Host immune system

(Cell-microbes interaction / Cell recognition)

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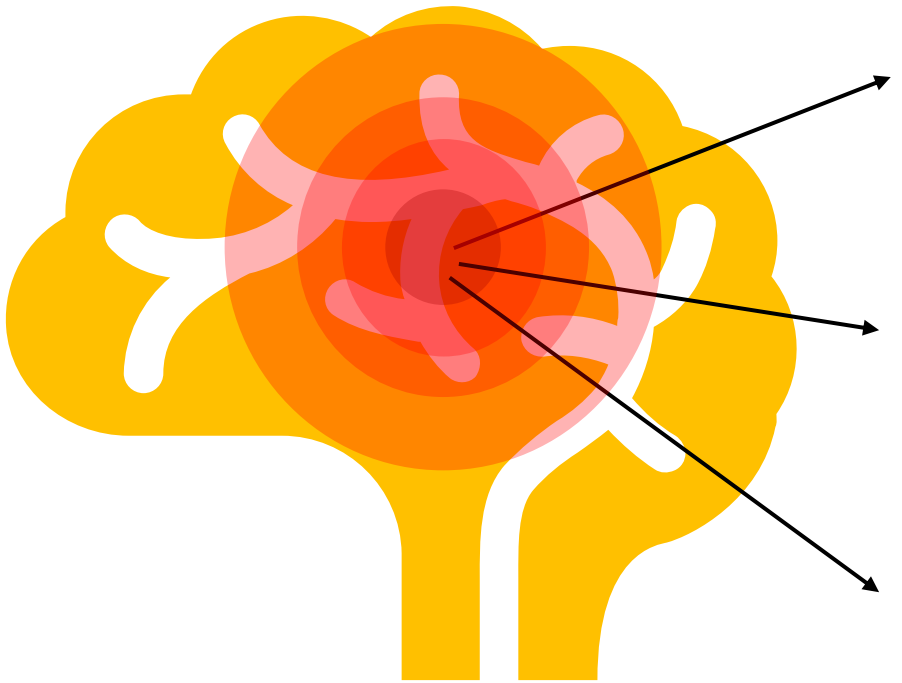
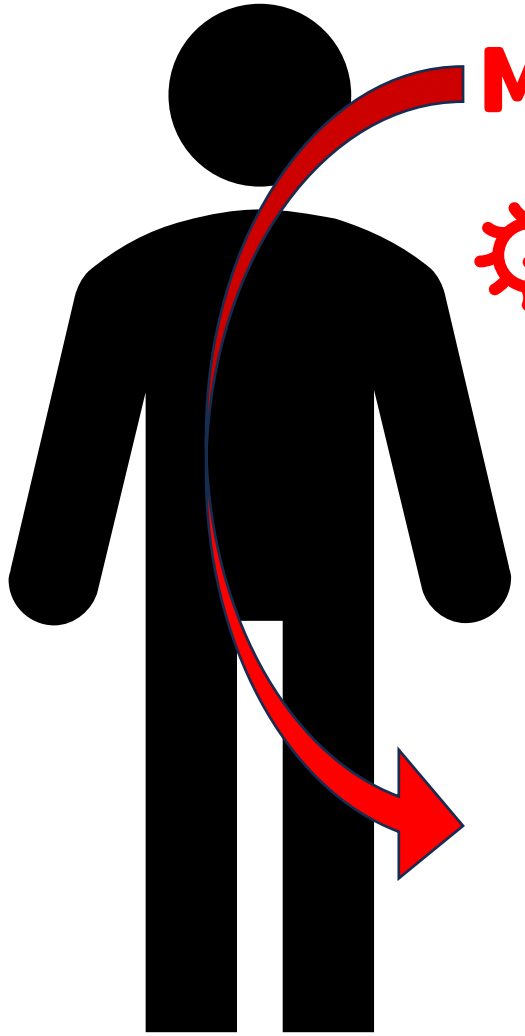
Learning objectives



1. Microbe → host interaction
2. Host → microbe recognition
3. Microbial evasion

Microbe → host interaction



Microbe

- Adherence
- Growing lifestyle

Host

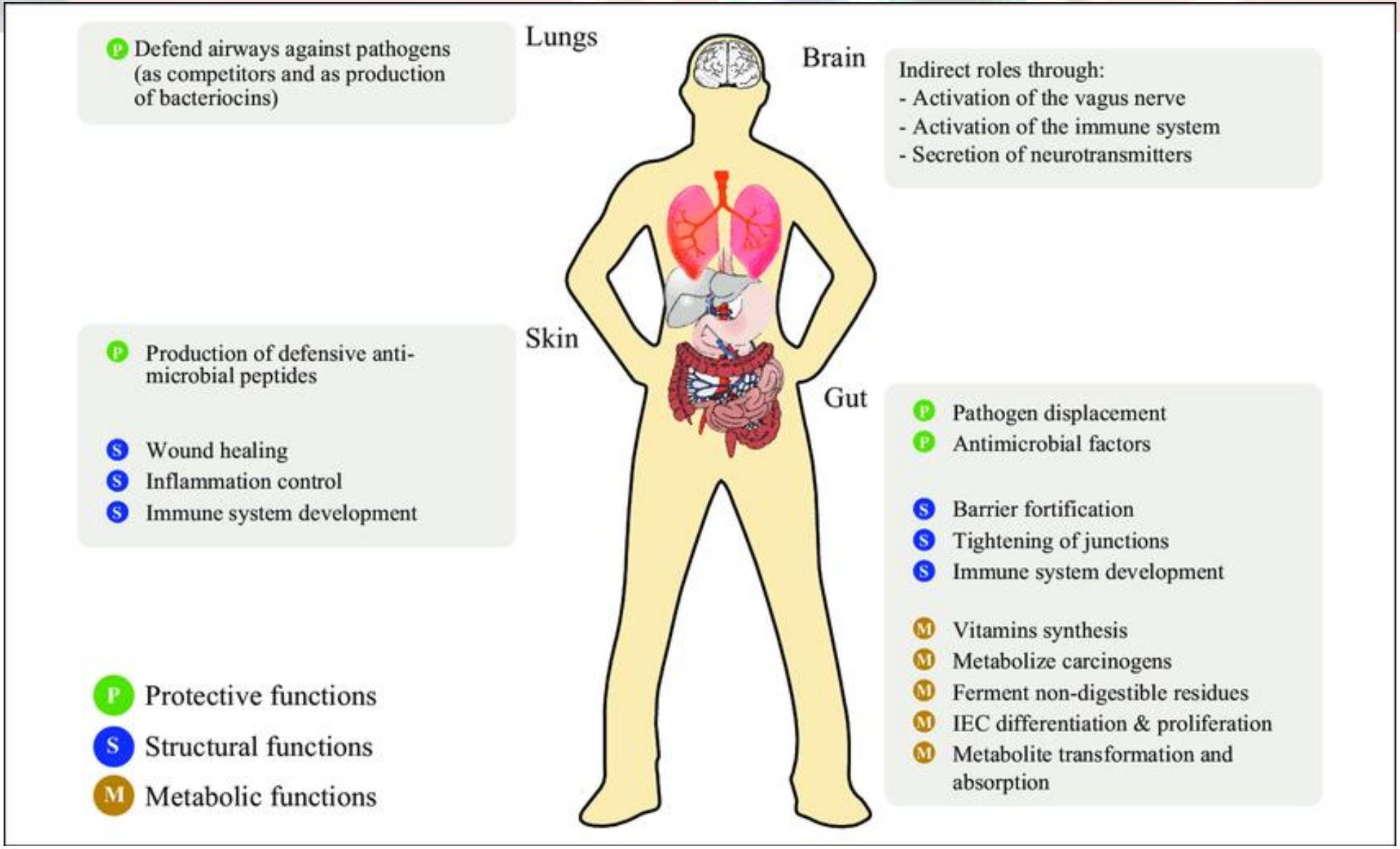
- Skin, mucus, pH, excretion, etc.

Mutualism

Commensalism

Parasite / Pathogenic

Microbe → host interaction



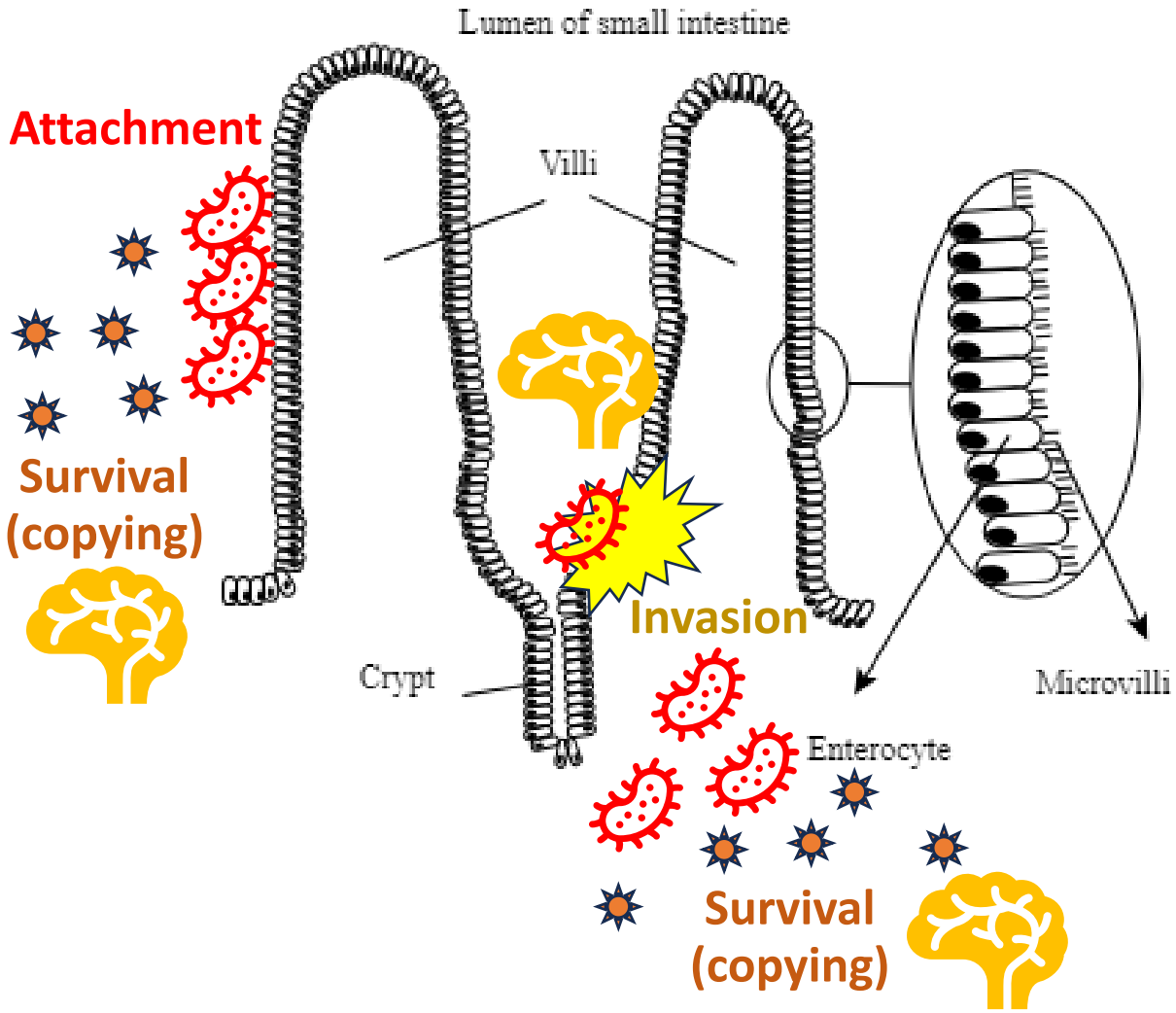
Mutualism

+

Commensalism

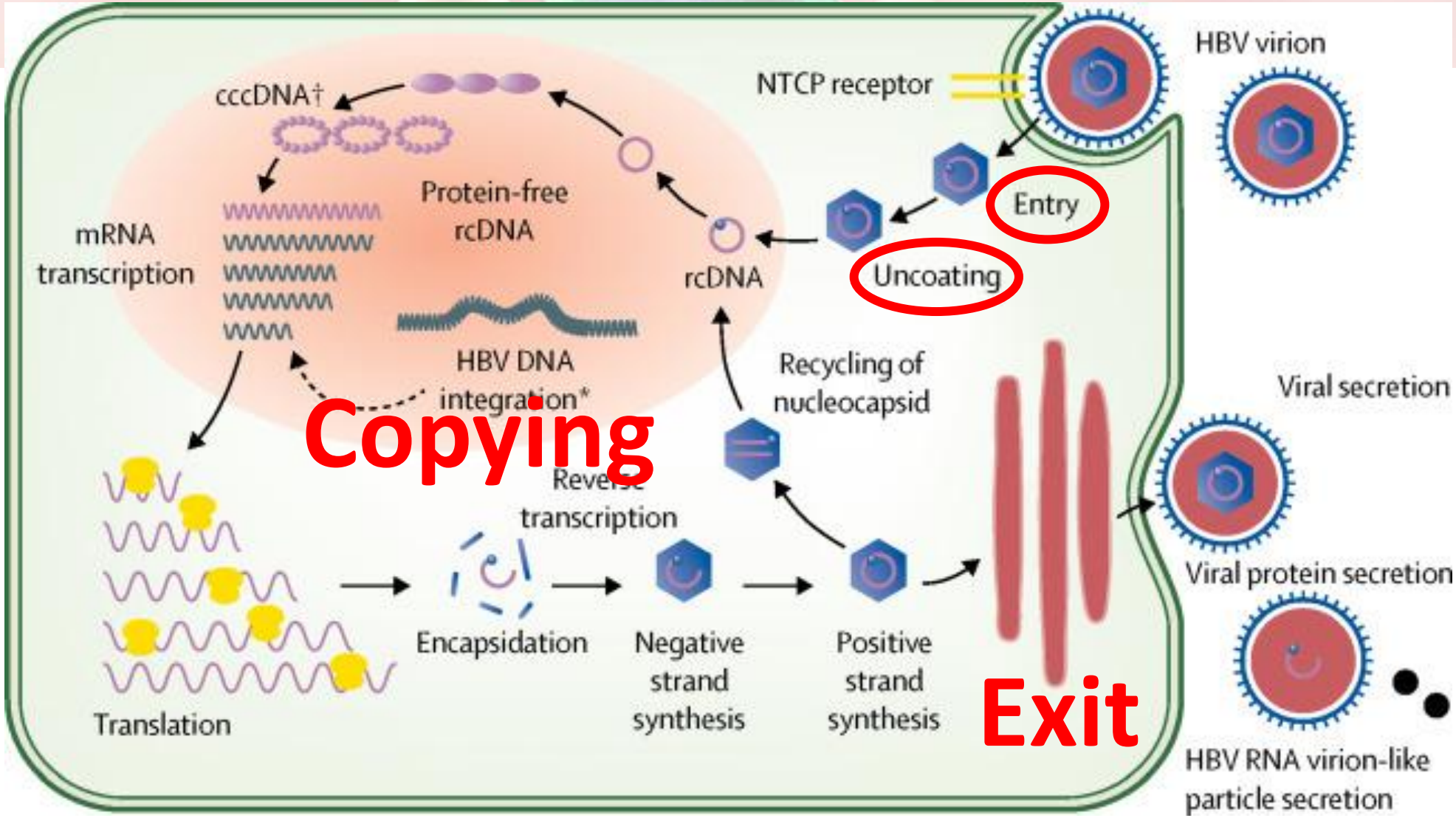
Pathogenic bacteria
-> Virulence factors

Function	Virulence factors
Attachment	Adhesins (fimbriae, afimbrial surface proteins) Exopolysaccharides Lipoteichoic acid Outer membrane proteins Outer membrane vesicles
Invasion	Flagella Enzymes (collagenase, hyaluronidase, chondroitin sulfatase, fibrinolysin, acid phosphatase, and Dnase)
Survival (evasion of host defenses or acquisition of nutrients)	Exopolysaccharides (capsule) IgA, IgG, IgM, C3, and C5 proteinases Lipopolysaccharide (antigen-O portion) -> Fever Flagella Exotoxins -> Toxin Heat-shock proteins -> Toxin Metabolic end-products
Direct damage	Exotoxins Enzymes (collagenase, hyaluronidase, chondroitin sulfatase, gingipains, aminopeptidases, phospholipase, neuraminidase, and acid phosphatase) Metabolic end-products (short-chain fatty acids, polyamines, volatile sulfur compounds, indole, ammonia)
Indirect damage	Lipopolysaccharide (mainly lipid A portion) Peptidoglycan Lipoteichoic acid Fimbriae Exopolysaccharides Outer membrane proteins (porins) Lipoproteins DNA Heat-shock proteins



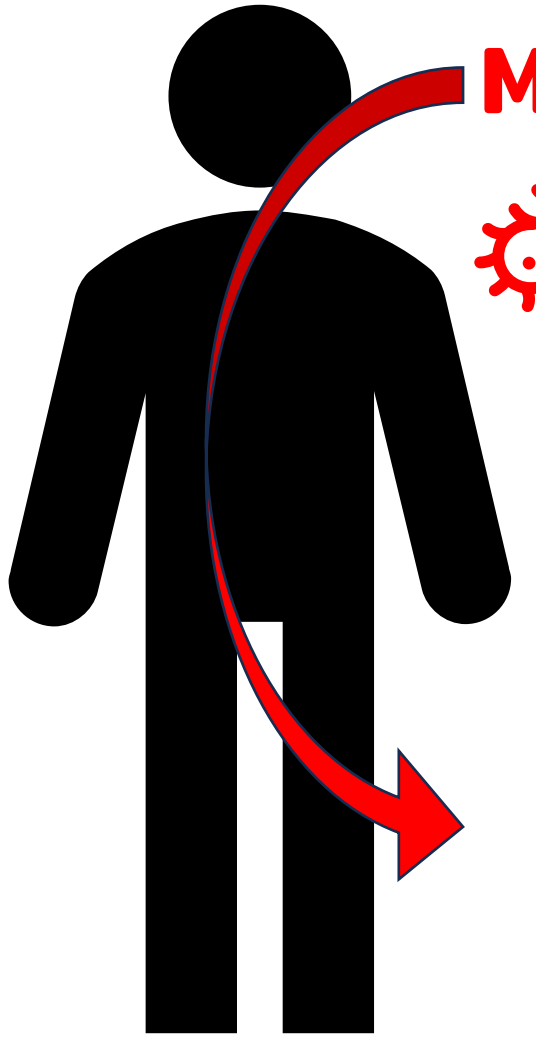
Ref: Siqueira JF, Jr., Rocas IN. Bacterial pathogenesis and mediators in apical periodontitis. Braz Dent J. 2007;18(4):267-80.

Pathogenic virus



Ref: Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. Lancet. 2018;392(10161):2313-24.

Microbe → host interaction



Microbe

- Adherence
- Growing lifestyle (survival factors to colonize)

Host

- Skin, mucus, pH, excretion, etc.

Mutualism (+/+)

Commensalism (+/0)

Parasite / Pathogenic (+/-)

-> Virulence factors

-> toxin w / wo invasion

DANONE NUTRICIA RESEARCH

FACTS, FIGURES & TIPS FOR YOUR GUT MICROBIOTA

DISCOVERING THE GUT MICROBIOTA

THE ESSENTIALS

THE MICROBIOTA

WHAT ARE WE TALKING ABOUT?

The community of microorganisms (bacteria, fungi, etc.) that live in harmony in and on our body.

Kho et al., 2018; Dore et al., 2017; Hooper et al., 2012

FOR EXAMPLE:

The skin microbiota, the oral microbiota or the gut microbiota.

Kho et al 2018

THE GUT MICROBIOTA: THE RICHEST COMMUNITY IN OUR BODY

AS MUCH GUT BACTERIA AS CELLS IN OUR WHOLE BODY

An ecosystem of **100,000** billion bacteria*, which represents **90%** of our total microbiota!

Sender et al. 2016; Doré et al., 2017 / *In adult individuals

Specific to each individual, just like our fingerprints!

HOST-MICROBIOTA SYMBIOSIS

A REALLY CLOSE RELATIONSHIP

We feed gut bacteria with some of the dietary fibers we eat.
In return they may play a key role in our general health, helping with:

He et al., 2016; Makki et al., 2018

DIGESTIVE COMFORT

NUTRIENT ASSIMILATION

IMMUNE SYSTEM

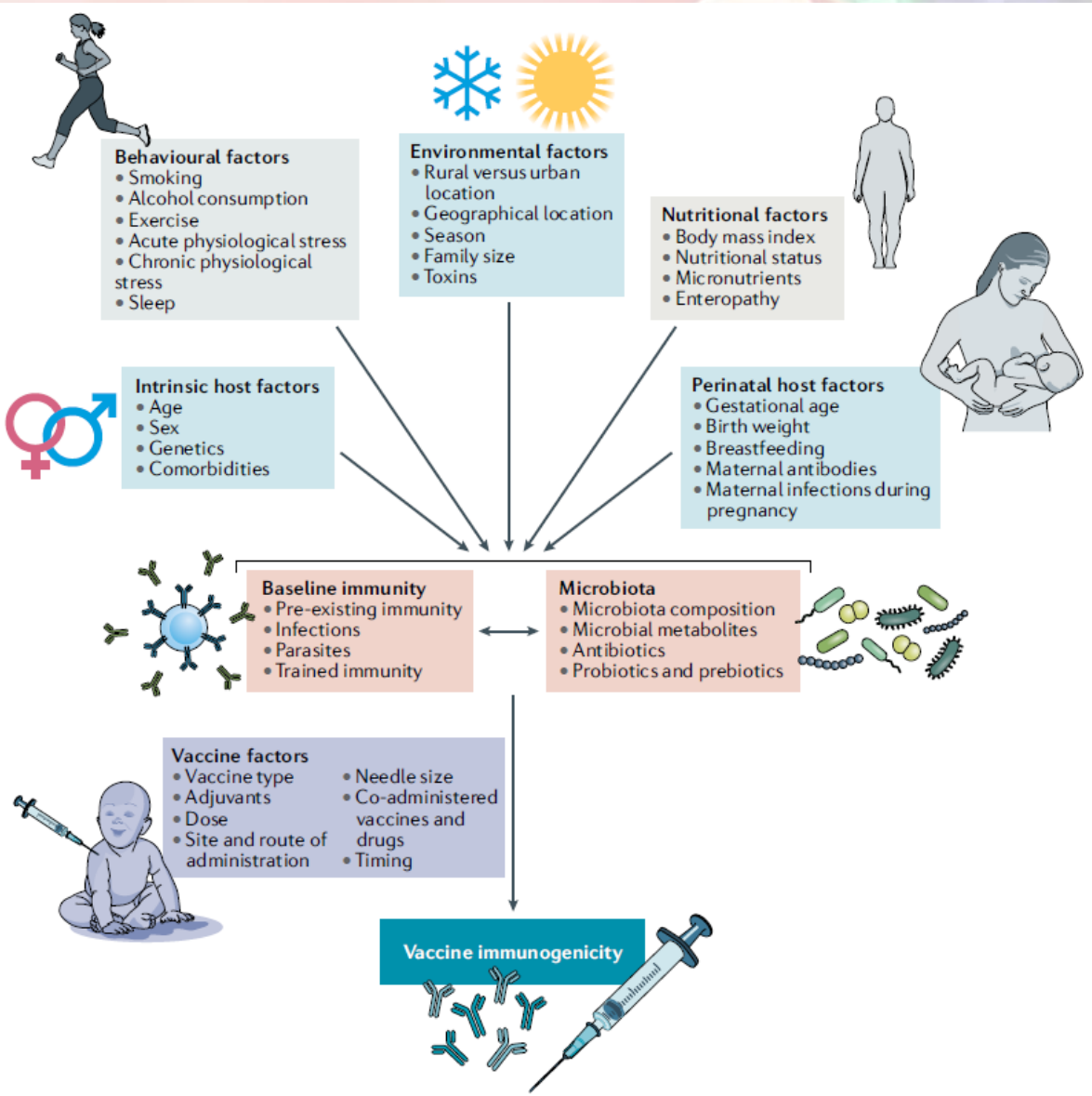
They are our silent little helpers!

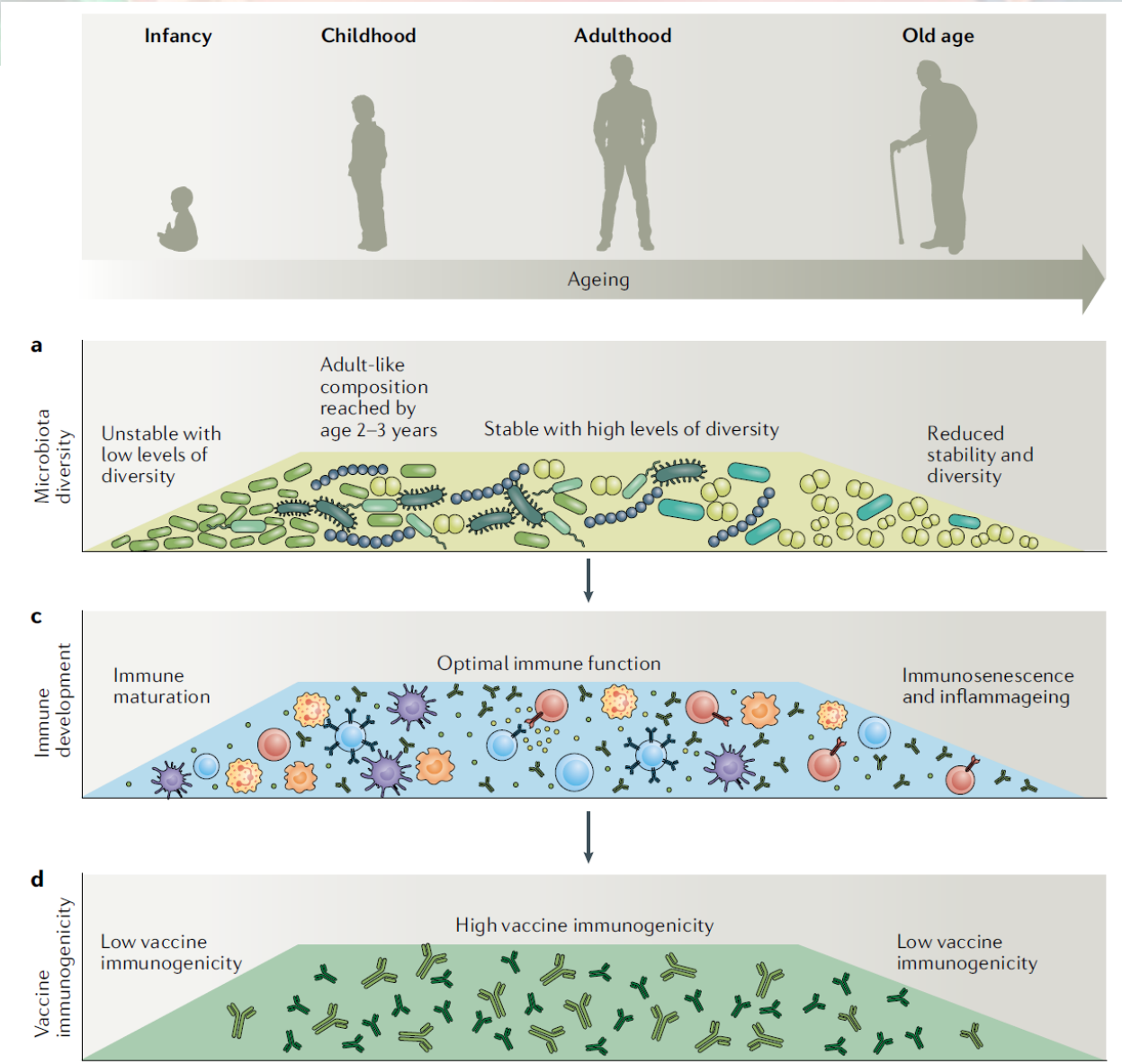
ALL ACTORS OF OUR OWN HEALTH

Since our gut microbiota is our partner for life, we need to support each other!
Through our diet, we can take care of it so that it will take care of us.

Senghor, 2018; Makki et al., 2018; Nie et al., 2018

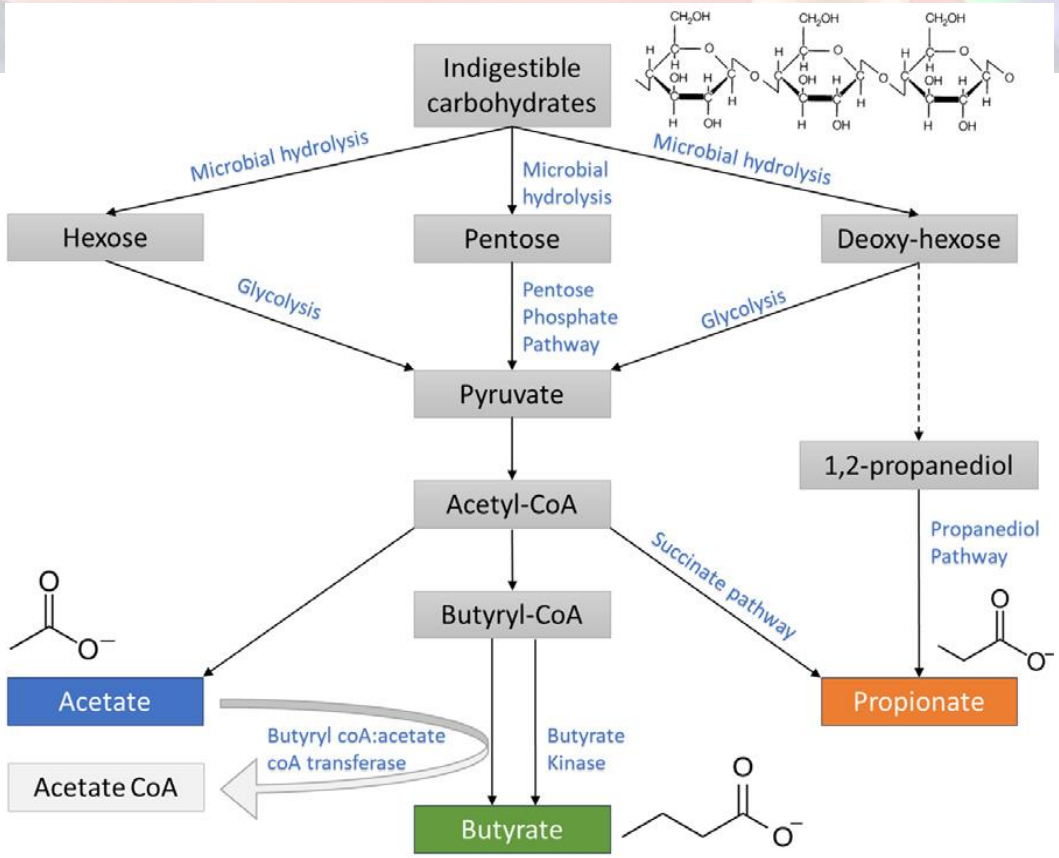
Microbiome and immunity development

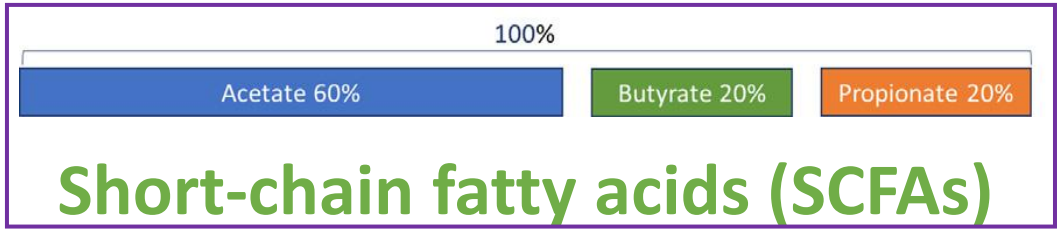




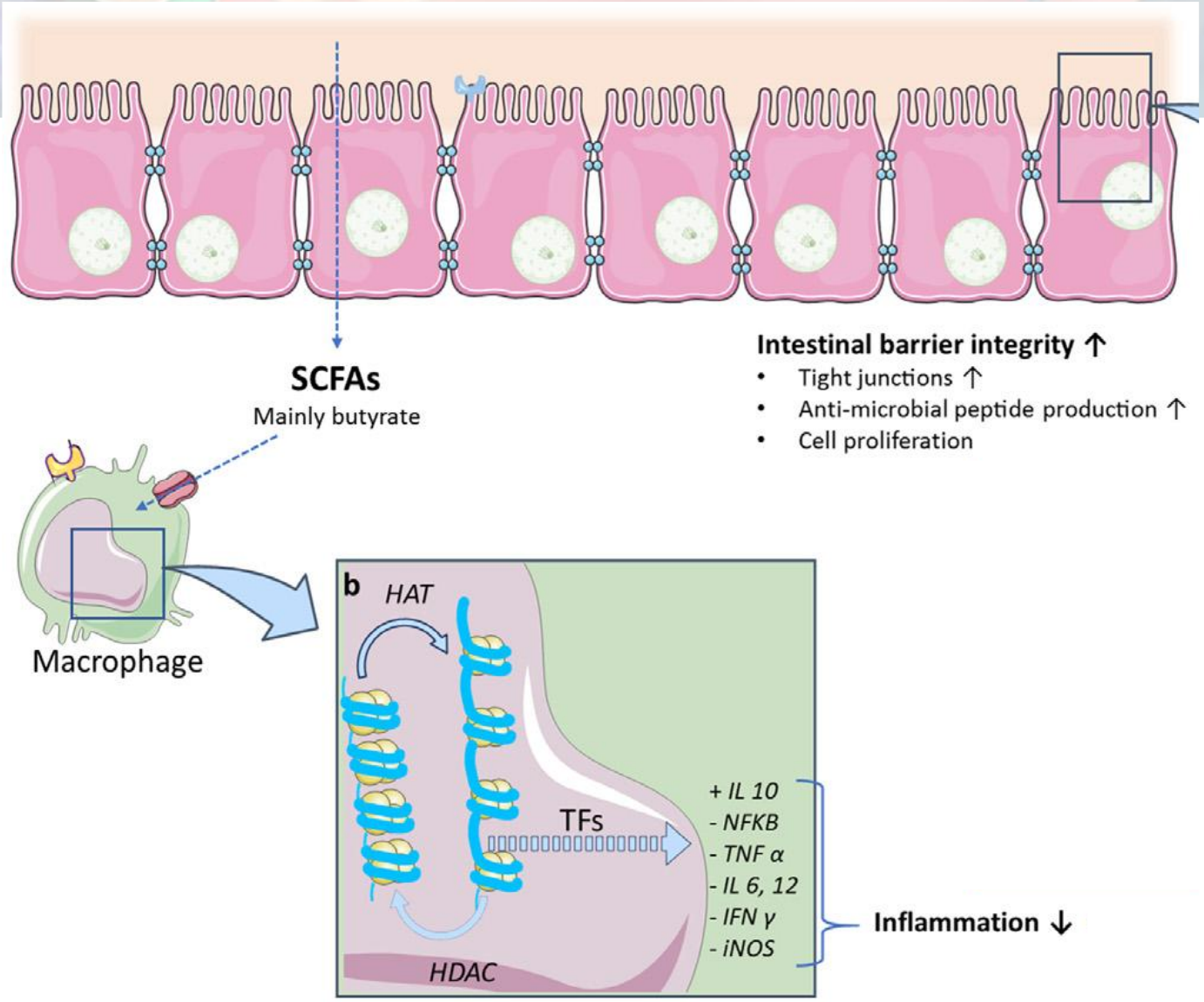
Ref: D. J. Lynn, S. C. Benson, M. A. Lynn, B. Pulendran, Modulation of immune responses to vaccination by the microbiota: implications and potential mechanisms. *Nat Rev Immunol*, (2021).

Microbiome and immunity development





Short-chain fatty acids (SCFAs)



Ref: S. Deleu, K. Machiels, J. Raes, K. Verbeke, S. Vermeire, Short chain fatty acids and its producing organisms: An overlooked therapy for IBD? *EBioMedicine* **66**, 103293 (2021).

GPR= G-protein coupled receptor, HAT= histone acetyl transferase, HDAC= histone deacetylase, HIF= hypoxia inducible factor, SLC= solute carrier, TCA= tricarboxylic acid cycle, TF= transcription factor

TOP 20 PREBIOTIC FOODS

FOR A HEALTHY GUT




PREBIOTIC vs PROBIOTIC

What's the difference?

Both offer a wide range of health benefits.

PREBIOTIC

- Plant-based fibers
- Come from your diet
- Act as a food source for healthy gut bacteria
- Found in bananas, oats, onions, artichokes and garlic


PROBIOTIC

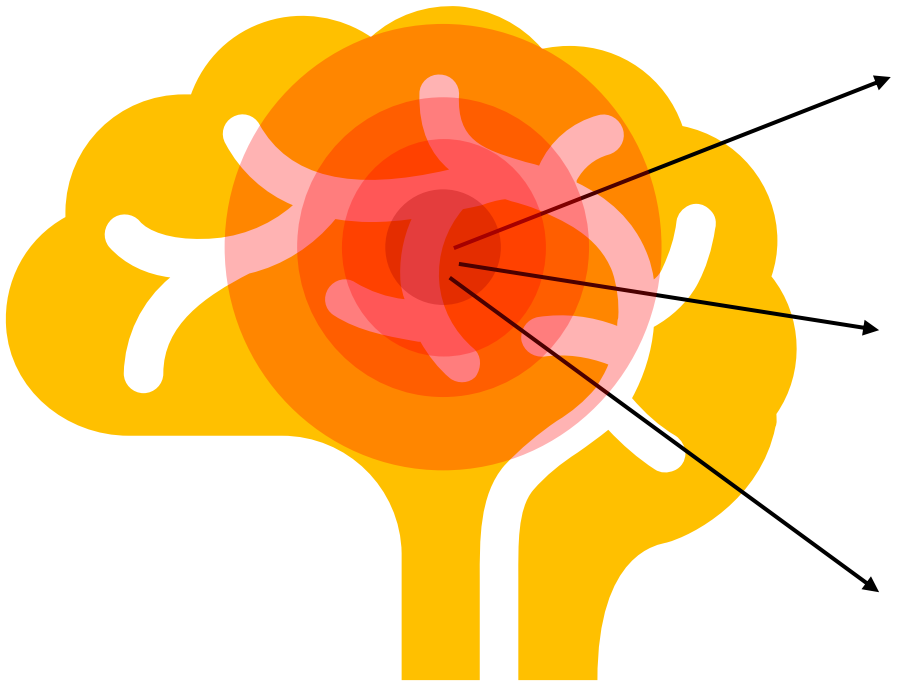
- Live bacteria in the digestive system
- Needed to support our digestive and immune systems.
- Can be found in yogurt, miso and kimchi


Sunfiber®

Take a break…

Time for you to ask questions

Learning objectives



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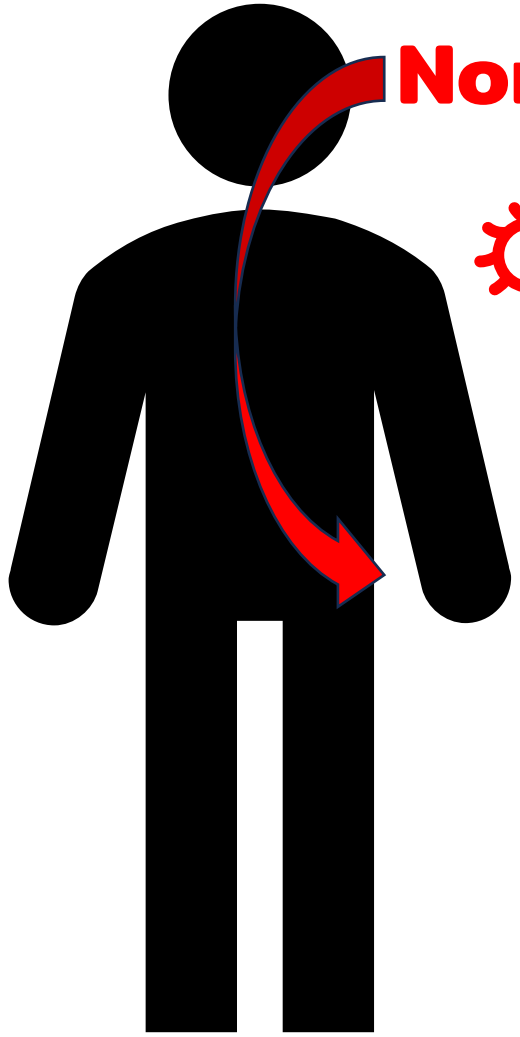


Non-invasive Microbe

- Adherence
- Growing lifestyle (colonize)

Host Innate immunity

- Skin, mucus, pH, excretion, etc.

(non-specific barrier)

Microbiome

- Mutualism (+/+)
- Commensalism (+/0)

VS (competitively growth)

Parasite / Pathogenic (+/-)

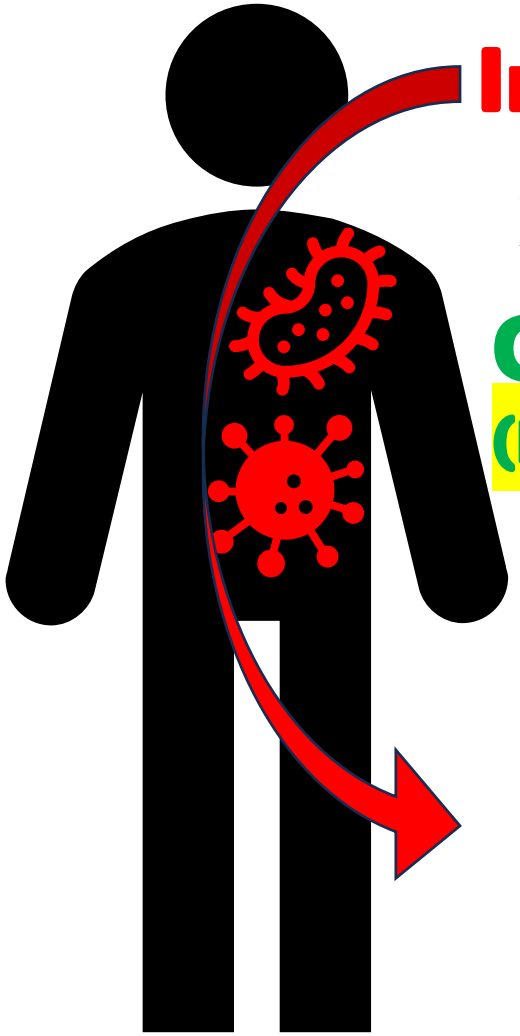
Non-invasive pathogens

Neutralize / prevent attachment

Adaptive immunity

(specific secretory IgA)

Host → microbe interaction



Invasive Microbes

VS

Cellular innate immunity

(less-specific barrier)

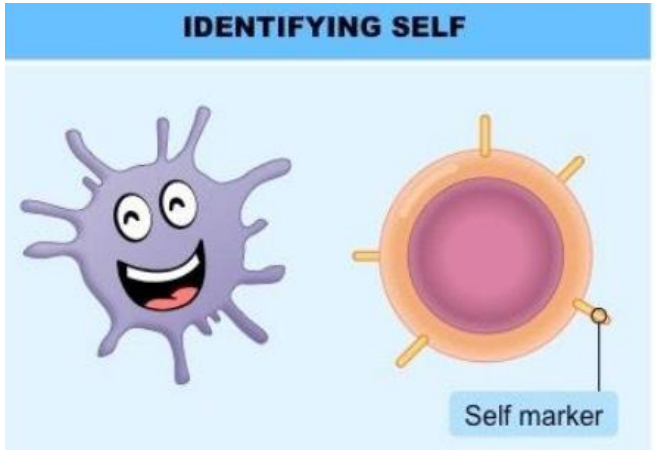
Pattern recognition receptor (PRR)

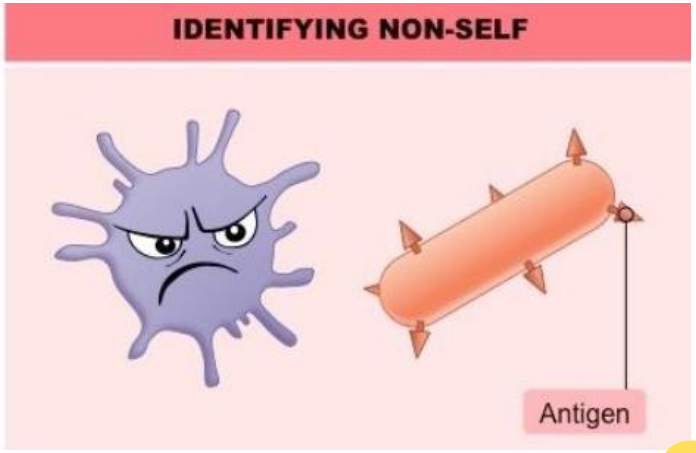
- **Pathogen** associated molecular patterns (**P**AMPs)
- **Damage** associated molecular patterns (**D**AMPs)

  → Danger signals (cytokines and chemokines)

General characteristic of normal immune responses

Identifying Self vs Non-self





3 LINES OF DEFENSE

NON-SPECIFIC DEFENCES (INNATE IMMUNITY)		SPECIFIC DEFENCES (ADAPTIVE IMMUNITY)
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic leukocytes • Antimicrobial proteins • Inflammatory response • Fever	• Lymphocytes • Antibodies • Memory cells

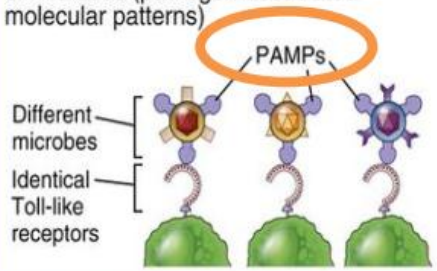
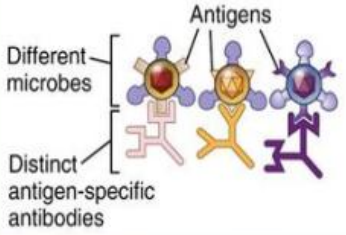
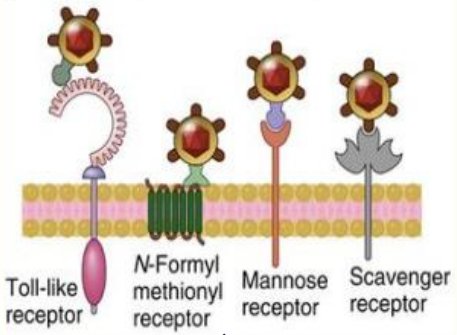
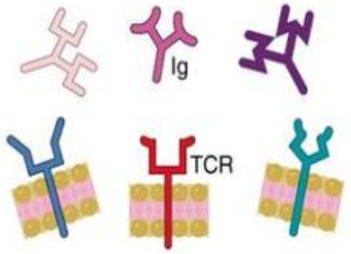
Humoral immune response

- B cells >> plasma cells >> antibodies

Cellular immune response

- Th >> cytokines
- Tc or CTLs >> perforin + granzymes

General characteristic of normal immune responses

Feature	Innate immunity	Adaptive immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns) 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Number of microbial molecules recognized	About 1000 molecular patterns (estimated)	>10^7 antigens
Receptors	Encoded in germline; limited diversity (pattern recognition receptors) 	Encoded by genes produced by somatic recombination of gene segments; greater diversity 

Feature	Innate immunity	Adaptive immunity
Number and types of receptors	<100 different types of invariant receptors	Only 2 types of receptors (Ig and TCR), with millions of variations of each
Distribution of receptors	Nonclonal: Identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Genes encoding receptors	Germline encoded, in all cells	Formed by somatic recombination of gene segments only in B and T cells
Discrimination of self and nonself	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (hence the possibility of autoimmunity)

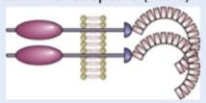
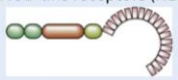
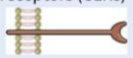
Recognition molecules

Host → microbe interaction

Pattern recognition receptor (PRR)

- Inflammation
  - TLRs
  - NLRs
  - CDSs
- Phagocytosis
  - CLRs
  - Scavenger receptors
  - Formyl peptide receptors (FPR)
- Antiviral state
  - TLRs
  - RLRs
  - CDSs

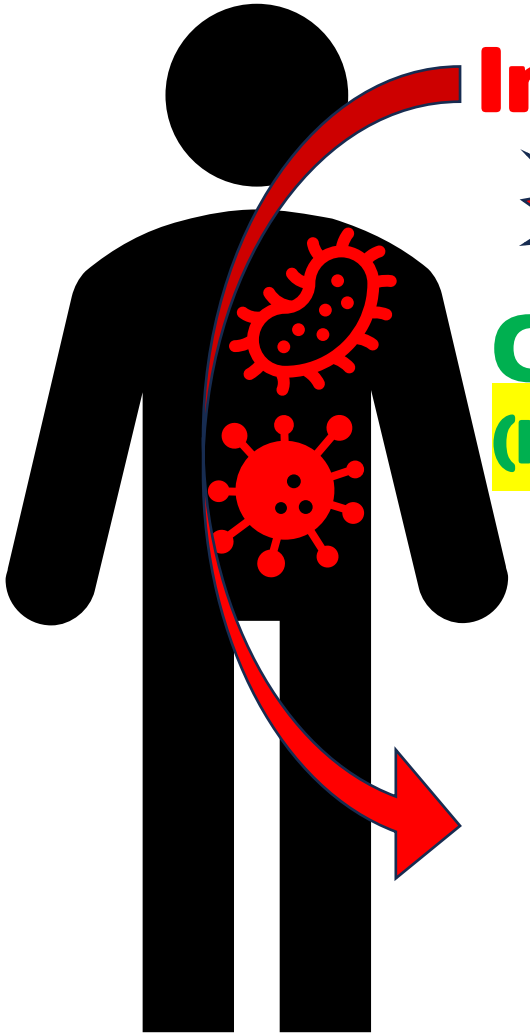
Cellular PRRs

Pattern Recognition Receptors	Location	Specific Examples	PAMP/DAMP Ligands
Toll-like receptors (TLRs) 	Plasma membrane and endosomal membranes of dendritic cells, phagocytes, B cells, endothelial cells, and many other cell types	TLRs 1-9	Various microbial molecules including bacterial LPS and peptidoglycans, viral nucleic acids
NOD-like receptors (NLRs) 	Cytosol of phagocytes, epithelial cells, and other cells	NOD1/2	Bacterial cell wall peptidoglycans
		NLRP family (inflammasomes)	Intracellular crystals (urate, silica); changes in cytosolic ATP and ion concentrations; lysosomal damage
RIG-like receptors (RLRs) 	Cytosol of phagocytes and other cells	RIG-1, MDA-5	Viral RNA
Cytosolic DNA sensors (CDSs) 	Cytosol of many cell types	AIM2; STING-associated CDSs	Bacterial and viral DNA
C-type lectin–like receptors (CLRs) 	Plasma membranes of phagocytes	Mannose receptor	Microbial surface carbohydrates with terminal mannose and fructose
		Dectin	Glucans present in fungal cell walls
Scavenger receptors 	Plasma membranes of phagocytes	CD36	Microbial diacylglycerides
N-Formyl met-leu-phe receptors 	Plasma membranes of phagocytes	FPR and FPRL1	Peptides containing *N*-formylmethionyl residues

Soluble PRRs

Pattern Recognition Receptors	Location	Specific Examples	PAMP/DAMP Ligands
Pentraxins 	Plasma	C-reactive protein	Microbial phosphorylcholine and phosphatidylethanolamine
Collectins 	Plasma	Mannose-binding lectin	Carbohydrates with terminal mannose and fructose
	Alveoli	Surfactant proteins SP-A and SP-D	Various microbial structures
Ficolins 	Plasma	Ficolin	*N*-Acetylglucosamine and lipoteichoic acid components of the cell walls of gram-positive bacteria
Complement 	Plasma	Various complement proteins	Microbial surfaces

Host → microbe interaction



Invasive Microbes

VS

Cellular innate immunity

(less-specific barrier)

Pattern recognition receptor (PRR)

- PAMPs
- DAMPs

Defense mechanisms

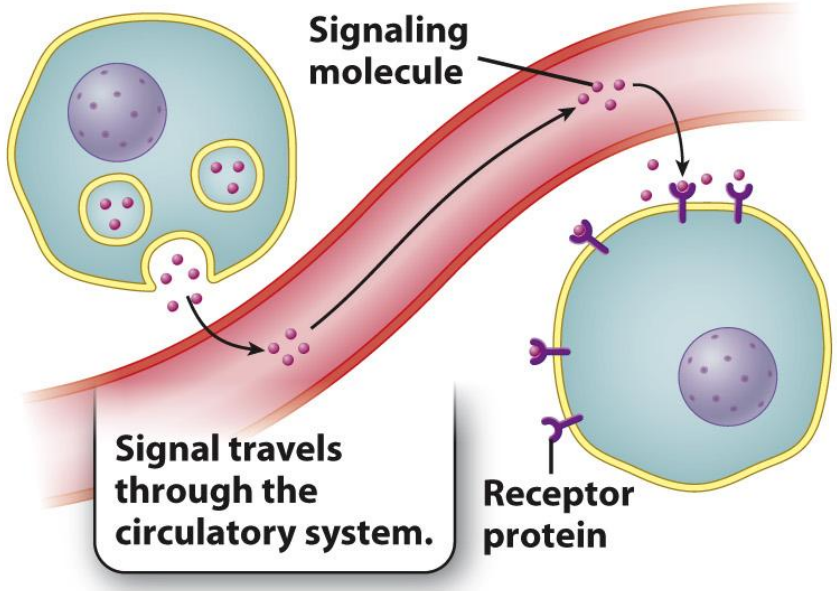
Danger signals (cytokines and chemokines)

Communication *Cell migration*

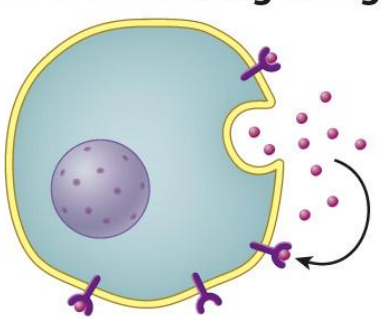
Cytokines → Cell-to-cell communication

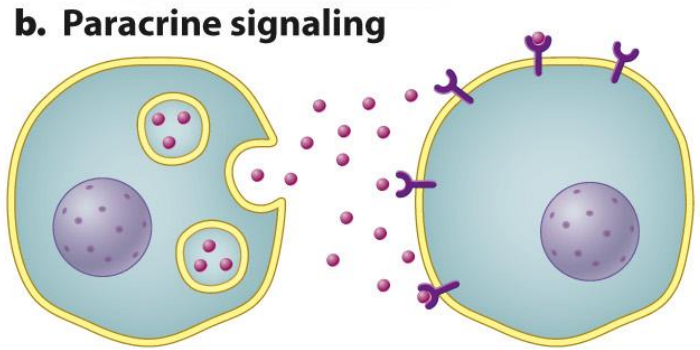
"Chemical language"

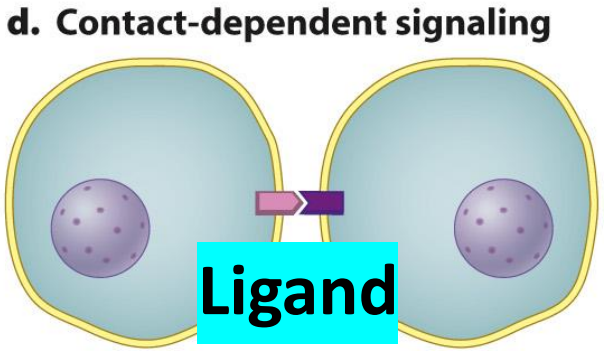
Cytokine



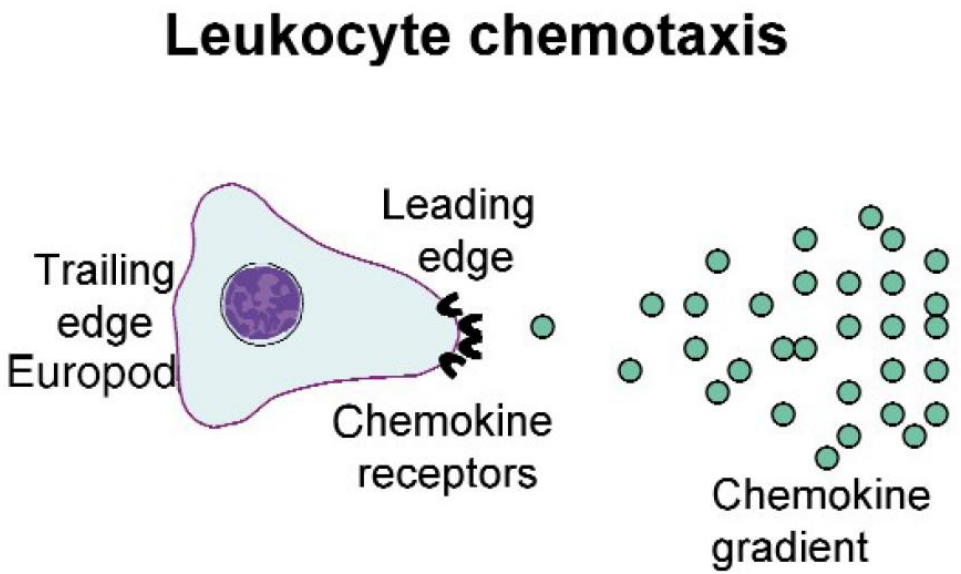
Cytokine

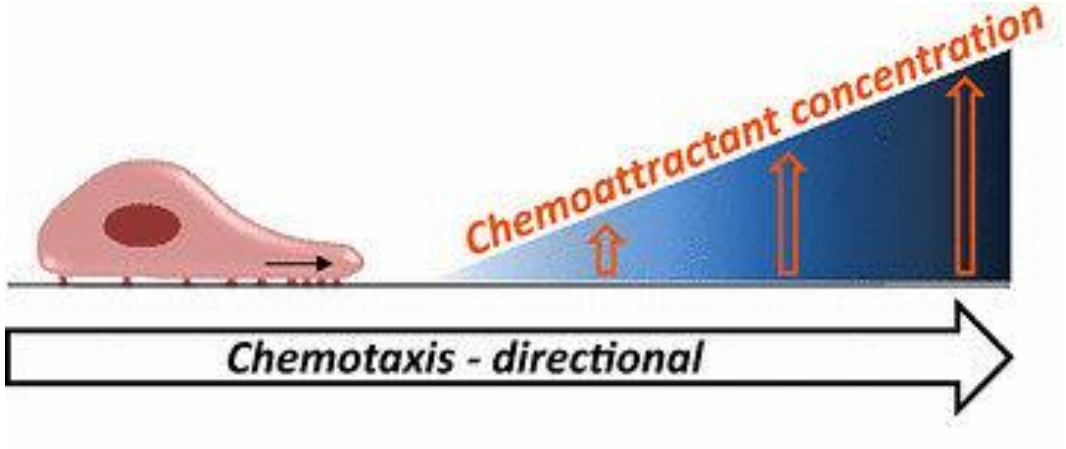




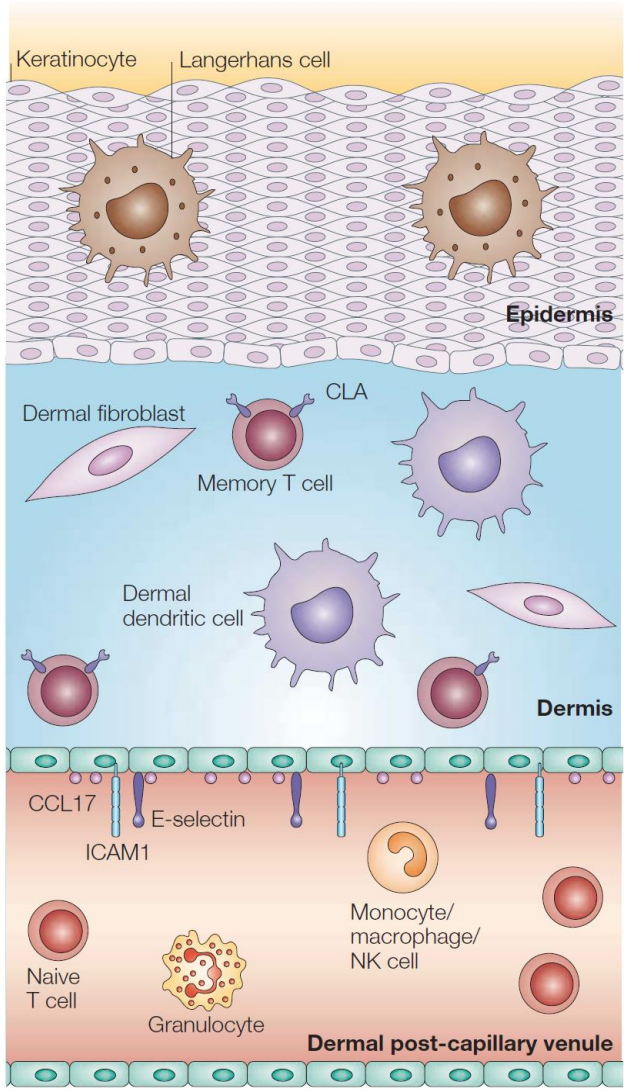


Chemokines → chemoattractant cytokines





Host → microbe interaction



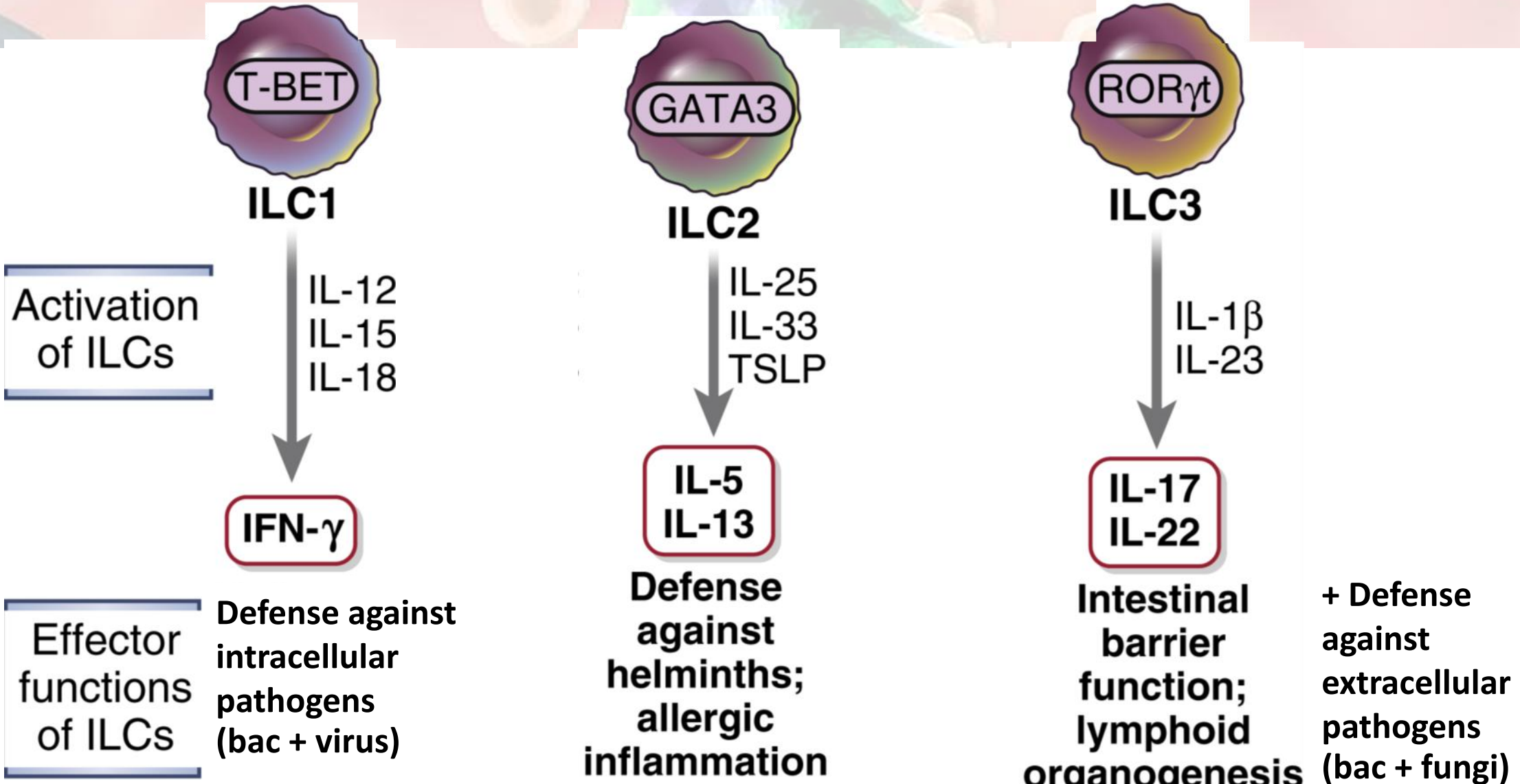
Tissue resident immune cells

- Minimal infection control (macrophages / T-cells)
- Danger signal provider (mast cells / ILCs / T-cells)

Blood / circulating / systemic immune cells

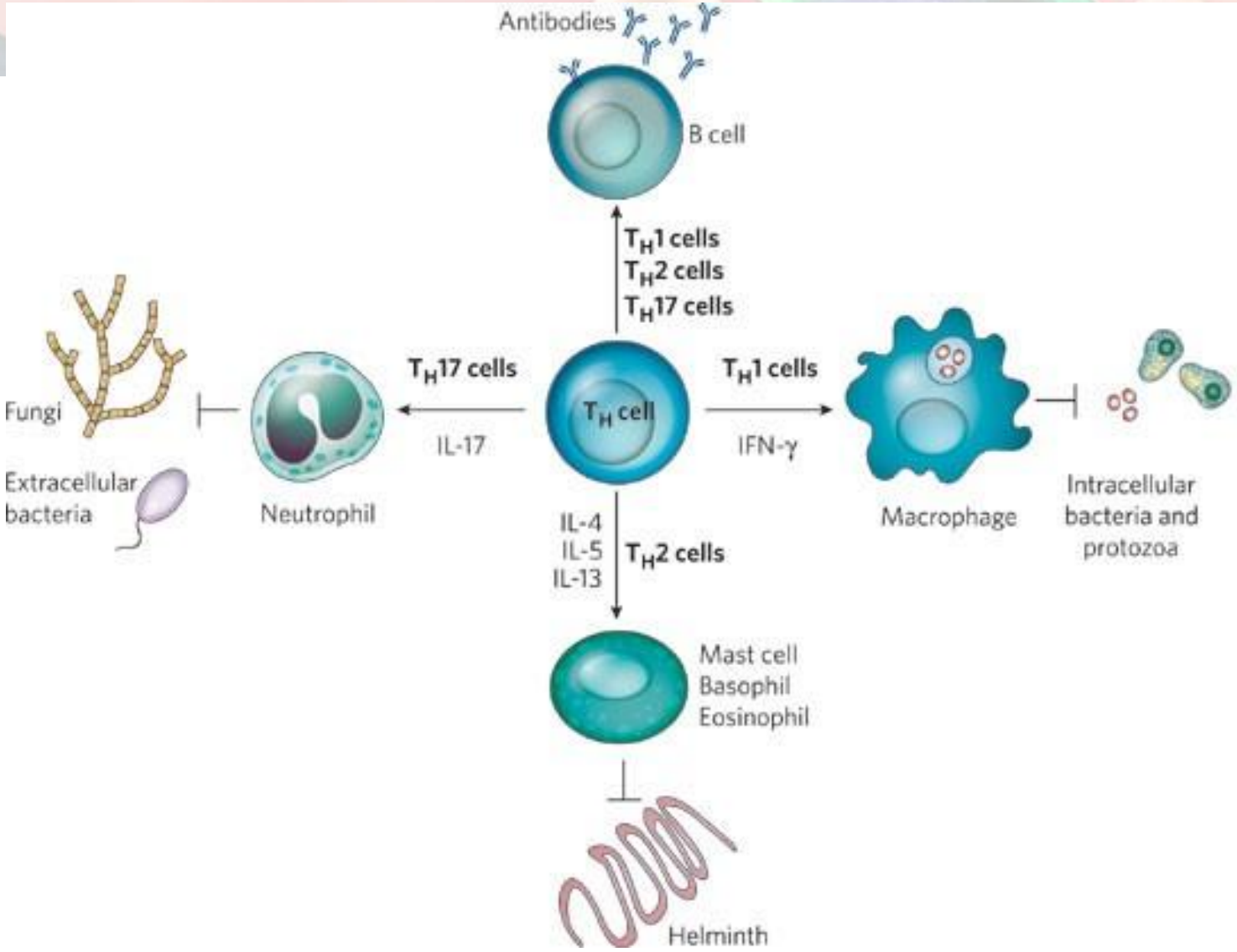
- Very effective infection control

Innate lymphoid cells (ILCs)



Ref: Abbas, A. K., Lichtman, A. H., & Pillai, S. (2007). Cellular and molecular immunology 10th ed.

Host → microbe interaction



Helper T cells : Help to provide an appropriate responses to pathogens

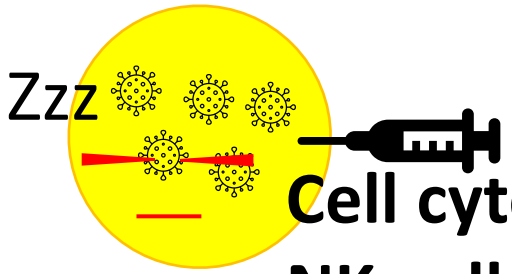
Recommended Ref: Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature. 2007;449(7164):819-26.

Host → microbe interaction

Defense mechanisms : Size, location and number are matter!!!!

Too small (virus)

Anti-viral state



Cell cytotoxicity by

NK-cell or CTL

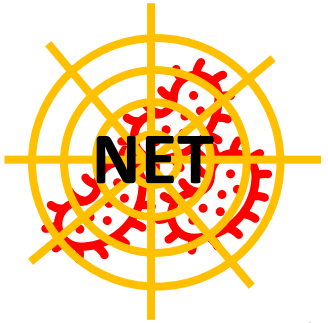
(natural killer cell) **(Cytotoxic T lymphocyte)**

Host → microbe interaction

Defense mechanisms : Size, location and number are matter!!!!

Small and can be ate (bacteria and yeast)

(Low number)

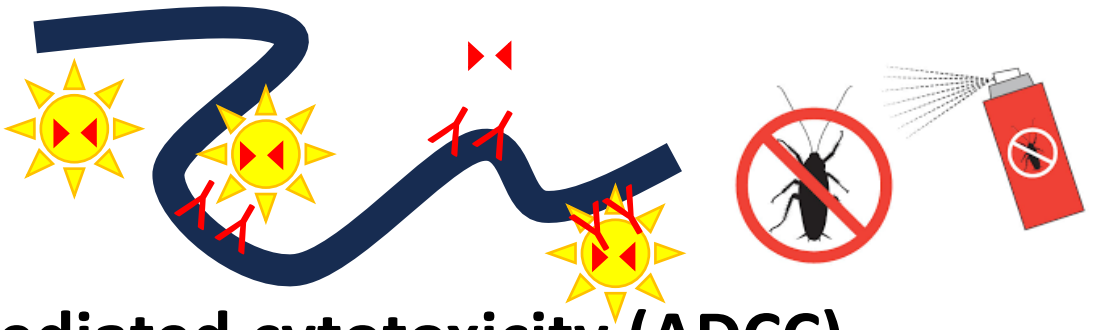


(Too many in number)

Host → microbe interaction

Defense mechanisms : Size, location and number are matter!!!!

Too big (parasite and mold)



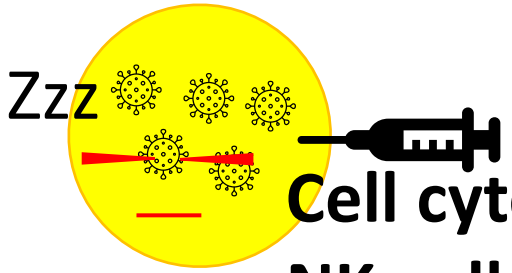
Antibody-dependent cell-mediated cytotoxicity (ADCC)

Host → microbe interaction

Defense mechanisms : Size, location and number are matter!!!!

Too small (virus)

Anti-viral state



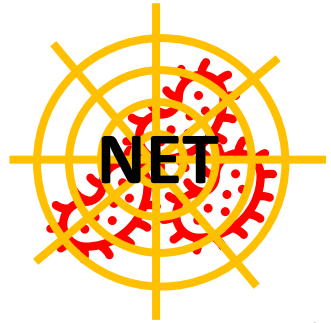
Cell cytotoxicity by NK-cell or CTL

(natural killer cell) (Cytotoxic T lymphocyte)

Small and can be ate (bacteria and yeast)

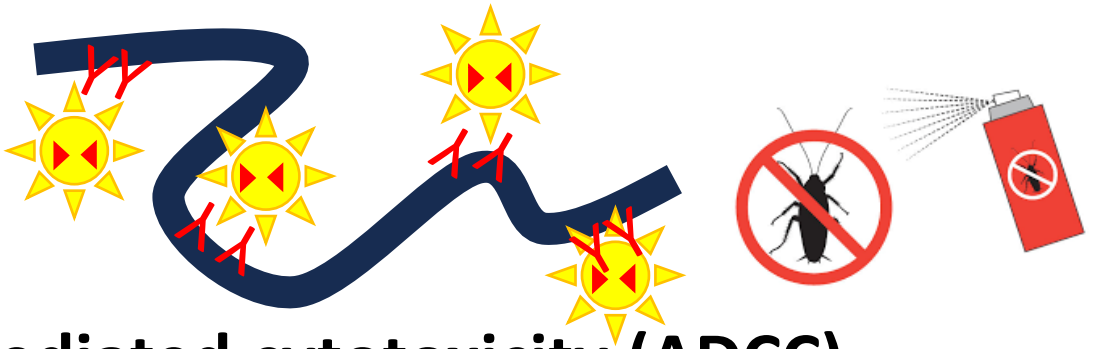
Phagocytosis

(Low number)



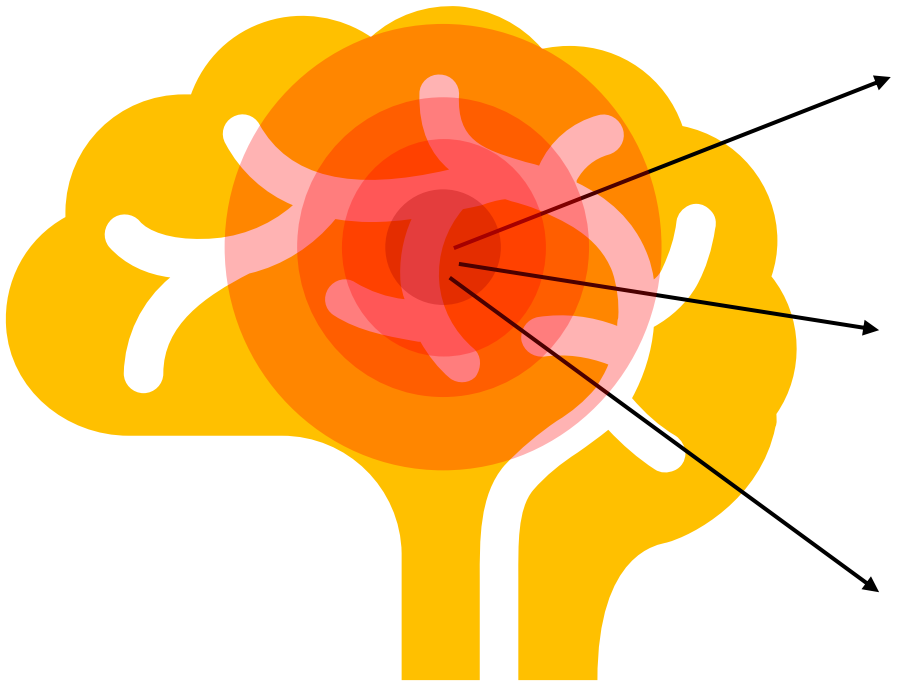
(Too many in number)

Too big (parasite and mold)



Antibody-dependent cell-mediated cytotoxicity (ADCC)

Learning objectives



1. Microbe → host interaction
2. Host → microbe recognition
3. Microbial evasion

Microbial evasion

Table 1. Anti-Immune Strategies of Viruses and Bacteria

	Strategy	Viral Examples	Bacterial Examples
2	(1) Secreted modulators or toxins	- ligand mimics (virokines) - receptor mimics (viroceptors)	- many toxins - proteases
1	(2) Modulators on the pathogen surface	- complement inhibitors - coagulation regulators - immune receptors - adhesion molecules	- Lipid A of LPS - carbohydrates such as capsules - outer membrane proteins - adhesins and invasins
3	(3) Hide from immune surveillance	- latency - infect immunopriviledged tissues	- avoid phagolysosomal fusion - inhibit phagocytosis
1	(4) Antigenic hypervariability	- express error-prone replicase - escape from antibody recognition - "outrun" T cell recognition	- vary many surface structures - pili, outer membrane proteins, LPS - strain to strain variation
2 4	(5) Subvert or kill immune cells/phagocytes	- infect and kill immune cells (DCs, APCs, lymphocytes, macrophage, etc.) - inhibit CTL/NK cell killing pathways - alter immune cell signaling, effector functions, or differentiation - express superantigens	- superantigens - avoid phagolysosomal fusion - block inflammatory pathways by injecting effectors - replicate within and overrun immune cells
2	(6) Block acquired immunity	- downregulate MHC-I or –II - block antigen presentation/proteosome - prevent induction of immune response genes	- IgA proteases - block antigen presentation
2	(7) Inhibit complement	- soluble inhibitors of complement cascade - viral Fc receptors	- proteases to degrade complement - produce capsules and long chain LPS to avoid complement deposition and MAC attack
2	(8) Inhibit cytokines/ interferon/chemokines	- inhibit ligand gene expression - ligand/receptor signaling inhibitors - block secondary antiviral gene induction - interfere with effector proteins	- block inflammatory pathways - activate alternate pathways - secrete proteases to degrade
2 3	(9) Modulate apoptosis/autophagy	- inhibit or accelerate cell death - block death signaling pathways - scavenge free radicals - downregulate death receptors or ligands - inactivate death sensor pathways	- inhibit apoptosis - activate death signaling pathways - alter apoptotic sigaling pathways
2	(10) Interfere with TLRs	- block or hijack TLR signaling - prevent TLR recognition	- alter TLR ligands to decrease recognition - bind to TLR to dampen inflammation - inject effectors to inhibit downstream inflammation signaling
2	(11) Block antimicrobial small molecules	- prevent iNOS induction - inhibit antiviral RNA silencing	- secrete proteases to degrade - alter cell surface to avoid peptide insertion - use pumps to transport peptide - directly sense small molecules to trigger defense mechanisms
2	(12) Block intrinsic cellular pathways	- inhibit RNA editing - regulate ubiquitin/ISGylation pathways	- alter ubiquitin pathway - alter transcriptional programs

1. Antigenic variation :

Avoid antibodies and PRR

2. Inhibition or degradation of immunity :

block pathways enzymes

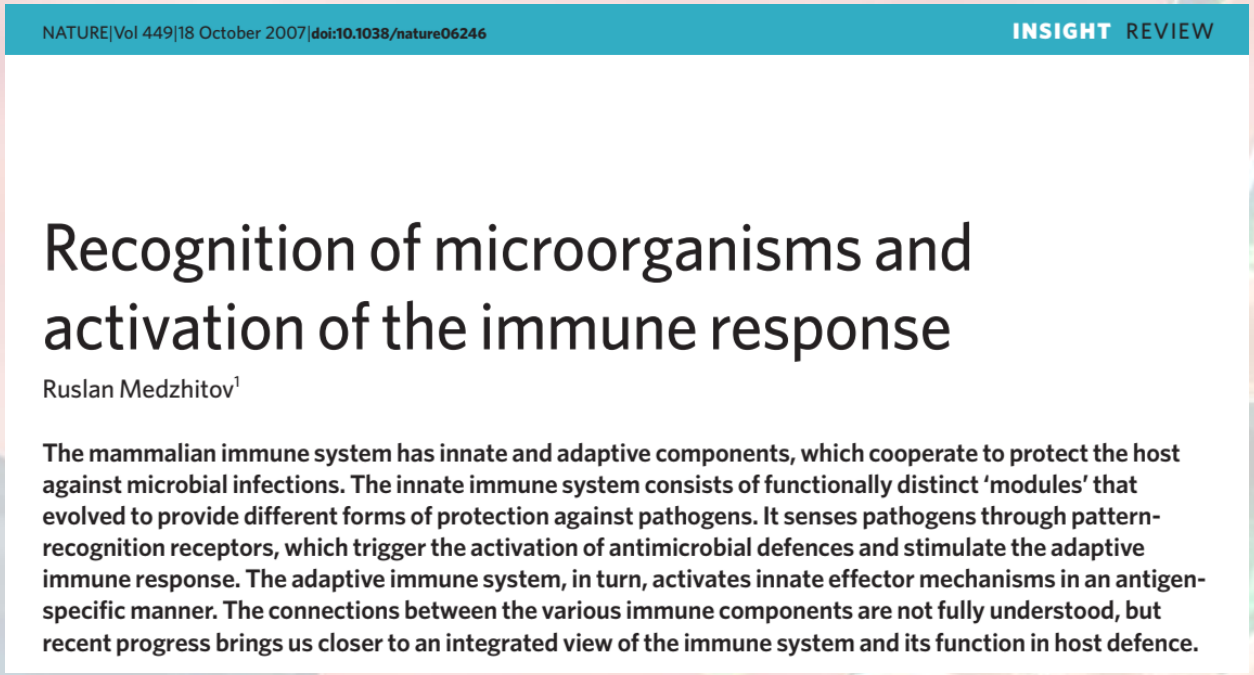
3. Hindrance / covering :

Live in somewhere that protecting themselves from immunity (inside cell / capsule / biofilm / fibrous / granule)

4. Killing the immune cells :

Recommended Ref: Finlay BB, McFadden G. Anti-immunology: evasion of the host immune system by bacterial and viral pathogens. Cell. 2006;124(4):767-82.

Recommended articles



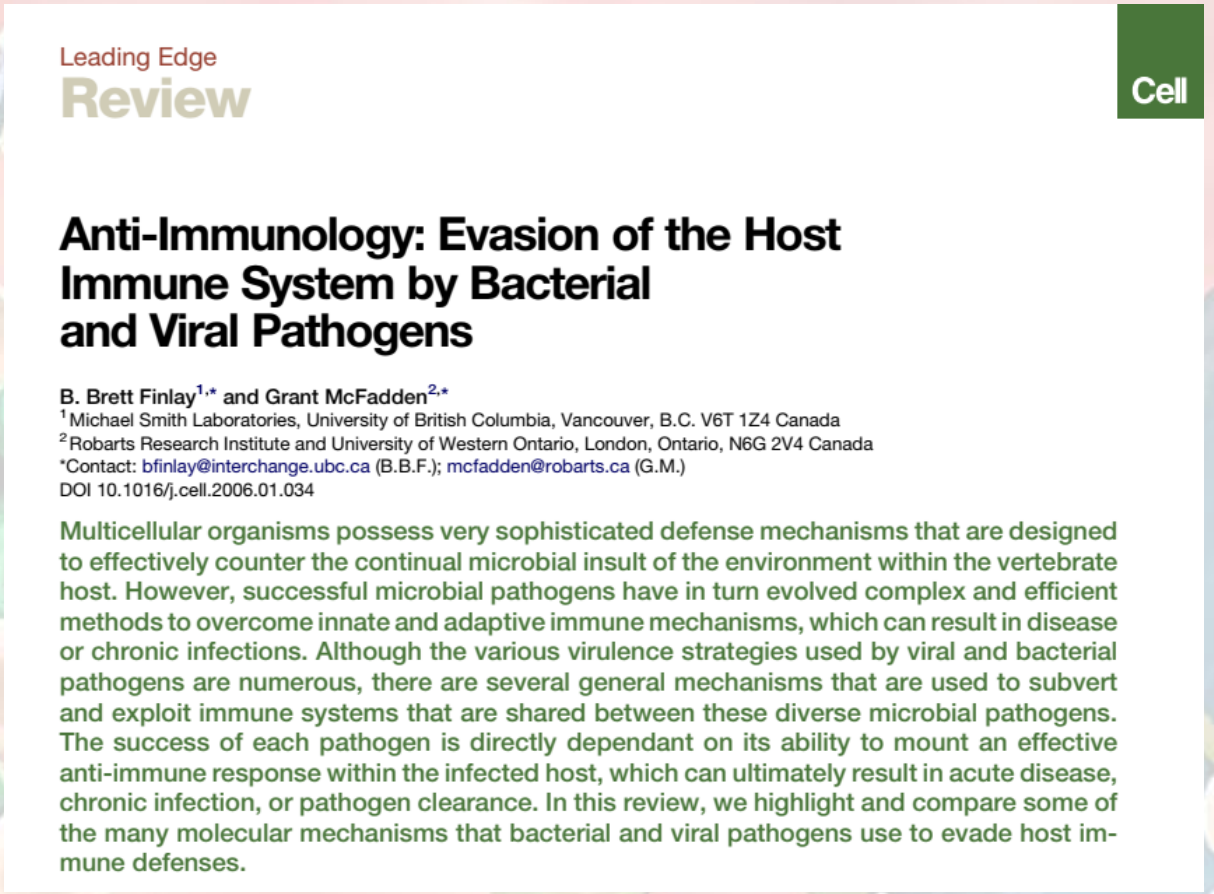
NATURE|Vol 449|18 October 2007|doi:10.1038/nature06246 INSIGHT REVIEW

Recognition of microorganisms and activation of the immune response

Ruslan Medzhitov[1]

The mammalian immune system has innate and adaptive components, which cooperate to protect the host against microbial infections. The innate immune system consists of functionally distinct 'modules' that evolved to provide different forms of protection against pathogens. It senses pathogens through pattern-recognition receptors, which trigger the activation of antimicrobial defences and stimulate the adaptive immune response. The adaptive immune system, in turn, activates innate effector mechanisms in an antigen-specific manner. The connections between the various immune components are not fully understood, but recent progress brings us closer to an integrated view of the immune system and its function in host defence.

Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature. 2007;449(7164):819-26.



Leading Edge
Review

Cell

Anti-Immunology: Evasion of the Host Immune System by Bacterial and Viral Pathogens

B. Brett Finlay[1,*] and Grant McFadden[2,*]
[1] Michael Smith Laboratories, University of British Columbia, Vancouver, B.C. V6T 1Z4 Canada
[2] Robarts Research Institute and University of Western Ontario, London, Ontario, N6G 2V4 Canada
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DOI 10.1016/j.cell.2006.01.034

Multicellular organisms possess very sophisticated defense mechanisms that are designed to effectively counter the continual microbial insult of the environment within the vertebrate host. However, successful microbial pathogens have in turn evolved complex and efficient methods to overcome innate and adaptive immune mechanisms, which can result in disease or chronic infections. Although the various virulence strategies used by viral and bacterial pathogens are numerous, there are several general mechanisms that are used to subvert and exploit immune systems that are shared between these diverse microbial pathogens. The success of each pathogen is directly dependant on its ability to mount an effective anti-immune response within the infected host, which can ultimately result in acute disease, chronic infection, or pathogen clearance. In this review, we highlight and compare some of the many molecular mechanisms that bacterial and viral pathogens use to evade host immune defenses.

Finlay BB, McFadden G. Anti-immunology: evasion of the host immune system by bacterial and viral pathogens. Cell. 2006;124(4):767-82.

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Time for you to ask questions

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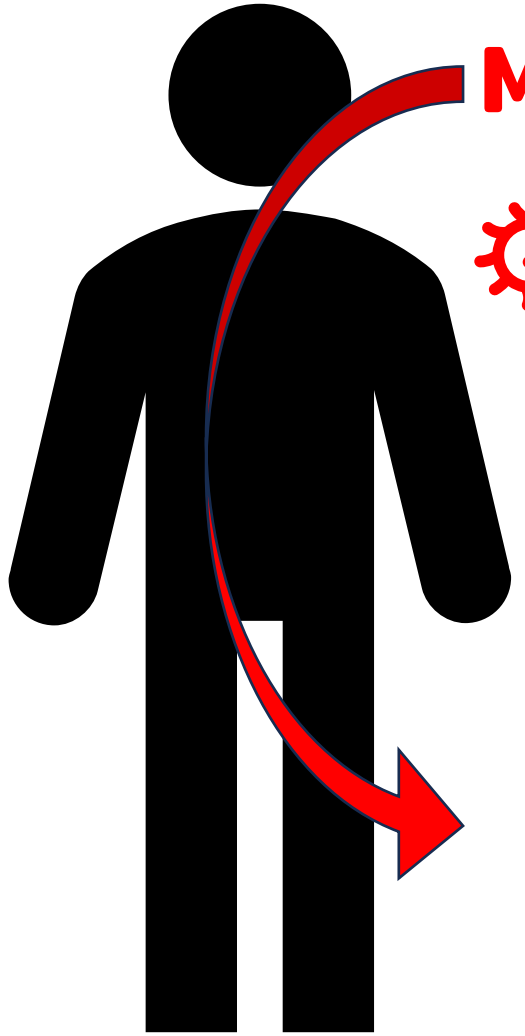
Take home message



Microbe

Adherence

Host

➢ Skin, mucus, pH, excretion, etc.

Growing lifestyle (survival factors to colonize)

Mutualism (+/+)

Commensalism (+/0)

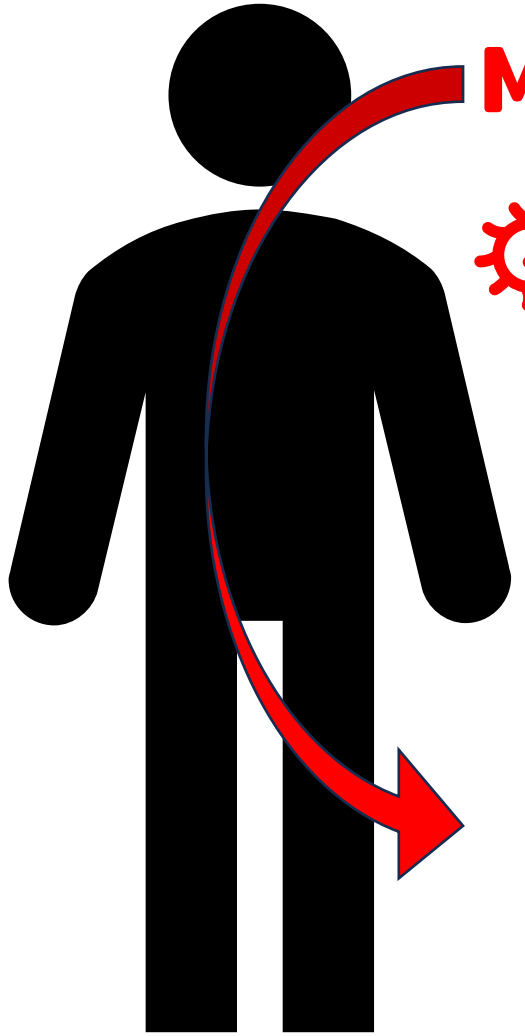
Quorum Sensing:
The Social Network of Bacteria

Parasite / Pathogenic (+/-)

-> Virulence factors

-> toxin w / wo invasion

Take home message



Microbe

- Adherence
- Growing lifestyle (colonize)

Host Innate immunity

- Skin, mucus, pH, excretion, etc.

(non-specific barrier)

Microbiome

- Mutualism (+/+)
- Commensalism (+/0)

VS (competitively growth)

Parasite / Pathogenic (+/-)

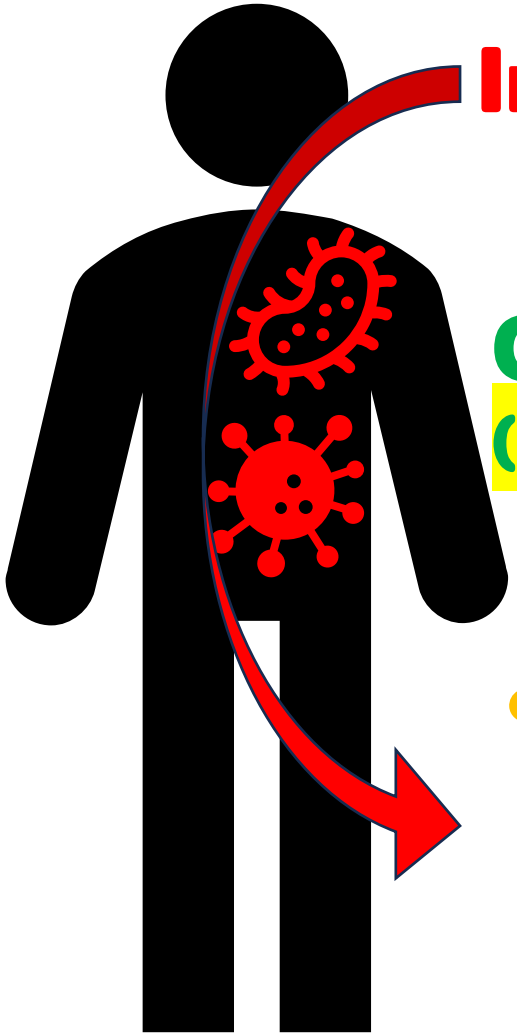
Non-invasive pathogens

Neutralize / prevent attachment

Adaptive immunity

(specific secretory IgA)

Take home message



Invasive Microbes

VS

Cellular innate immunity

(less-specific barrier)

Pattern recognition receptor (PRR)

- PAMPs
- DAMPs

Defense mechanisms

Danger signals (cytokines and chemokines)

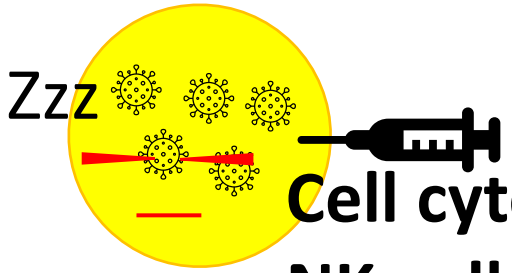
Communication *Cell migration*

Take home message

Defense mechanisms : Size, location and number are matter!!!!

Too small (virus)

Anti-viral state



Cell cytotoxicity by NK-cell or CTL

(natural killer cell) (Cytotoxic T lymphocyte)

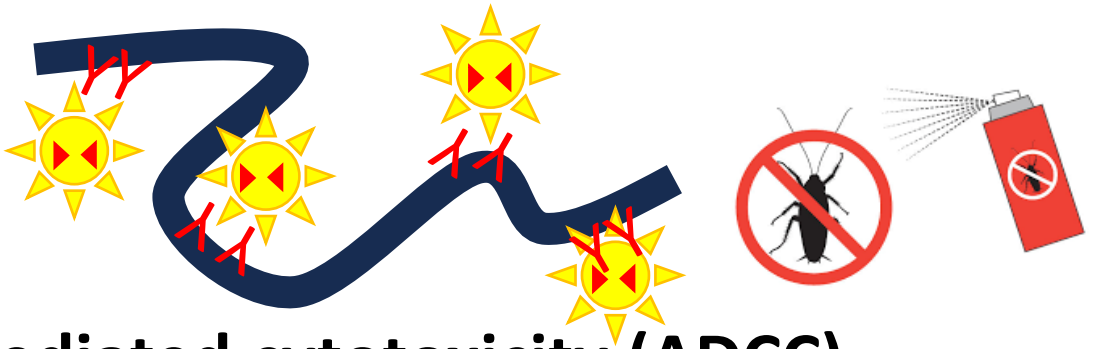
Small and can be ate (bacteria and yeast)

Phagocytosis

(Low number)

(Too many in number)

Too big (parasite and mold)



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Take home message

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2. Inhibition or degradation of immunity :

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3. Hindrance / covering :

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4. Killing the immune cells :