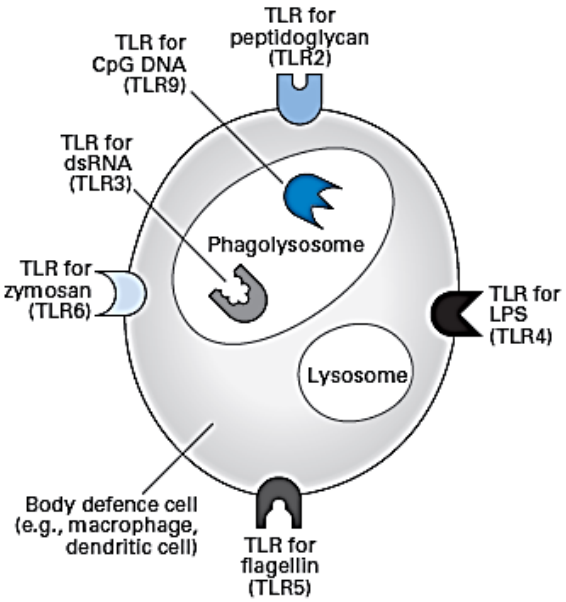


Fig. 8.2 Toll-like receptors (TLRs). LPS, lipopolysaccharide.

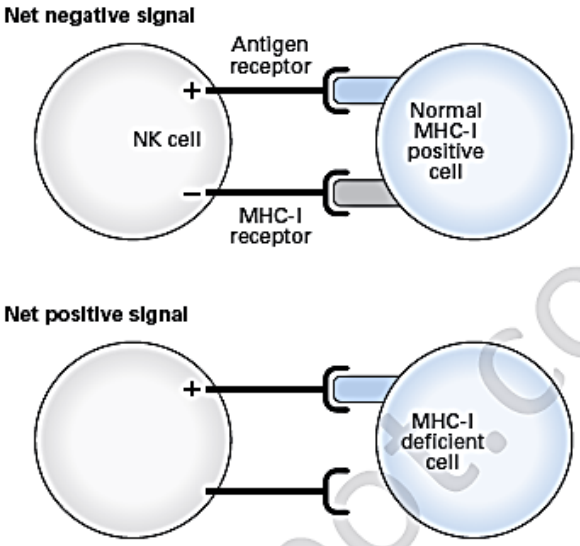


Fig. 8.3 Killing of major histocompatibility complex (MHC) I-deficient cells by natural killer (NK) cells.

*Bacteria DNA .

*N-formyl methionin found in bacterial protein .

*Double strand RNA from virus .

*Glucans from fungal cells wall .

This promotes the attachment of microbes to phagocytes and their subsequent engulfment and destruction. Most defense cells (Macrophages ,dendrites ,endothelial cells ,mucosal epithelial cells ,lymphocytes) have on their surface a variety of receptors called pattern recognition receptors (PRRs) capable of binding specifically to conserved portions of PAMPs so there is an immediate response against invading microbes .These receptors enable phagocytes to attach to microbes so they can be engulfed and destroyed by lysozyme .There are two functionally different classes of PRRs :

- Endocytic PRRs (mannose receptors ,scavenger receptors and opsonin receptors) .

- Signaling PRRs .

Signaling PRRs bind a number of microbial molecules such as flagellin , pilin, glycolipids ,zymosan from fungi and viral double –stranded RNA .A major class of signaling PRRs is Toll-Like Receptors(TLRs) so named because their similarity to the protein coded by Toll gene identified in *Drosophila melanogaster*

Binding of PAMPs to signaling PRRs promotes the synthesis and secretion of regulatory molecules such as cytokines that are crucial to initiating innate immunity .Various types of TLRs bind deferent PAMPs and initiate different types of innate immunity responses .PAMPs can also be recognized by a series of soluble PRRS in the blood that function as opsonins and initiate the complement pathway .

3-Natural killer cells

_ NK cells are a type of cytotoxic non phagocytic lymphocyte critical to the innate immune system .

_15% of blood lymphocyte .

_ NK cells provide rapid responses to viral-infected cells and malignant cells , acting at around 3 days after infection.

_Typically, immune cells detect major histocompatibility complex (MHC) presented on infected cell surfaces, triggering cytokine release, causing lysis or apoptosis. NK cells are unique, they have the ability to **recognize stressed cells in the absence of antibodies** and **MHC**, allowing for a much faster immune reaction. They were named "natural killers" because of the initial notion that they do not require activation to kill cells that are missing "self" markers of MHC class 1. This role is especially important because harmful cells that are missing MHC I markers cannot be detected and destroyed by other immune cells, such as T lymphocyte cells .The killing mechanisms is activated by cytokines released by virues infected cells , tissue cells ,lymphocyte and natural killing cells themselves .The NK cells are also important in the adoptive immune response ,being the effector cells for killing antibodies coated microorganisms .

4-Acute- phases proteins

Acute –phases proteins are serum proteins produced by the liver in response to tissue damaging infections and other inflammatory stimuli such as cytokines (e.g. interleukins -1 and IL-6) .Although the physiological role of the acute phase proteins is not fully understood ,it has been recognized to enhance the efficiency of innate immunity .

Positive acute phase proteins increase in plasma concentration in the acute phase response to inhibit or kill microbes through opsonization , coagulation ,antiprotease activity and /or complement activation .

Negative acute phase proteins including human serum albumin and transferrin are reduce in concentration in the acute phase response and act to limit inflammation .Together acute phase proteins provide immediate defense and enable the body to recognize and react to foreign substance prior to more extensive activation of the immune response .The concentration of the following positive acute phase proteins in body fluids increases rapidly during tissue injury or infection .

***C-reactive protein** functions as soluble PRRs and can bind to bacteria to promote their removal by phagocytosis .It is a major acute phase protein, so named as it bind to the C-polysaccharide cell wall component on a Variety of bacteria and fungi .This binding activate the classical complement system resulting in increased clearance of the pathogen.

***α 1 Antitrypsin** neutralized proteases released by bacteria, activated polymorphonuclear leukocytes or damaged tissue to limit damage caused by excessive enzyme activity .

***Mannose binding protein** functions as a soluble PRR and activate the lectin complement pathway to promote inflammation and attract phagocytes .

5-Interferon

Interferon produced by virus infected cell ,comprises a group of cytokines that mediate innate immunity and includes those that protect against viral infection and those that initiate inflammatory reactions that protect against bacterial pathogens .

Effects of INTERFERON

Activation of endoribonuclease and protein kinase

Destruction of viral mRNA

(Inhibition of protein synthesis (EF-2 phosphorylation

Upregulation of MHC class I

Enhancement of T cytotoxic activity

Activation of Natural Killer (NK) cells

References

-Essential microbiology for Dentistry 4 th edition 2012