WEEK NO. 4

MICROBIOLOGY & IMMUNOLOGY

DOCTOR 2019 | MEDICINE | JU

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SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

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Lecture 7

* The innate immune system
  - Barriers
  - Antimicrobial peptides & proteins
  - Humoral components
  - Cellular components

The Epithelial Barrier ⟹ Fixed defense against infections (Epithelia + Macrophages)

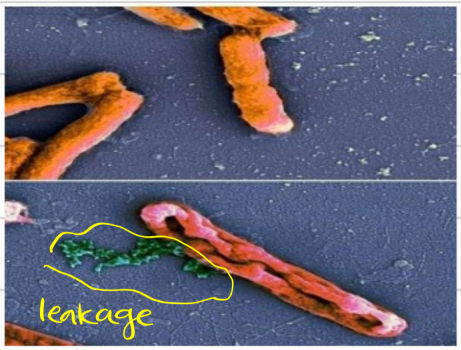
- The epithelial lining the skin & internal organs forms a PHYSICAL & CHEMICAL barrier.
- Held by junctions
- Secrete mucus ⟹ Carry microbes and get pushed through the body by cilia, peristalsis
- The most prominent immunoglublin in the mucus is IgA.

* Epithelial Barrier ⟹ Chemical barrier?

- Secretion of Antimicrobial Peptides (AMP) = Host Defense Peptides (HDP): Secreted by epithelial cells and phagocytes.

Antimicrobial Peptides

- Histatins (not required)
- Defensins
  - Small cationic
  - produced by epithelia & granules containing leukocytes
  - act within minutes, insert a hydrophobic region ruining the membrane of the microbe
- Cathelicidins
  - Produced by neutrophiles & various barrier epithelia
  - Bactericidal & immunodulatory functions

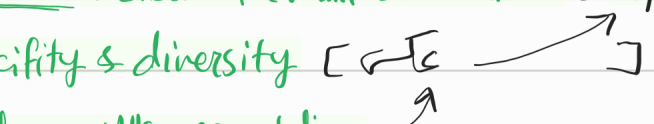


* Peptides have a net positive charge ⟹ attracted to the negative membrane of bacteria.

- Microbiota [Normal flora] ⇒ Non pathogenic bacteria, play a crucial role in the innate immunity.

  Can strengthen the epithelial barrier by stimulating it to produce more (AMB)

- Lymphocytes of the innate immune system - WHAT ?!

  * Intraepithelial T-cells, consists of (γ and δ) heterodimers [adaptive T-cells ⇒ α and β]
  * limited specifity & diversity []
  * Don't depend on MHC presentation
  * Both (adaptive + innate T cells) mature in the thymus.

Leukocytes migration to tissues

* Delivery of immune cells from their maturation site to the injured tissue through blood, so they → Differentiate and encounter.
* Leukocytes in resting state → Haven't been activated.
* The mechanism: Adhere → Bind → move out the barrier

Selectins	Integrins
Carbohydrate-Binding adhesion mole.	Heterodimeric cell surface protein
Expressed in response to IL-1 & TNF	Tight binding, recieve a signal → change their conformation
L-selectins ⇒ On leukocytes	Chemokines activate integrins & induce membrane clustring of integrins
E-& P- selectins ⇒ On the vascular wall	Important integrin ⇒ leukocyte function-associated antigen 1 LFA-1
Low affinity binding	Important ligand ⇒ Intracellular adhesion molecule ICAM-1
Ligands bind to E&P selectins are called sialylated.	

* Chemokines ⇒ Homologous cytokines, stimulat the leukocytes movement and regulate their migration, very small & have two types:

Produced by ← leukocytes & several tissue cells

① CC chemokines → 2 cystine linked together
② CXC chemokines → " " separated by an aminoacid

- The role chemokines in all recruitment:

Trigger conformational changes in the integrins → bind tightly to the endothelial cells → the leukocytes cross the membran (paracellular transmission)

- The receptor for chemokines ⇒ GPCR

- Example ⇒ Interleukin-8 (CXCL8 [chemokine]) : attracts neutrophiles & infiltrate acting on (CXCR1/2)

- Chemokines have multiple effects on multiple cells ⇒ Can be malignant.

Clinical Cases

① Cystic fibroses ⇒ An inherited mutation in the gene of the protein (CFTR), make the body produce very thick and sticky mucus. so it doesn't move easily, so it accumulate, clogging the body passages and causing infections in thes areas.

② Primary Ciliary Dyskinesia ⇒ inherited mutation causing a problem in the cilia so it don't function or move normally. Lead to accumulation of the mucus causing respiratory infections.

③ Eczeama ⇒ A defective skin barrier leads to reccurnt infections [staphylococci aureus]

Lecture 8

Antibodies

- Antigen-binding region (Fab) ⇒ variable, 2-light chains, 2-heavy chains
- fragment crystallizable region (Fc) ⇒ Constant, 2-heavy chains, interact with (cell surface receptors, complement Proteins)
- Isotypes ⇒ IgE, IgA, IgG, IgM, IgD
  - IgM: The first

* Functions ⇒ ① Neutralisation
  ② Phagocytosis
  ③ Antibody-dependent cellular cytotoxicity
  ④ Complement-mediated lysis of pathogens or of infected cell
  ⑤ Transcytosis, mucosal immunity & neonatal immunity.

Innate immunity response to extracellular pathogen

* When the extracellular pathogens penetrate the skin barrier:-

The mechanisms ⇒

① The complement cascade: by phagocytes & antibodies clear the microbes & promote inflammation.

+ **Pathways**

- Classical pathway: triggered by C_1 binding to the antigen-antibody complex forming $C4b2a$
- Alternative pathway: triggered by C_3 binding to the microbe directly forming C_3 convertase → activate more C_3 [amplification loop]
- Mannose-binding lectin pathway: activated by the binding of mannos-binding lectin to the mannose residues → activate MASP-1 & 2 → activate C_4 & C_2 → form C_3 convertase ($C4b2a$)

+ All pathways end up forming C_3 convertase → activates

C_3 splitting → C_{3a} ⇒ small, activate mast cells → inflammation.

→ C_{3b} ⇒ large, attaches to pathogens & opsonise them

activates ↓

(Lytic pathway)

C_6 splitting → C_{5b} ⇒ unites w/ $C_{6,7,8,9}$ & attack (MAC) which promotes the pathogen death

→ C_{5a} ⇒ attracts macrophages & neutrophiles & activate mast cells.

② Professional phagocytes: Macrophages & Neutrophils

+ functions → ① Internalise and kill microbes

② Producing various cytokines.

+ Macrophages → have complement receptors & Fc-γ receptors

↓ opsonised antigens ↓ antibody-coated antigens

→ F-actins form the phagosomes, then the degradation:

① Oxygen-Independent: lysosomes, phospholipases, nucleases...

② Oxygen-Dependent: Fc-receptors increase oxygen uptake [respiratory burst]

Cause damage to the microbe [creation of highly reactive molecules]

→ Macrophages are plastic, diverse and have many functions

- Embryonic-derived & Maintance of homeostasis
- Bone marrow-derived: Defense reactions & inflammatory diseases.

→ Macrophages are categorised as:

① M1: activated by pathogens (PAMPs & DAMPs & inflammatory cytokines [TNF-α, IFN-γ])

② M2: Cause chronic inflammation, activated by anti-inflammatory cytokines (IL-10, IL-13)

+ Dendritic cells → Bone-derived heterogenous family

Sense PAMPs & DAMPs

TLR induce the expression of cytokines & stuff.

① Plasmacytoid DC : type I interferons upon viral infections.

② Conventional Dc : antigen capture → process → present

Adaptive immunity role ⇒ when the innate fails.

+ APCs → macrophages & dendritic cells present antigens to T-cells

in tissues — in lymph nodes

The most powerful (APC)

Innate immunity response to intracellular pathogens

mainly by Natural killer cells.

- lymphocytes
- perform phagocytosis without clonal expansion or differentiation
- Distinguish infected cells from the healthy ones.
- NK activation is determined by inhibitory & activating receptor stimulation.

① Activating → recognise infected cells → stimulate dendritic cells → produce IL-12 & IS.

Protein tyrosine kinase is activated → tyrosine phosphorylation → eliminating the pathogen. This is inhibited by this.

② Inhibitory → recognise healthy cells → kill cells that lack MHC I

+ Possible scenarios showing the balance of inhibitory & activating receptors [that regulate NKCs]

① Activating receptors recognise ligands activate (PTK)

- if MHC-1 → inhibatory response activate Protein kinase phosphatase (PKP) inhibit NK

② Viruse infections inhibit MHC-1 inducing expression activity of ligands → activating receptors dominate & kill targeted cells

③ Neoplastic cells may express an increase in the amount of activating ligands activate NK cells → kill more stressed cells.

+ antibodies cytotoxicity → antibodies recognised by (CD16) on NK cells activate NK release cytolytic granules → cell apoptosis

+ NK cells secrete IFNγ & TNFα.

IFNγ: viral infections by macrophages

TNFα: promot direct NK tumor-cell killing