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Principles of Innate Immunity√

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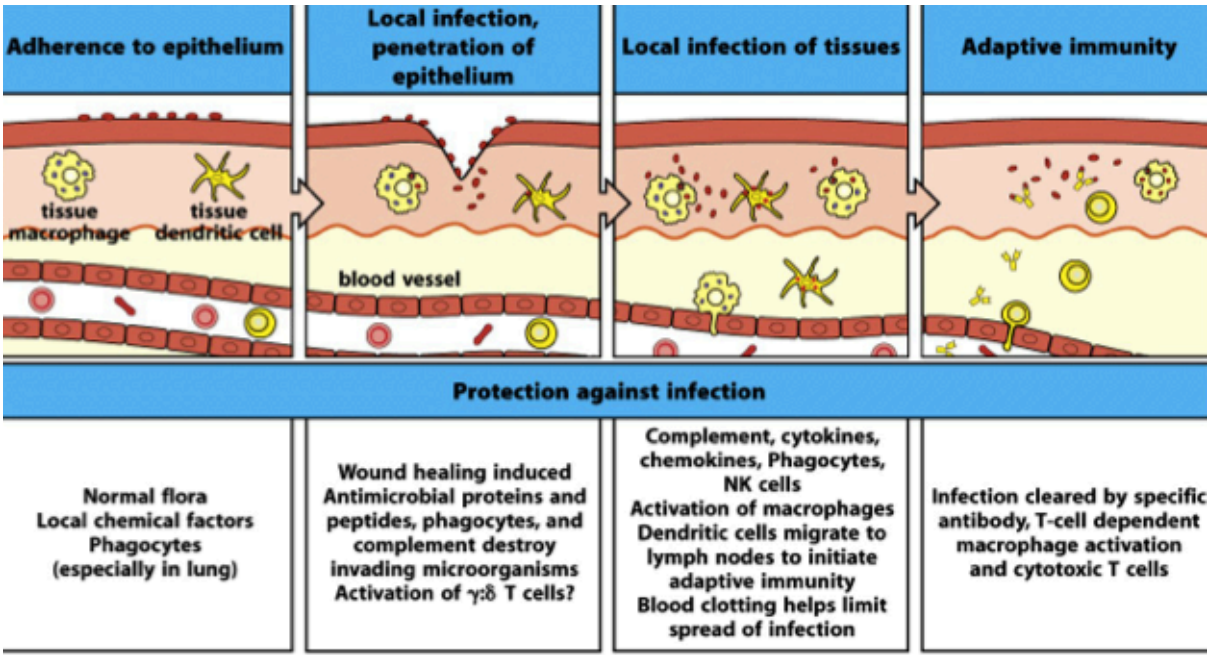
- **1. Speed** (early, rapid)- resident cells sit in peripheral sites and are already there, neutrophils are in the blood so they can rush there. Happens within minutes to hours and finished 12 hours
- **2. Duration** (short-lived)- very inflammatory and attracts lymphocytes to the area, but if it continues and is chronic it can be bad.
- **3. Repetitive-** responds the same way each time a microbe is encountered
- **4. Interactive-** with other cells of innate and adaptive immune system.

Components of the innate immune system

1. Epithelial barriers: physical + they produce peptide antibiotics that kill bacteria + contain intraepithelial lymphocytes which act as guards against infectious agents.
2. Cells in circulation and tissues: phagocytes (resident macrophages as well as circulating) and exocytes (eosinophils, mast cells, basophils- release active mediators from granules)
3. Molecules: cytokines, plasma proteins

Just underneath the epithelial barrier, are the innate resident cells.



- Innate immunity recognises structures that are shared by various classes of microbes and are not present on host cells. E.g. Phagocytes expres receptors for bacterial lipopolysaccharide LPS (aka endotoxin)

that is present on the cell wall of many bacterial species. Phagocytes recognise doule stranded RNA found in viruses and to unmethylated CpG oligonucleotides common in microbial DNA. These microbial molecules that are the targets of innate immunity are also called pathogen associated molecular patterns (see below). The components of innate immunity has evolved to recognise structures of microbes that are essential for survival and infectivity of these microbes- so they cant just mutate and avoid recognition, cos then they lose their ability to infect and colonise. (They can mutate and avoid lymphocytes tho). The receptors in innate are encoded in the germline and not produced by somatic recombination of genes (limited diversity). Nonclonal- Identical receptors are expressed on all the cells of a particular type e.g. Macrophages. The innate immune system does not react against the host (only recognises microbes + host vells express regulatory molecules that prevent reaction)

-Cells recognise and respond to patterns

- Pattern recognition receptors (PRRs): Epithelial cells, endothelial cells and resident immune cells have receptors that only recognise patterns on surface of microbes. e.g. in the skin (keratinocytes, fibroblasts, endothelial cells, dermal mast clels, Langerhans Cells, dendritic cells. These receptors recognise the shared structures (PAMPs).
- PAMPS Pathogen associated molecular patterns- different molecules express different microbial patterns.
- DAMPS Damage associated molecular patterns: the receptors can recognise these molecules that are released from damaged or necrotic cells.
- The innate immune system does not react against the host.
- Binding of PAMPs, DAMPs, ad PRRs triggers release of cytokines, recruitment of innate immune cells (neutrophils, monocytes).

Examples of PRRs

- Toll-like receptors (TLR): on the surface (extracellular), anchored to the plasma membrane, some are on the endosomal membrane of vesicles (where the microbes are ingested) and detects nucleic acids of ingested microbes.
    - TLR-2 binds peptidoglycan (e.g. LTA)
    - TL-3 binds viral double stranded RNA

    - TL-4 binds lipopilysaccharaide LPS (endotoxin)
    - TL-7 recognises influenza virus single stranded RNA
- Nuclear Oligomerization domain (NOD)-like receptors (NLR): Cytosolic (inside the cell). Some pathogens (like viruses) gets inside the cell. Can also detect damaged cells. Activate the inflammasome
- Mannose binding protein (lectin): Binds multiple mannose molecules in fungi and bacteria

- RIG-like receptor: detects viral RNA

- They all send a signal to the nucleus to begin transcription.
- Binding of microbial patterns triggers a cascade of events. Activation of transcription factors NFKB or IRF-3→ gene transcription→ expression of inflammation cytokines, chemokines, endothelial adhesion molecule, co-stimulatory molecules, antiviral cytokines.

Dendritic Cells: are the first responders and are tissue resident , strategically located. E.g in epithelial tissues. Look for bacteria etc, they phagocytose things, they communicate with the adaptive immune system. Dendritic cell finds its way to a lymph node once it gets activated to tell the B and T cells there.

Mast cells: also first responders, tissue resident. Are right near the blood vessels, immediately release their histamine granules (makes it itchy) when you scratch, the blood vessels underneath undergo dilation which allows more blood flow (redness) and fluid to go in (swelling).

Binding of microbial patterns to specific cell surface recognition receptors triggers a cascade of events:

- Release of inflammatory mediators, histamine and cytokines like tumour necrosis factor TNF and interleukin 1 which

→ dilates blood vessels, allowing more blood flow to the area (redness) and fluid to come in (swelling)

→Induces expression of adhesion molecules on endothelial cells lining blood vessels

→Attracts other innate immune cells (neutrophils and monocytes).

→Attracted cells adhere to endothelial cells only at sites of inflammation.

Leukocytes roll along the blood vessels (ONLY veins, not arteries) and then squeeze through the walls into the surrounding tissue.

Phagocytes recognise microbes using PRRs.

- recruited neutrophils and macrophages have PRRs (membrane receptors that distinguish PAMPs expressed on microbes, not host). Binding of PAMPS to PRRs triggers phagocytosis and production of soluble mediators.
- Neutrophils and macrophages both ingest microbes by phagocytosis- membrane closes around it and puts it in a phagosome.
- Lysosome fuses with phagosome which activates the phagocyte and allows toxic stuff to go in
- Enzymes and toxic substances in phagosome kills microbes once it is actually inside (nitric acid NO, reactive oxygen species ROS- production triggered or enhanced by PRR binding).
- The they produce cytokines and chemokines that recruit and activate leukocytes. Secrete growth factors and enzymes that function to repair injured tissue and replace it with connective tissue.