Immunology

Title : Innate immunity

Lec no : 7

Done By : Johainah Taha

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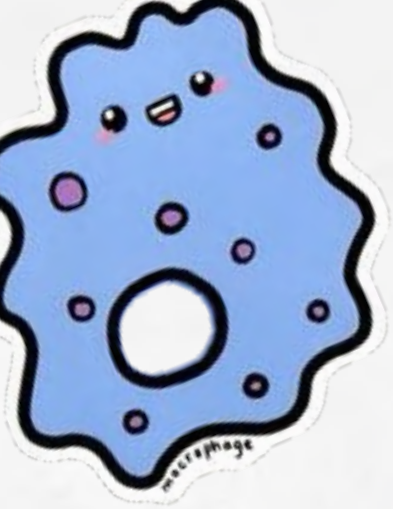

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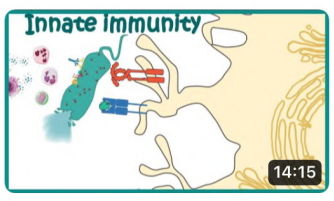
1. 

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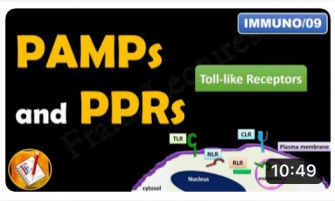
3. 

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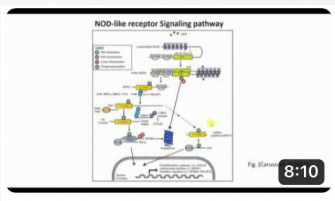
4. 

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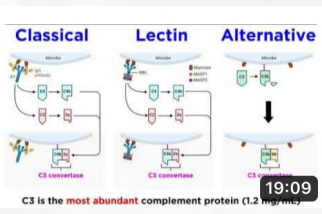
5. 

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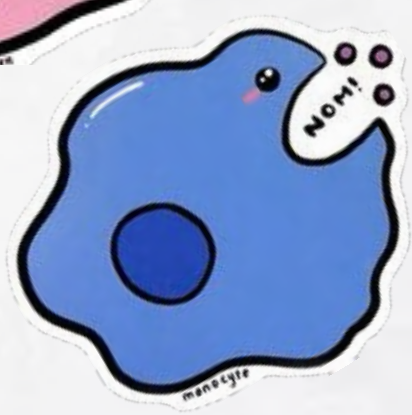

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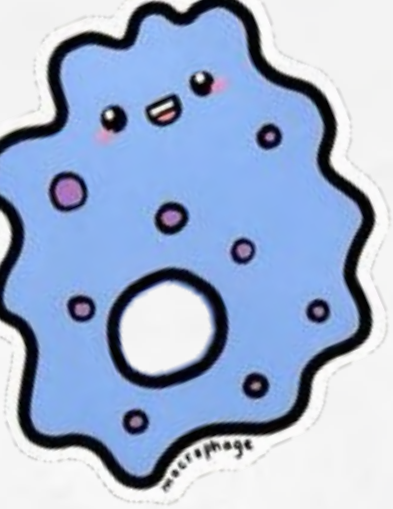


Introduction

• protection against infections that relies on the mechanisms that exist before infection and are capable of rapid response to pathogens
• Innate immunity is the first line of defence against infection
• Characteristics:
– set up at birth
– non–specific
– hereditable
– no immune memory
– Little individual difference

Innate (Nonspecific) Immunity	
First line of defense	**Second line of defense**
• Intact skin • Mucous membranes and their secretions • Normal microbiota	• Natural killer cells and phagocytic white blood cells • Inflammation • Fever • Antimicrobial substances

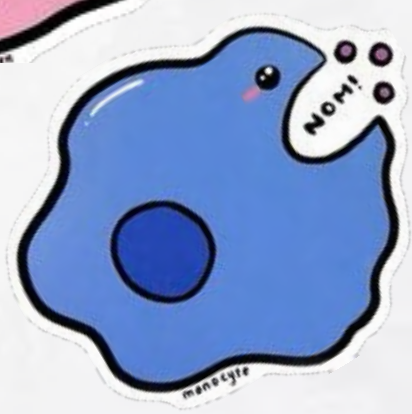
The two principal types of reactions of the innate immune system are inflammation and antiviral defense. Inflammation consists of the accumulation and activation of leukocytes and plasma proteins at sites of infection or tissue injury. These cells and proteins act together to kill mainly extracellular microbes and to eliminate damaged tissues. Innate immune defense against intracellular viruses, even in the absence of inflammation, is mediated by natural killer (NK) cells, which kill virus-infected cells, and by cytokines called type I interferons (IFNs), which block viral replication within host cells.

ADCC : is one of the effector mechanisms of antibody binding
بس يرتبط ال antibody مع ال microbe كامل، بعدها الNK cell بترتبط على Fc تبع IgG بتعمل perforins and granenzymes مثل ال cytotoxic T cell

الدكتور بعدها سأل سؤال ؟ مين بشتغل مثل ال NK cells بهالشغلة ؟
الجواب كان : Neutrophils و eosinophils و macrophage

Innate Host Defense Mechanisms

• Physical factors
• Biochemical factors
• Microbiological factors
• Fever
• Innate Immune cells
• Cytokines
• Complement system
• Inflammation



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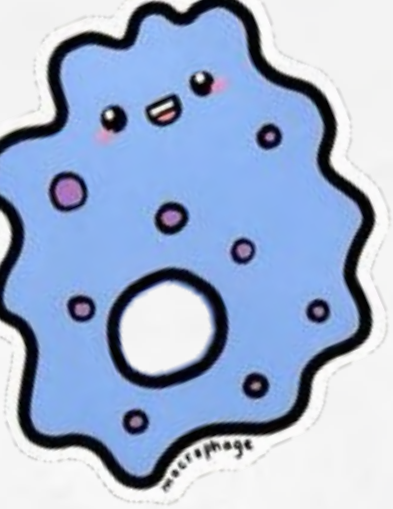


1. Physical Factors

1. Skin: microbes sloughed off along with skin cells, Microbes must penetrate several layers.
    - Stratified and cornified epithelium provides a mechanical barrier
    - Indigenous microbial flora competes with pathogens
    - Acid pH inhibits growth of disease producing bacteria
    - Bactericidal long chain fatty acids in sebaceous gland secretions

2. Mucous Membranes: produce mucus to trap microbes, Most lined with cilia

2. Biochemical Factors

1. Low pH in vaginal and urinary tracts, and stomach
2. Defensins: short antimicrobial peptides, insert into bacterial membranes and form pores
3. Lysozyme: degrades peptidoglycan
    - Tears contain a high concentration of lysozymes (effective against gram positive MO)
4. Interferon: are cytokines that trigger:
    - macrophage activation
    - production of substances to interfere with RNA viral reproduction

حنفصل عنهم✅

Cytokines are 4 families, the interferone are one of them.

Antimicrobial Peptides/Defensins

- Originally isolated from frog skin based on their ability to kill bacteria
- Four hundred peptides described to date
- Defensins (four families in eukaryotes)

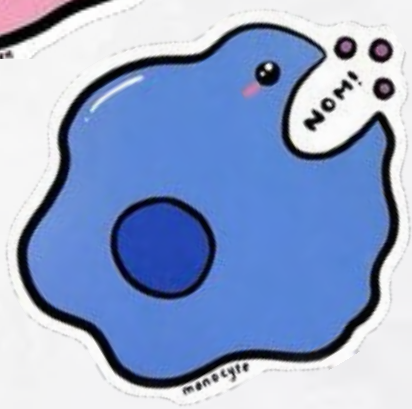
– a-defensins (neutrophils and intestinal Paneth cells)
– b-defensins(epithelialcells)
– Insectdefensins
– Plantdefensins

→ in humans

- Defensins appear to act by binding to outer membrane of bacteria, resulting in increased membrane permeability
- Classified based on their secondary structural features.
- Cathelicidins (CATionic HELIcal bacteriCIDal proteIN) are α-helical peptides
- Human cathelicidin LL37 is highly expressed by PMNs and numerous mucosal and epithelial cell types.

↳ neutrophils

- Defensins are β-strand peptides connected by disulfide bonds
- Most are short peptides (<100 amino acids) and carry a positive charge
- AKA – "cationic antimicrobial peptides"
- Interact with microbial cell membrane components to increase cellular permeability resulting in cell death. They also act to modulate the inflammatory response and wound repair.



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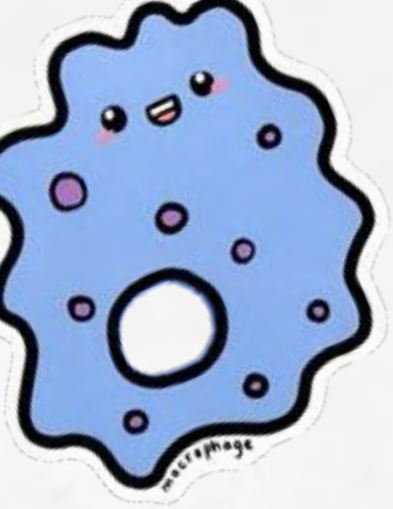


3. Microbiological Barriers

- Normal Flora: not part of immune system, but are part of first line of defense
- Protection they provide is considerable
  - Competitive exclusion of invading microbes
  - Produce compounds that are toxic to other bacteria
  - Stimulates immune system, providing a moderate amount of "exercise" to system, thereby enhancing it's function

4. Fever

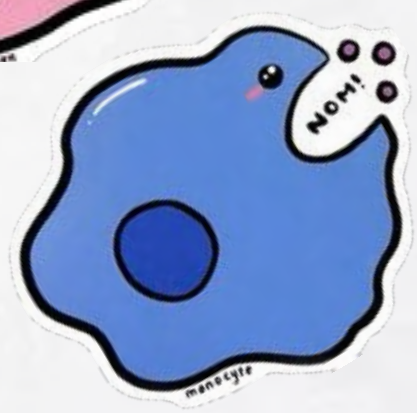
- Mechanism of fever:
- Results from:
- release of pyrogens such as interleukin 1, interferons
- toxins from infectious agents, drug reactions toxins, brain tumors
- Pyrogens released and circulate through the body
- target hypothalamus and cause release of prostaglandin E2
- raises temperature set point of hypothalamus

- Benefits of fever
- Inhibits reproduction of bacteria and viruses
- Promotes interferon activity
- Increases activity of adaptive immunity
- Accelerates tissue repair
- Increases ICAMs on endothelium of capillaries in lymph nodes
- additional immune cells migrating out of blood
- Recommended to leave a low fever untreated

- Risks of a high fever significant above 100 degrees F
- High fevers potentially dangerous above 1030 in children
- Changes in metabolic pathways and denaturation of proteins
- Possible seizures, irreversible brain damage at greater than 1060, death above 1090

$103^{\circ}F = 39.4^{\circ}C$

ال Febrile convulsion هي ارتفاع بالحرارة بصيب الاطفال تحت الخمس سنوات، مثلا بترتفع لدرجة 40 فجأة.
ال presentation بتكون طفل معه تشنج، رقبته معلقة، eye rolling ، saliva
طيب شو لازم اعمل ؟-
اول شي بنزل الحرارة (بستخدم كمادات، بخطه تحت حنفية دافية، بعطيه خافض حرارة بس مو IV بعطيه تحميله Rectal
ثاني شي بسأل اهله لو هاي اول مرة تصيبه او لا ؟
فلو مش اول مرة، مثلا سادس مرة، بدي اطلع عن الfebrile convulsion و ابدأ افكر بال seizure و احول المريض لطبيب اعصاب اطفال و بكون اله more investigations
لو كان لأول مرة بدنا ندور عن سبب الحرارة الي هو infection فمثلاً لو كان السبب follicular tonsilitis بدي اوصي الاهل يعطوا الابن anti-pyretics كل ٤-٦ ساعات
في طالب سأل سؤال هل ممكن يكون سبب ال febrile convulsion و لكن السبب غالبا infection



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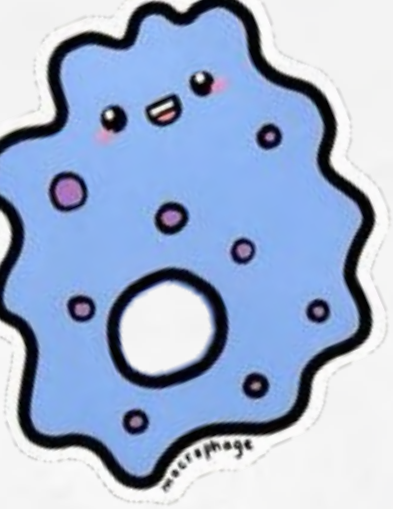

5. Innate Immune Cells

Cell type	Pricipal function(s)
Monocytes/Macrophages	Phagocytosis, inflammation, T-cell activation, tissue repair
Neutrophils NK cells	Phagocytosis, inflammation
Dendritic cells	Killing of infected or tumor cells
Mast cells	Phagocytosis, activation of naive T-cells Inflammation
Eosinophils	Defense against parasites

ال macrophages و ال dendritic calls هم antigen presenting cell
ولكن ال dendritic cell فقط هي نقطة الوصل بين innate و addaptive
Question ? Does Innate immunity activate adaptive immunity ?
Yes, By dendritic cells
ولازم يكون عنا 2 signals

الأولى ال antigen itself لما
يرتبط عال Tcell مثلا

و الثانية مجرد ما ال dc تتعرف على ال Ag و تعمل اله
co stimulatory proteins حتنتج phagocytosis
على suface و حترتبط مع ال T cell

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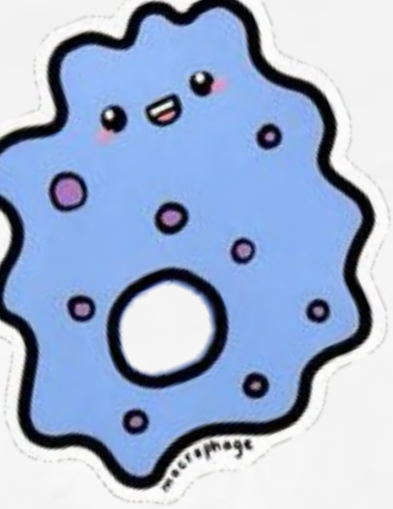


Phagocytes

- Performed by Neutrophils and Macrophages

1. Phagocytosis is the capture and digestion of foreign particles
2. Chemokines are cytokines that attract macrophages and neutrophils to infected tissues

Ex: microbial peptide, C3A, -> ما فهمت قصد الدكتور هون

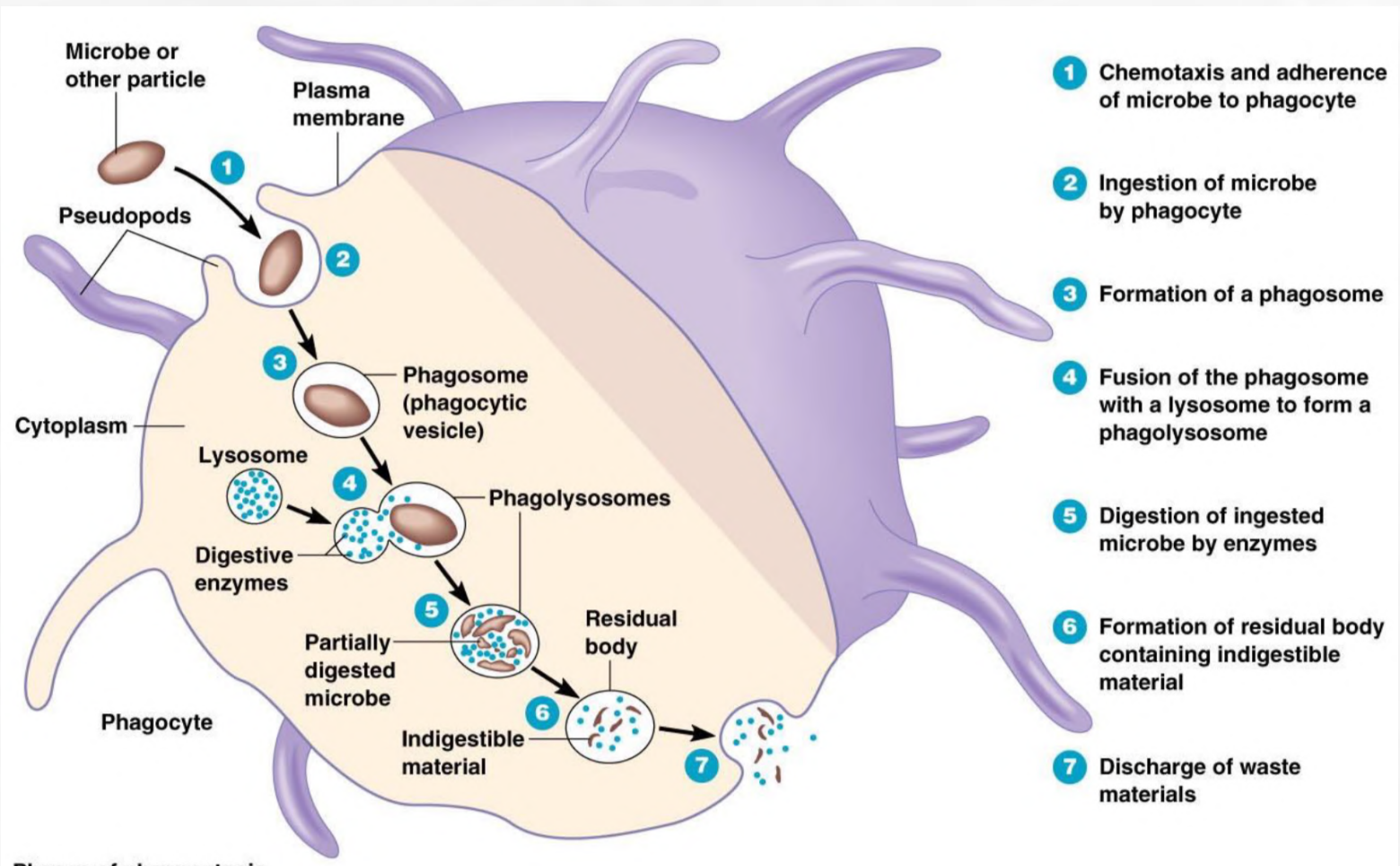
3. Opsonins attach to microbes to increase the ability of phagocytes to adhere (opsonization)

Steps of Phagocytosis

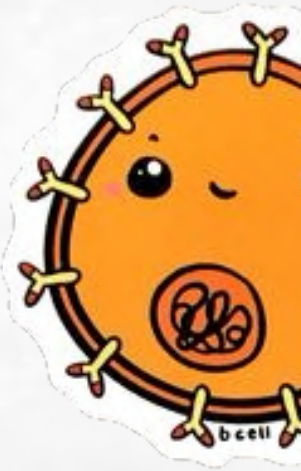
- Recognition
- Ingestion- pseudopods engulf microbe through endocytosis
- Vacuole Formation- vacuole contains microbe
- Digestion- vacuole merges with enzymes to destroy microbes
- Exocytosis- microbial debris is released

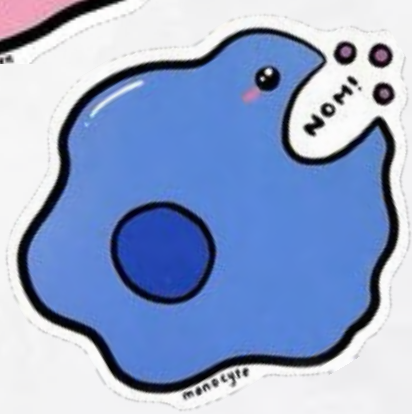
If the antigrn is a protein or peptide, it is easy for phagocytes and dc to bind to and phagoctose them

But if this antigen is made of carbohydrate, opsonization is important for phagocytosis and binding



Phases of phagocytosis





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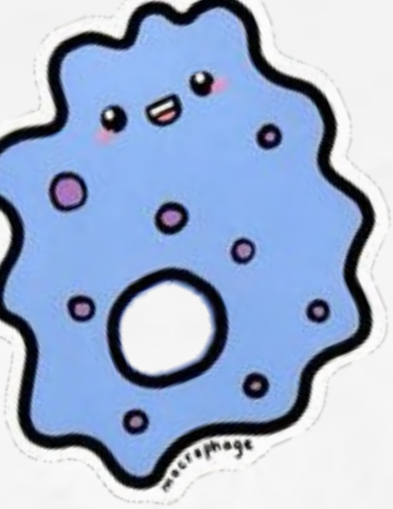


Innate Immune Recognition

- All multi-cellular organisms are able to recognize and eliminate pathogens
- Despite their extreme heterogeneity, pathogens share highly conserved molecules, called "pathogen-associated molecular patterns" (PAMPs)
- Host cells do not share PAMPs with pathogens
- PAMPs are recognized by innate immune recognition receptors called pattern-recognition molecules/ receptors (PRMs/PRRs)

The pattern recognition receptors of the innate immune system are nonclonally distributed; that is, identical receptors are expressed on all the cells of a particular type, such as macrophages. Therefore, many cells of innate immunity may recognize and respond to the same microbe. This is in contrast to the antigen receptors of the adaptive immune system, which are encoded by genes formed by rearrangement of gene segments during lymphocyte development, resulting in many clones of B and T lymphocytes, each expressing a unique receptor. It is estimated that there are about 100 types of innate immune receptors that are capable of recognizing about 1000 PAMPs and DAMPs. In striking contrast, there are only two kinds of specific receptors in the adaptive immune system (immuno-globulin [Ig] and T cell receptors [TCRs]), but because of their diversity they are able to recognize millions of different antigens

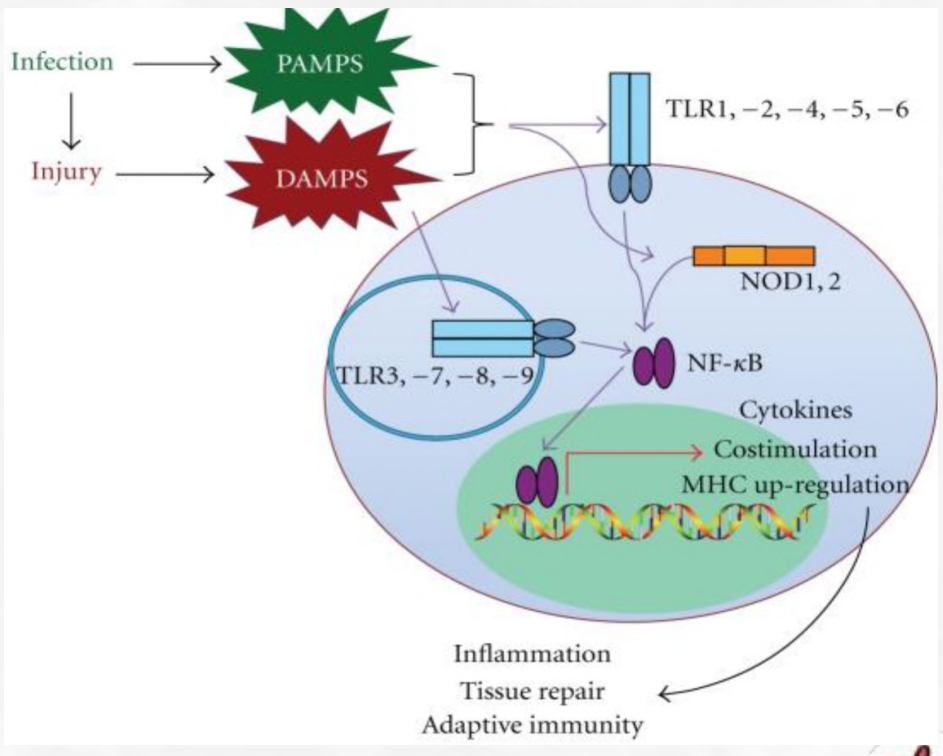
Damage-associated molecular patterns (DAMPs) Endogenous molecules that are produced by or released from damaged and dying cells that bind to pattern recognition receptors and stimulate innate immune responses. Examples include high mobility group box 1 (HMGB1) protein, extracellular ATP, and uric acid.

Pathogen-associated molecular patterns (PAMPs) Structures produced by microorganisms but not mammalian (host) cells, which are recognized by and stimulate the innate immune system. Examples include bacterial lipopolysaccharide and viral double-stranded RNA.

Typical PAMPs

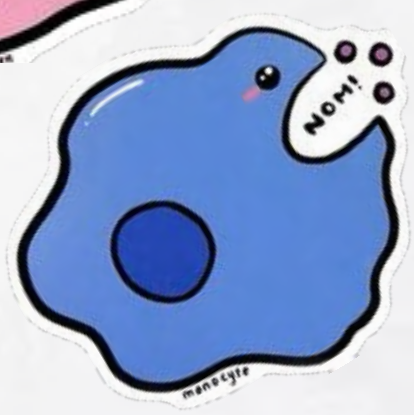
- Typical PAMPs:
  - Lipopolysaccharides
  - Peptidoglycans
  - Certain nucleotide sequences unique to bacteria
  - Other bacterial components

- Binding of Innate immune receptors and PAMPs:
  - Mediate inflammatory cytokines
  - Antigen-presenting cells recognize PAMPs



عدد ال receptors بالadaptive immunity اقل لتتعرف على ال pathogen بس نوعين b cell
بس قادرين على التعرف ععدد لا نهائي and t cell receptor
بينما بال innate immunity عنا اكثر من مية نوع بس بتعرفوا على pathogen اقل

هسا هدول المية receptor بندرجوا تحت شي بنسميه pattern recognision receptor
و بنقسمهم لانواع : (كل نوع حيكون مشروح بصفحة)



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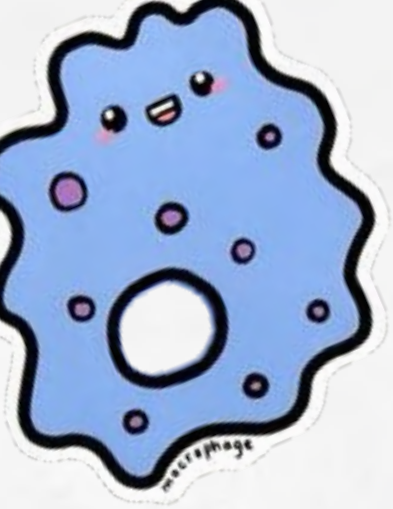
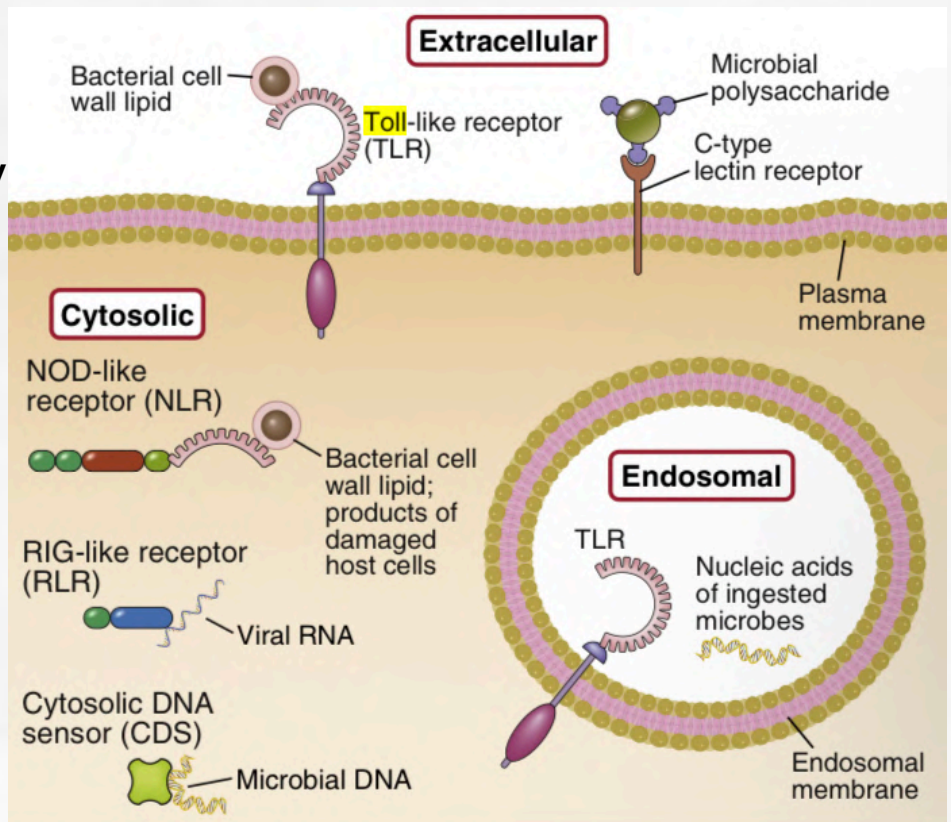


The Pattern Recognition Receptors (PRR)

من الكتاب (مهم)

The pattern recognition receptors used by the innate immune system to detect microbes and damaged cells are expressed on phagocytes, dendritic cells, and many other cell types and are located in different cellular compartments where microbes or their products may be found. These receptors are present on the cell surface, where they detect extracellular microbes; in vesicles (endosomes) into which microbial products are ingested; and in the cytosol, where they function as sensors of cytoplasmic microbes and products of cell damage. These receptors for PAMPs and DAMPs belong to several protein families.



1- Toll-Like Receptors

Toll-like receptors (TLRs) are homologous to a Drosophila protein called Toll, which was discovered for its role in the development of the fly and later shown to be essential for protecting flies against fungal infections. In vertebrates, there are 10 different TLRs specific for different components of microbes.

TLR-2 recognizes several glycolipids and peptidoglycans that are made by gram-positive bacteria and some parasites.

***TLR-3 is specific for double-stranded RNA.**

TLR-7 and TLR-8 are specific for single-stranded RNA.

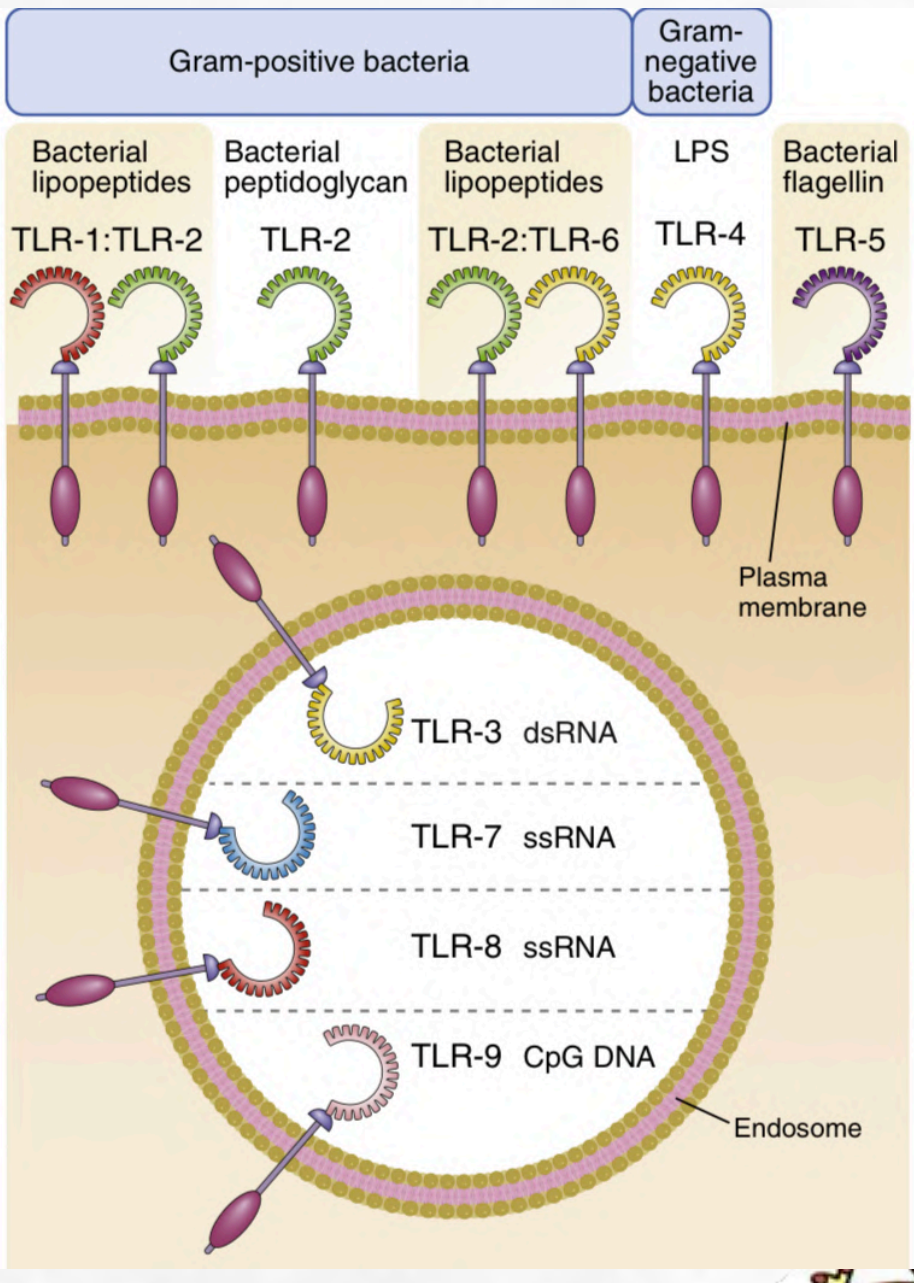
TLR-4 is specific for bacterial LPS (endotoxin), made by gram-negative bacteria.

***TLR-5 is specific for a bacterial flagellar protein called flagellin. Example : Salmonella**

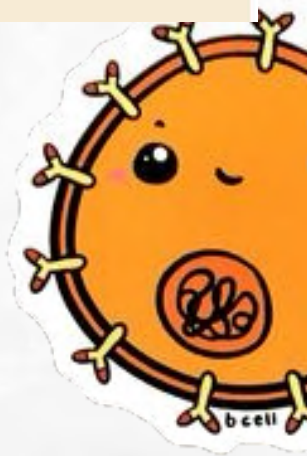
TLR-9 recognizes unmethylated CpG DNA, which is abundant in microbial genomes.

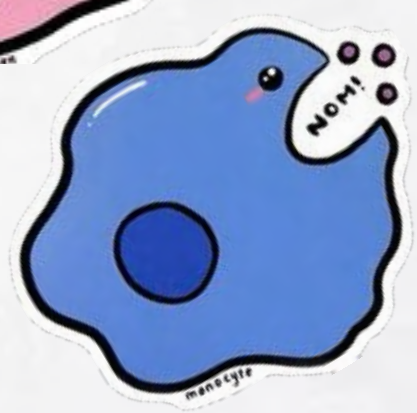
anti-inflamatory ال TLR 10 مو واضحة وظيفته ولكن يقال انها

TLRs specific for microbial proteins, lipids, and polysaccharides (many of which are present in bacterial cell walls) are located on cell surfaces, where they recognize these products of extracellular microbes. TLRs that recognize nucleic acids are in endosomes, into which microbes are ingested and where they are digested and their nucleic acids are released.



لاحظوا مين ال receptors الموجودين على ال cell surface و الي بكونوا على شكل endosome





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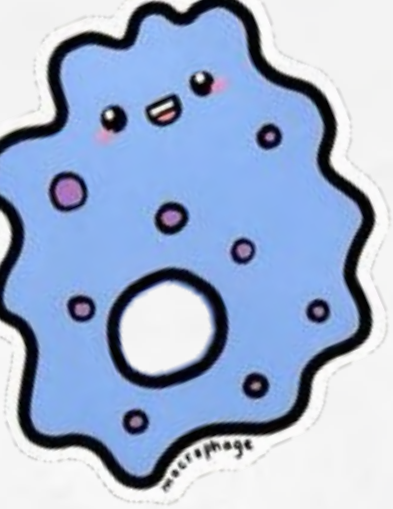


من الكتاب

Signals generated by TLRs activate transcription factors that stimulate expression of cytokines and other proteins involved in the inflammatory response and in the antimicrobial functions of activated phagocytes and other cells.

Among the most important transcription factors activated by TLR signals are members of the nuclear factor κB (NF-κB) family, which promote expression of various cytokines and endothelial adhesion molecules that play important roles in inflammation, and interferon regulatory factors (IRFs), which stimulate production of the antiviral cytokines, type I interferons.

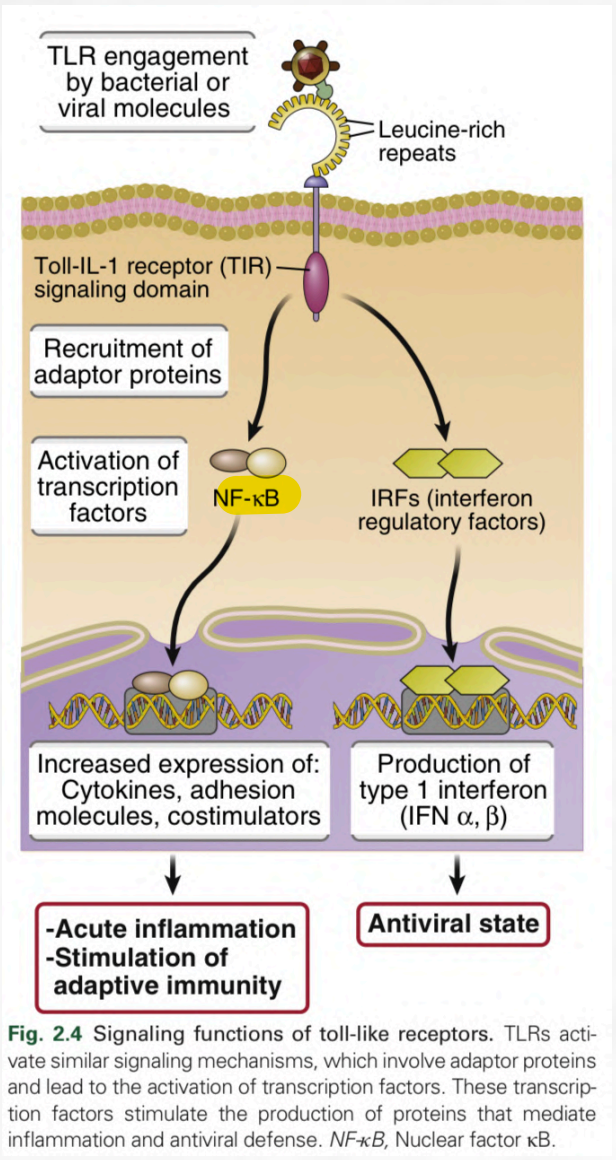
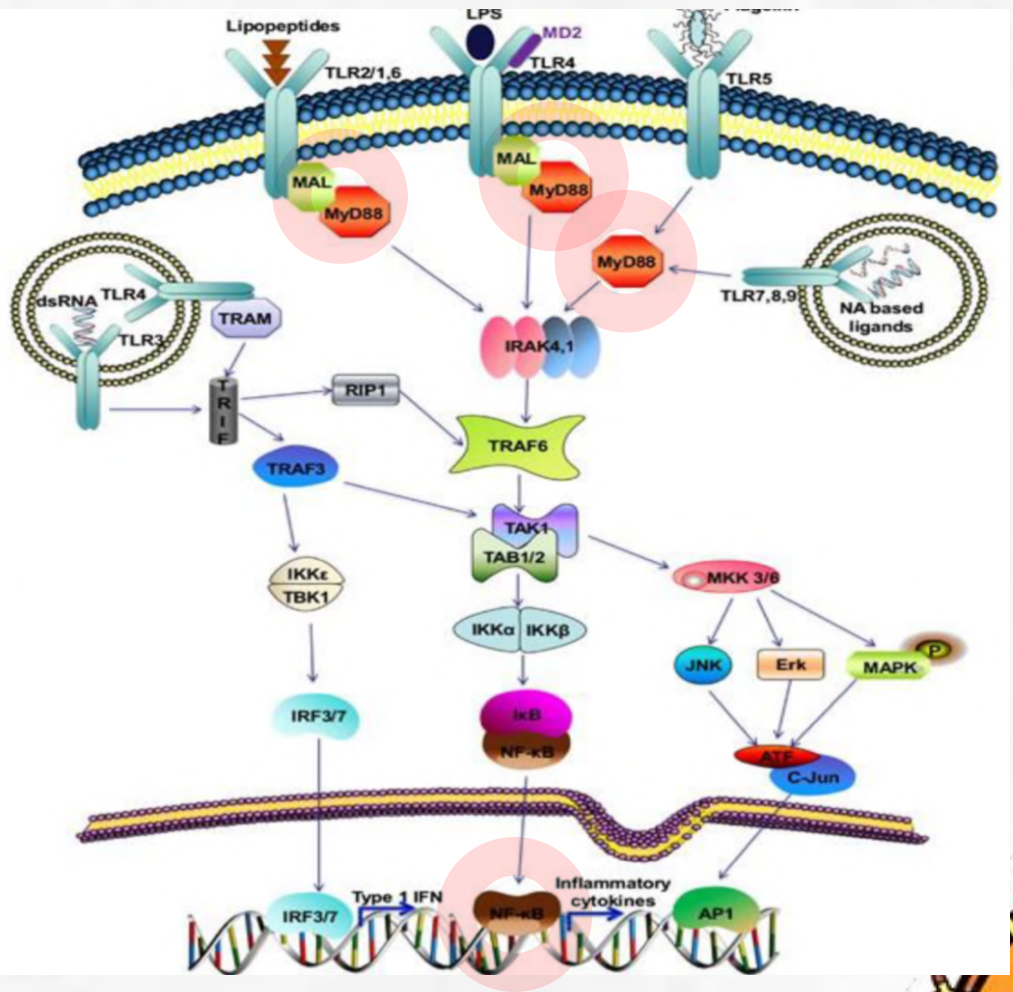


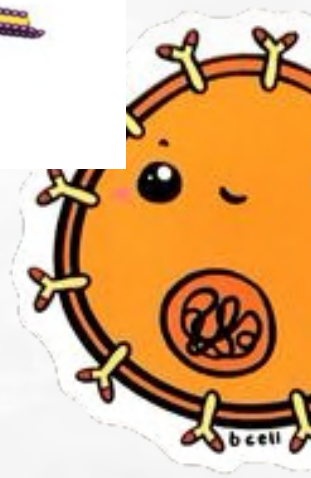
Fig. 2.4 Signaling functions of toll-like receptors. TLRs activate similar signaling mechanisms, which involve adaptor proteins and lead to the activation of transcription factors. These transcription factors stimulate the production of proteins that mediate inflammation and antiviral defense. *NF-κB,* Nuclear factor κB.

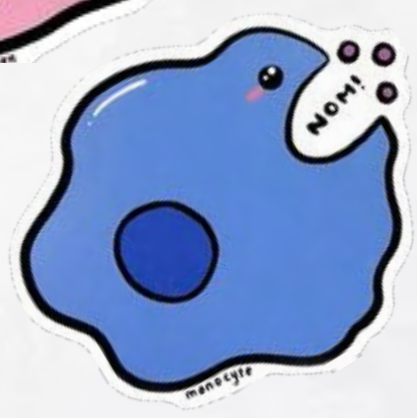
Rare autosomal recessive diseases characterized by recurrent infections are caused by mutations affecting TLRs or their signaling molecules, highlighting the importance of these pathways in host defense against microbes.

For example, individuals with mutations affecting TLR-3 are susceptible to herpes simplex virus infections, particularly encephalitis, and mutations in MyD88, the adaptor protein downstream of several TLRs, make individuals susceptible to bacterial pneumonias.

- **Types:** TLR1, TLR2, TLR3,TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10.
- **How do they work??**
- 1) Recognition of foreign body: either Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMS).
- 2) Activation of various expression factors, most important are: NF-kB and Interferon Regulatory Factors (IFR).
- **Mutations:** very rare, include:
- 1) mutation affecting TLR3: individuals susceptible to Herpes encephalitis.
- 2) mutation in MyD88: susceptible to bacterial pneumonias.







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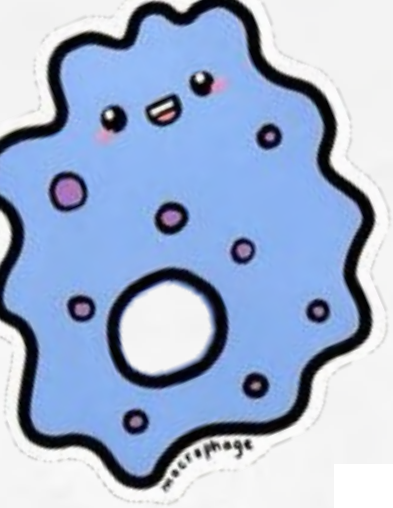
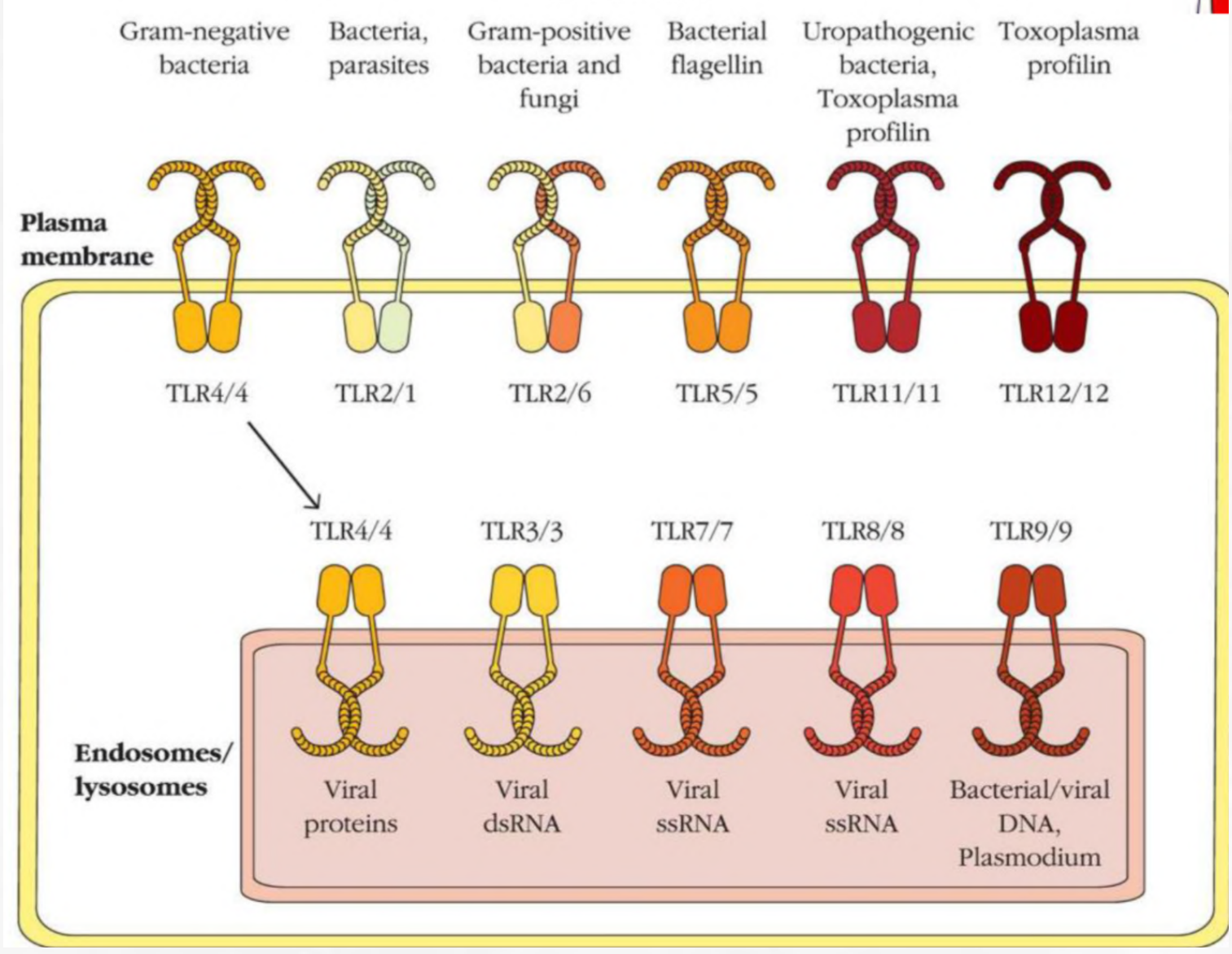


TLRs



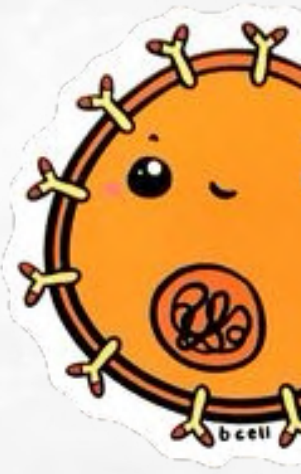
Classification of TLRs according to their site in cells

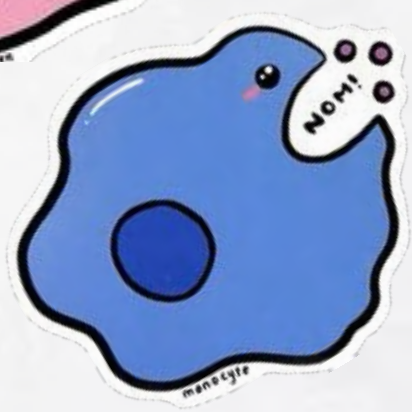
TLRs at the cell surface

- **TLR1:** recognizes bacterial lipopeptides of Gram positive bacteria.
- **TLR2:** recognizes bacterial lipopeptides and peptidoglycans of Gram positive bacteria and some parasites.
- **TLR4:** recognizes bacterial endotoxin (LPS) of Gram negative bacteria.
- **TLR5:** recognizes bacterial flagellin protein of flagellated bacteria.
- **TLR6:** recognizes bacterial lipopeptides of Gram positive bacteria.

TLRs at endosomes

- **TLR3:** recognizes double-stranded RNA.
- **TLR7:** recognizes single-stranded RNA.
- **TLR8:** recognizes single-stranded RNA.
- **TLR9:** recognizes unmethylated CpG regions on microbial cell DNA.
- **TLR10:** UNKNOWN , some articles suggest it might has an ANTI- inflammatory role!!!!





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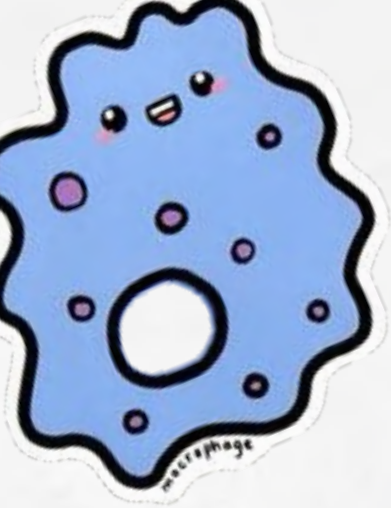


من الكتاب

2- NOD-Like Receptors

The NOD-like receptors (NLRs) are a large family of innate receptors that sense DAMPs and PAMPs in the cytosol of cells and initiate signaling events that promote inflammation. All NLRs contain a nucleotide oligomerization domain (NOD, named because of the activity it was originally associated with) but different NLRs have different N-terminal domains.

Two important NLRs, NOD1 and NOD2, have N-terminal caspase related domains (CARDs), and are expressed in several cell types including mucosal barrier epithelial cells and phagocytes.

هم receptor، و الreceptor عبارة عن بروتين، بالتالي عنا C terminal و N terminal ، هاي النوعية من ال reseptors
بكون عنا domain ماسك بال N terminal ، مثلا الNOD1 و ال NOD2 بكون ماسك في ال N terminal : Caspase

NOD1 and NOD2 both recognize peptides derived from bacterial cell wall peptidoglycans, and in response, they generate signals that activate the NF-κB transcription factor, which promotes expression of genes encoding inflammatory proteins. NOD2 is highly expressed in intestinal Paneth cells in the small bowel, where it stimulates expression of antimicrobial substances called defensins in response to pathogens. Some polymorphisms of the NOD2 gene are associated with inflammatory bowel disease, perhaps because these variants have reduced function and allow luminal microbes to penetrate the intestinal wall and trigger inflammation.

NOD-like Receptors (NLR)

-Types: according to the domain present on N-terminal end:

NOD1 and NOD2 have N-terminal caspase related domains

-In the body: *mucosal barrier epithelial cells

** Phagocytes

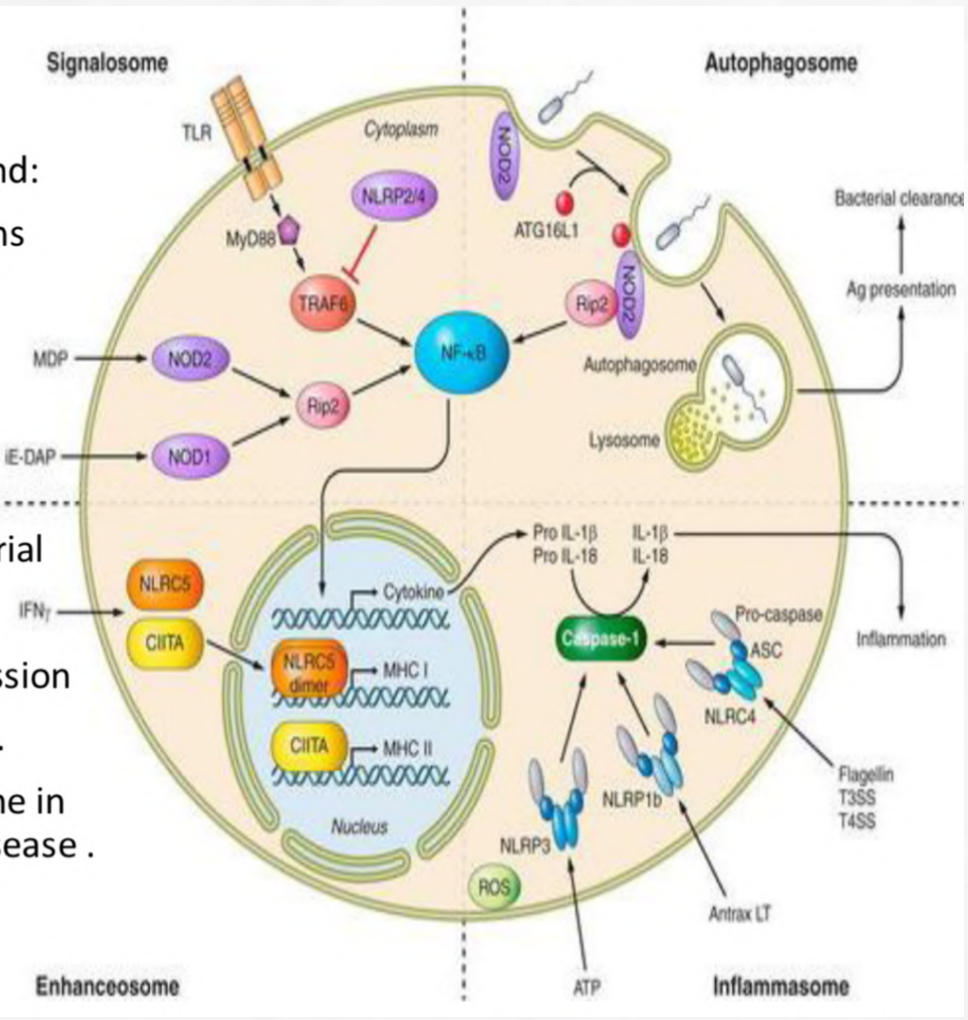
NOD2 is also present at Paneth cells in the small bowl

-Inside cells: located in the cytosol

-Functions: * they recognize peptides derived form bacterial Cell wall polypeptides—> NF-KB activation

** NOD2 in Paneth cells stimulate the expression of Denfensins (antimacrobial substances).

Pathologies: it is thought that polymorphism in NOD2 gene in the small bowel is responsible for inflammatory bowel disease .



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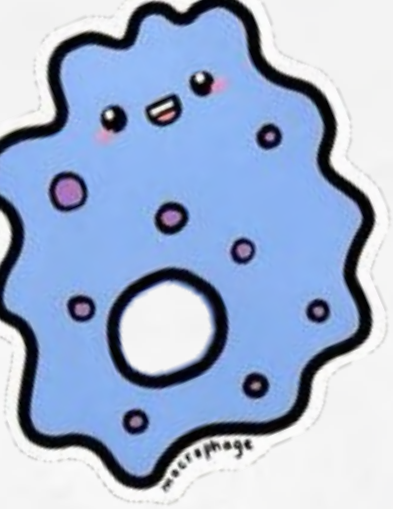
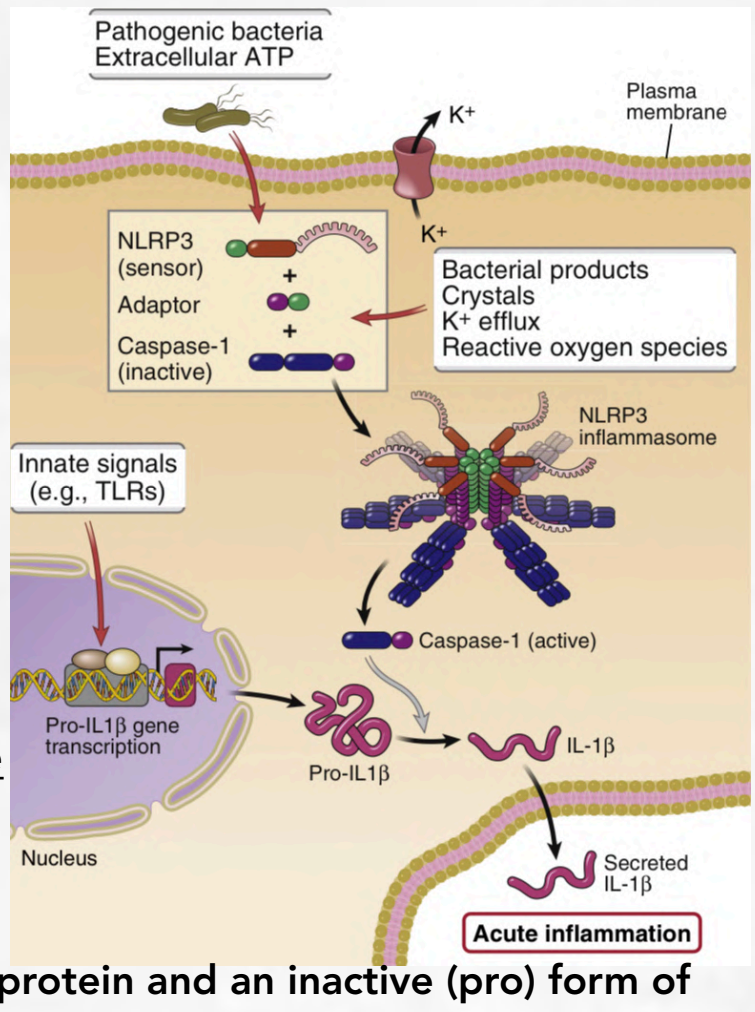


من الكتاب

Inflammasomes

Inflammasomes are multiprotein complexes that assemble in the cytosol of cells in response to microbes or changes associated with cell injury, and proteolytically generate active forms of the inflammatory cytokines IL-1β and IL-18. IL-1β and IL-18 are synthesized as inactive precursors, which must be cleaved by the enzyme caspase-1 to become active cytokines that are released from the cell and promote inflammation.



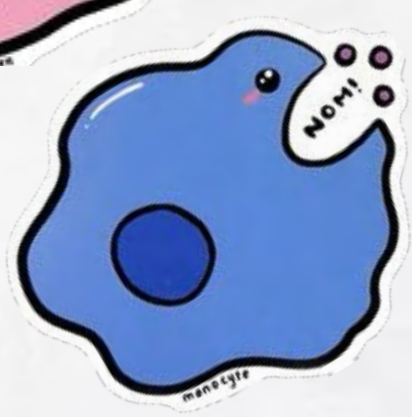
Inflammasomes are composed of oligomers of a sensor, caspase-1, and an adaptor that links the two. There are many different types of inflammasomes, most of which use 1 of 10 different NLR-family proteins as sensors. These sensors directly recognize microbial products in the cytosol or sense changes in the amount of endogenous molecules or ions in the cytosol that indirectly indicate the presence of infection or cell damage. Some inflammasomes use sensors that are not in the NLR family, such as AIM-family DNA sensors and a protein called pyrin. After recognition of microbial or endogenous ligands, the NLR sensors oligomerize with an adaptor protein and an inactive (pro) form of the enzyme caspase-1 to form the inflammasome, resulting in generation of the active form of caspase-1.

Active caspase-1 cleaves the precursor form of the cytokine interleukin-1β (IL-1β), pro-IL-1β, to generate biologically active IL-1β. As discussed later, IL-1 induces acute inflammation and causes fever.

One of the best characterized inflammasomes uses NLRP3 (NOD-like receptor family, pyrin domain containing 3) as a sensor. The NLRP3 inflammasome is expressed in innate immune cells including macrophages and neutrophils, as well as keratinocytes in the skin and other cells. A wide variety of stimuli induce formation of the NLRP3 inflammasome, including crystalline substances such as uric acid (a by-product of DNA breakdown, indicating nuclear damage) and cholesterol crystals, extracellular adenosine triphosphate (ATP) (an indicator of mitochondrial damage) binding to cell surface purinoceptors, reduced intracellular potassium ion (K+) concentration (which indicates plasma membrane damage), and reactive oxygen species. Thus, the inflammasome reacts to injury affecting various cellular components. How NLRP3 recognizes such diverse types of cellular stress or damage is not clearly understood. Inflammasome activation is tightly controlled by post-translational modifications such as ubiquitination and phosphorylation, which block inflammasome assembly or activation, and some micro-RNAs, which inhibit NLRP3 messenger RNA.

Inflammasome activation also causes an inflammatory form of programmed cell death of macrophages and DCs called pyroptosis, characterized by swelling of cells, loss of plasma membrane integrity, and release of inflam- matory cytokines. Activated caspase-1 cleaves a protein called gasdermin D. The N-terminal fragment of gasdermin D oligomerizes and forms a channel in the plasma membrane that initially allows the egress of mature IL-1β, and eventually permits the influx of ions, followed by cell swelling and pyroptosis.

The inflammasome is important not only for host defense but also because of its role in several diseases. Gain-of-function mutations in NLRP3, and less frequently, loss-of-function mutations in regulators of inflammasome activation, are the cause of autoinflammatory syn- dromes, characterized by uncontrolled and spontaneous inflammation. IL-1 antagonists are effective treatments for these diseases. The common joint disease gout is caused by deposition of urate crystals and subsequent inflam- mation mediated by inflammasome recognition of the crystals and IL-1β production. The inflammasome may also contribute to atherosclerosis, in which inflammation caused by cholesterol crystals may play a role.



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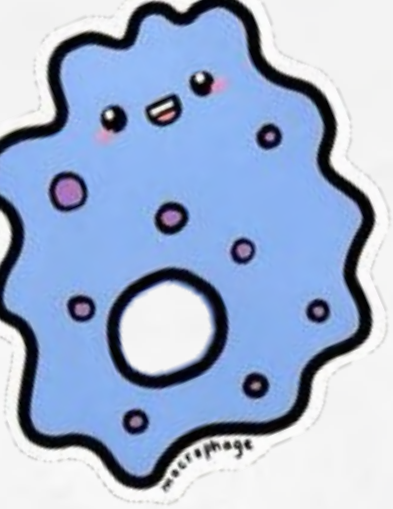
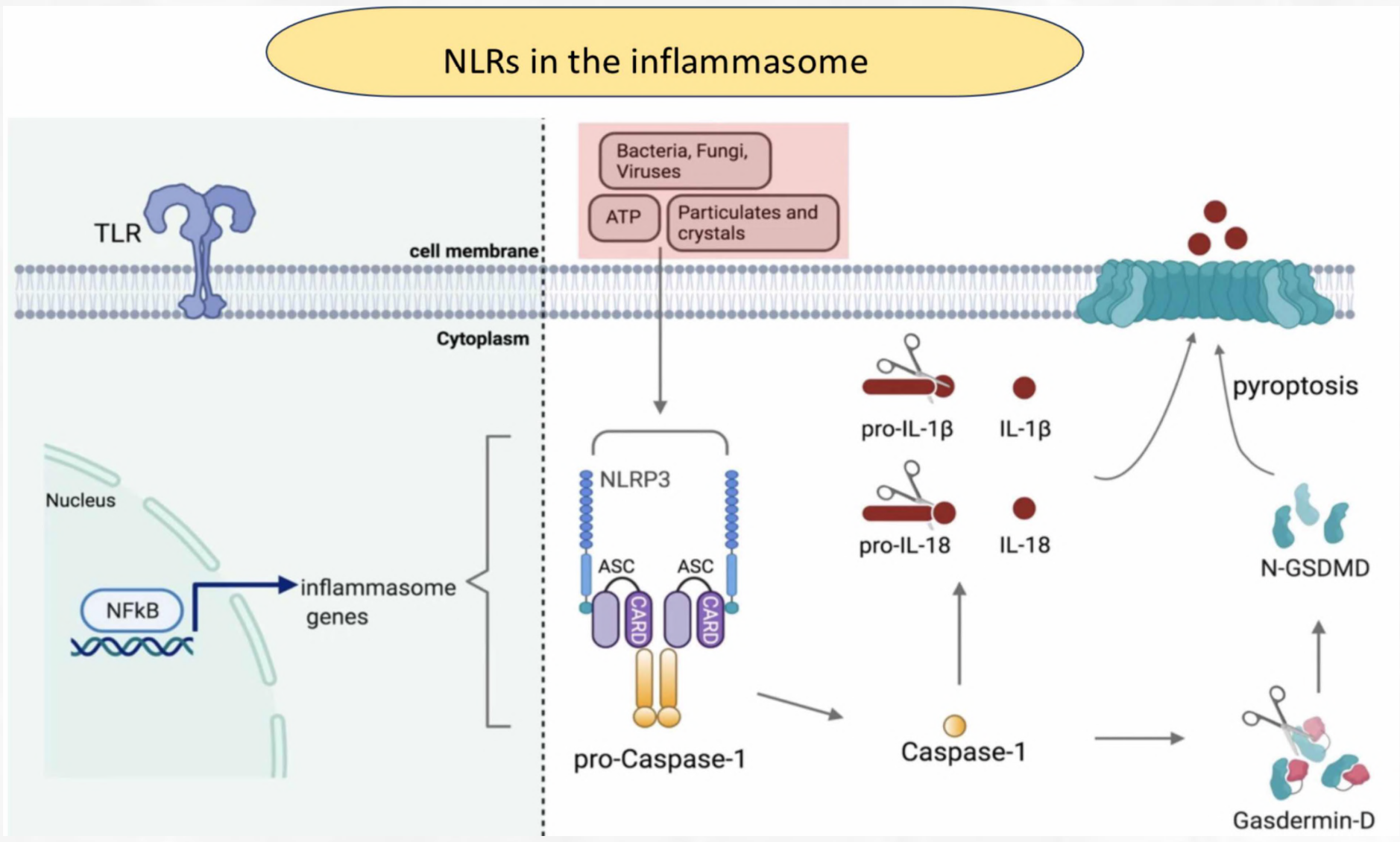




THE INFLAMMASOME

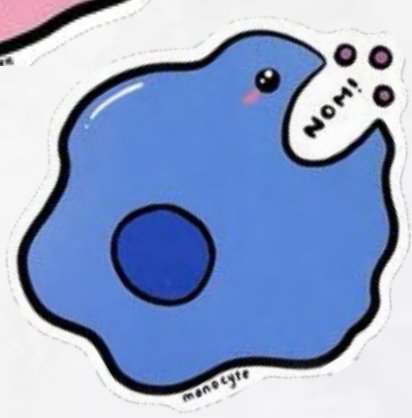
- **Definition:** a multiprotein complex which gets activated upon exposure to an antigen, composed of: 1) *Sensor*: usually from **NLR** family (NLR3p). Others can be of AIM family DNA sensors or a protein called Pyrin
  2) *Adaptor protein:* to link between the sensor and the caspase.
  3) *Caspase 1 enzyme:* responisble for cleavage of effectors.
- **Location:** in the cytosol of macrophages, neutrophils, dendritic cells, keratinocytes
- **Antigens recognized by NLR3P inflammasome:** uric acid, cholesterol crystals, extracellular ATP, reduced intracellular K+, ROS.
- **Results of inflammasome activation:**

1. Release of pro-inflammatory molecules to recruit more leukocytes and potentiate the inflammatory response (IL-B1, IL-18).
2. Pyroptosis: programmed cell death of macrophages and dendritic cells.

- **Related pathologies:** *loss/gain of function mutations in NLRP3:

Treatment with IL-1 antagonists has proven its effectiveness

* contributes to pathogenesis of gout and atherosclerosis



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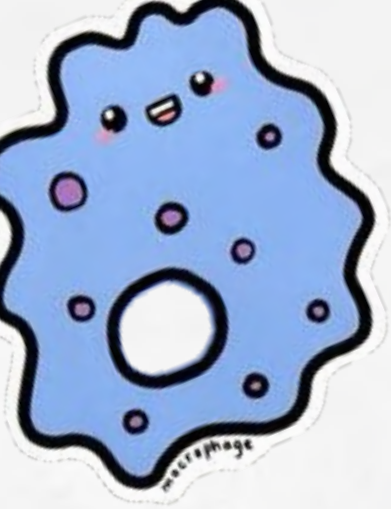


من الكتاب

3- Cytosolic RNA and DNA Sensors

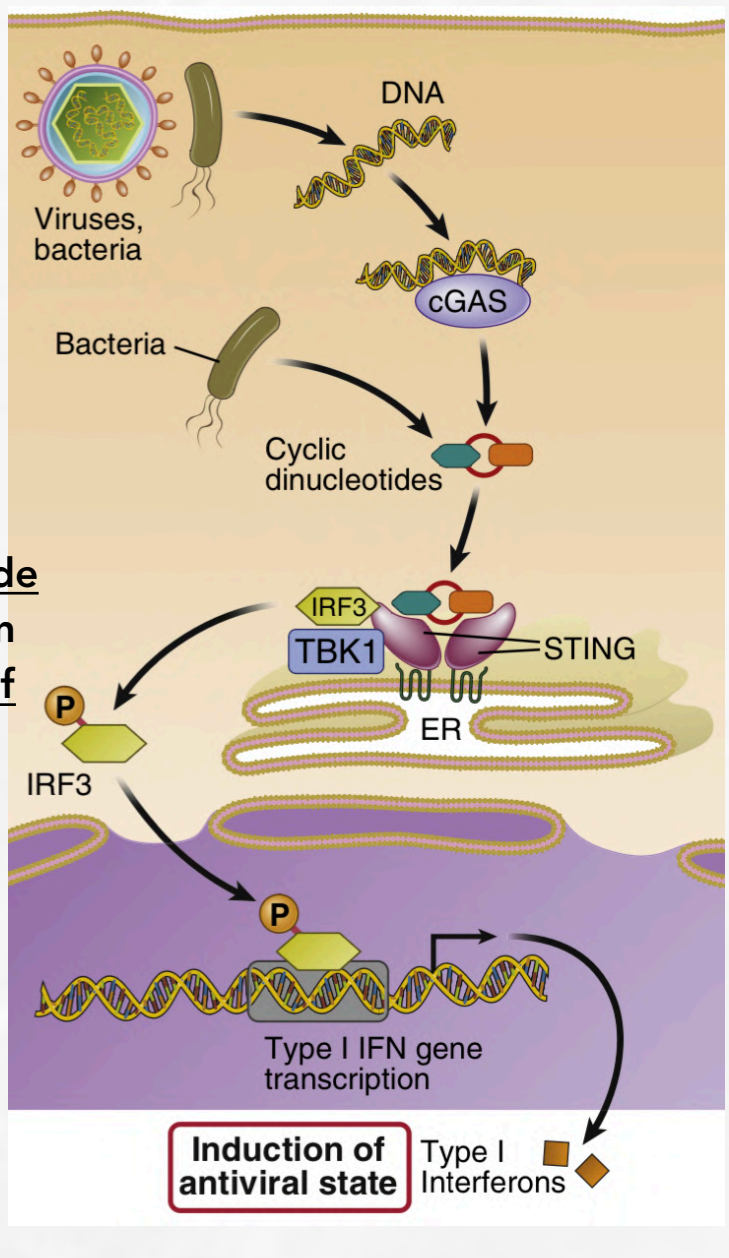
The innate immune system includes several cytosolic proteins that recognize microbial RNA or DNA and respond by generating signals that lead to the production of inflammatory and antiviral cytokines.

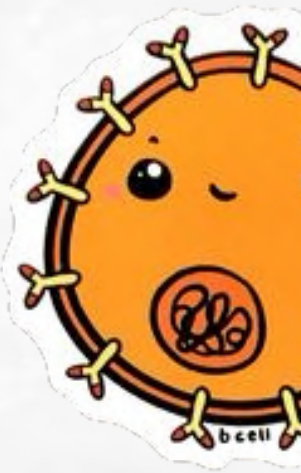
• The RIG-like receptors (RLRs) are cytosolic proteins that sense viral RNA and induce the production of the antiviral type I IFNs. RLRs recognize features of viral RNAs not typical of mammalian RNA, such as dsRNA that is longer than dsRNA that may be formed transiently in normal cells, or RNA with a 5′ triphosphate moiety not present in mammalian host cell cytosolic RNA. (Host RNAs are modified and have a 5′ 7methyl-guanosine "cap.") RLRs are expressed in many cell types that are susceptible to infection by RNA viruses. After binding viral RNAs, RLRs interact with a mitochondrial membrane protein called mitochondrial antiviral-signaling (MAVS), which is required to initiate signaling events that activate transcription factors that induce the production of type I IFNs.

• Cytosolic DNA sensors (CDSs) include several structurally related proteins that recognize microbial double-stranded (ds) DNA in the cytosol and activate signaling pathways that initiate antimicrobial responses, including type 1 IFN production and autophagy. DNA may be released into the cytosol from various intracellular microbes. Since mammalian DNA is not normally in the cytosol, the innate cytosolic DNA sensors will see only microbial DNA.

Most innate cytosolic DNA sensors engage the stimulator of IFN genes (STING) pathway to induce type 1 IFN production. In this pathway, cytosolic dsDNA binds to the enzyme cyclic GMP-AMP synthase (cGAS), which activates the production of a cyclic dinucleotide signaling molecule called cyclic GMP-AMP (cGAMP), which binds to an endoplasmic reticulum membrane adaptor protein called stimulator of interferon gene (STING). In addition, bacteria themselves produce other cyclic dinucleotides that also bind to STING. Upon binding these cyclic dinucleotides, STING initiates signaling events that lead to transcriptional activation and expression of type I IFN genes.

STING also stimulates autophagy, a mechanism by which cells degrade their own organelles in lysosomes. Autophagy is used in innate immunity to deliver cytosolic microbes to the lysosome, where they are killed by proteolytic enzymes. Other cytosolic DNA sensors besides cGAS can also activate STING.





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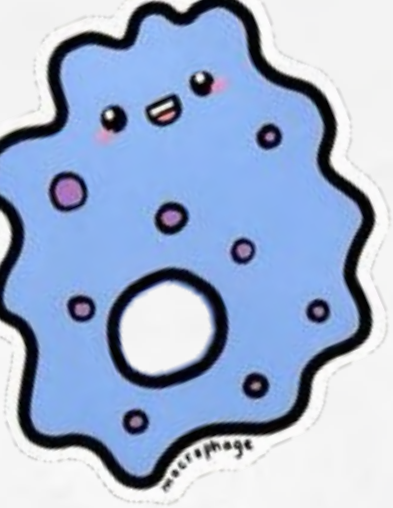

حنشرحهم بتفاصيلهم بمحاضرة خاصة

6. Cytokines

• Cytokines are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling. Their release has an effect on the behavior of cells around them.
• In response to microbes, macrophage and other cells secrets proteins called cytokines that mediate many cellular reaction in innate immunity
• Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cell

• Cytokines act as
– Inflammatory mediators
– Communication between leukocytes and leukocytes and other cells

• 4 kinds:
– Chemokines: important in chemotaxis of immune cells
– Interferons: glycoproteins important in the control of viral infections; also help regulate cells involved in immune response
– Interleukins: important in innate immunity, inflammation, and adaptive immunity: The vast majority of these are produced by T-helper cells
– Tumor necrosis factors: help kill tumor cells, initiate programmed cell death (apoptosis)

Functional features

Potent

Some function at 10-15 Molar

Local

autocrine
paracrine
(sometimes) endocrine

Highly interactive

pleiotropic
redundant
synergistic / antagonistic

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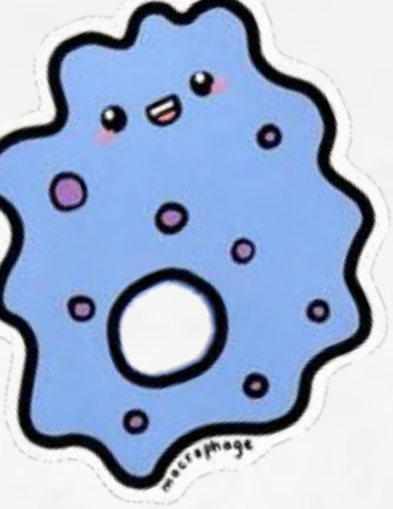
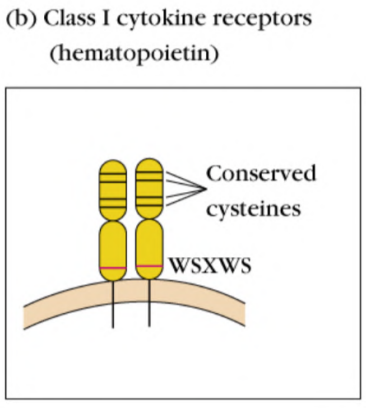


Cytokine families

I. Hematopoietic family
II. Interferon family
III. Tumor necrosis factor family
IV. Chemokine family
I, II, and III elicit physiological responses. IV serves as a chemoattractant.

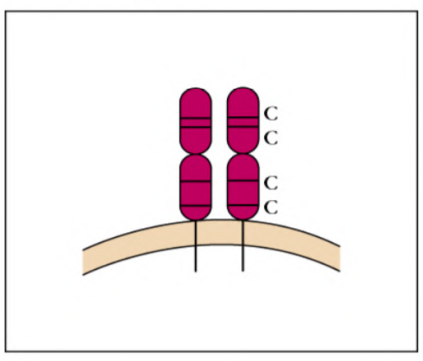
The receptor families:

(b) Class I cytokine receptors (hematopoietin)



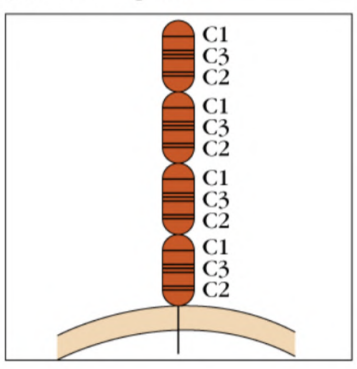
IL-2	IL-13
IL-3	IL-15
IL-4	GM-CSF
IL-5	G-CSF
IL-6	OSM
IL-7	LIF
IL-9	CNTF
IL-11	Growth hormone
IL-12	Prolactin

(c) Class II cytokine receptors (interferon)



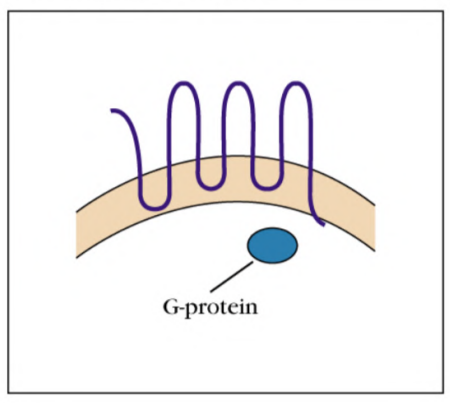
IFN-α
IFN-β
IFN-γ
IL-10

(d) TNF receptors



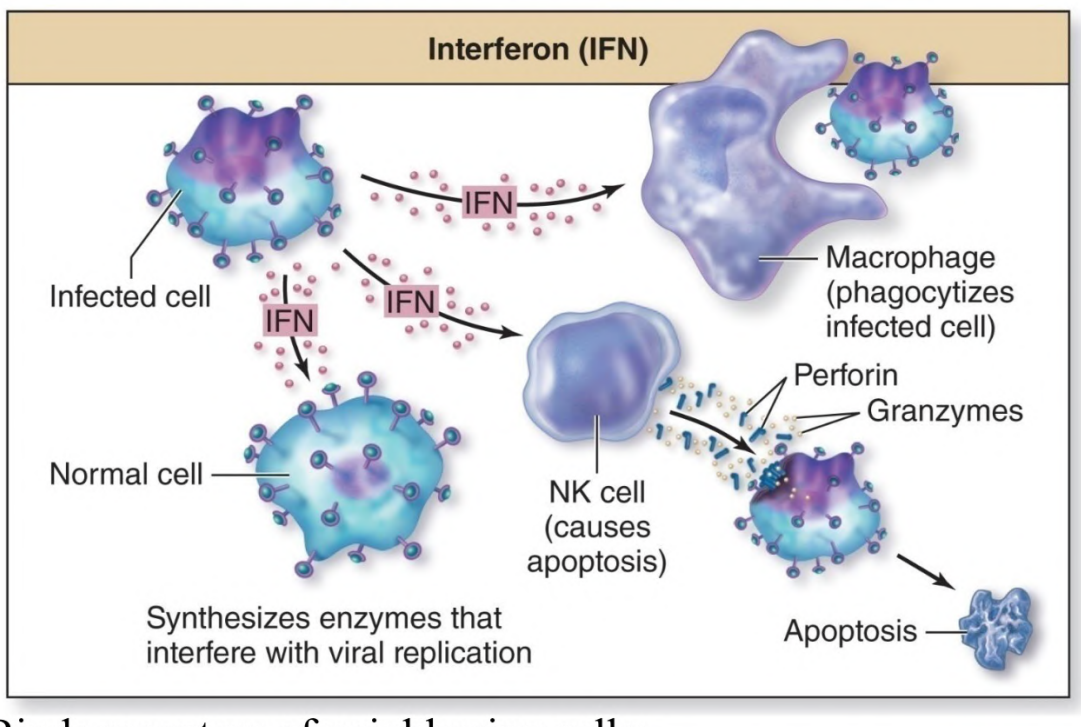
TNF-α
TNF-β
CD40
Nerve growth factor (NGF)
FAS

(e) Chemokine receptors

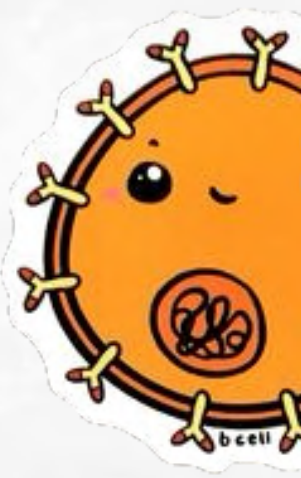


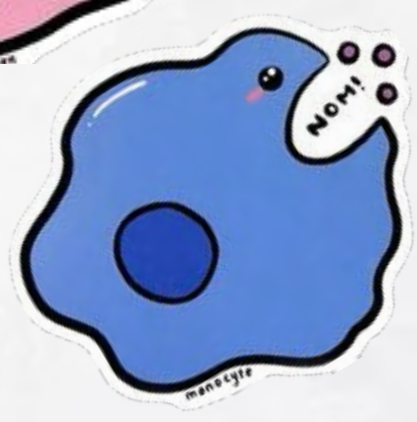
IL-8
RANTES
MIP-1
PF4
MCAF
NAP-2

Interferons – signaling molecule (cytokine) released by viral-infected cells



- Binds receptors of neighboring cells:
  - promotes macrophage function and apoptosis of infected cell
  - triggers synthesis of enzymes destroying viral RNA or DNA
  - triggers synthesis of enzymes that inhibit synthesis of viral proteins





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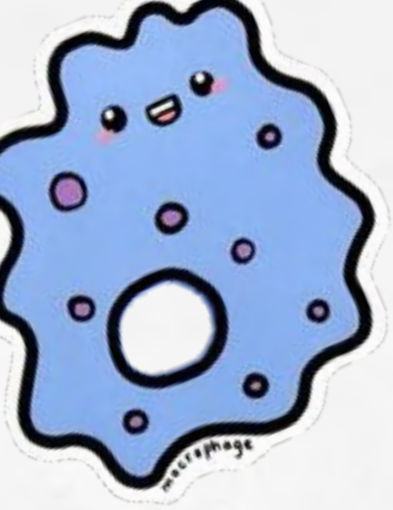
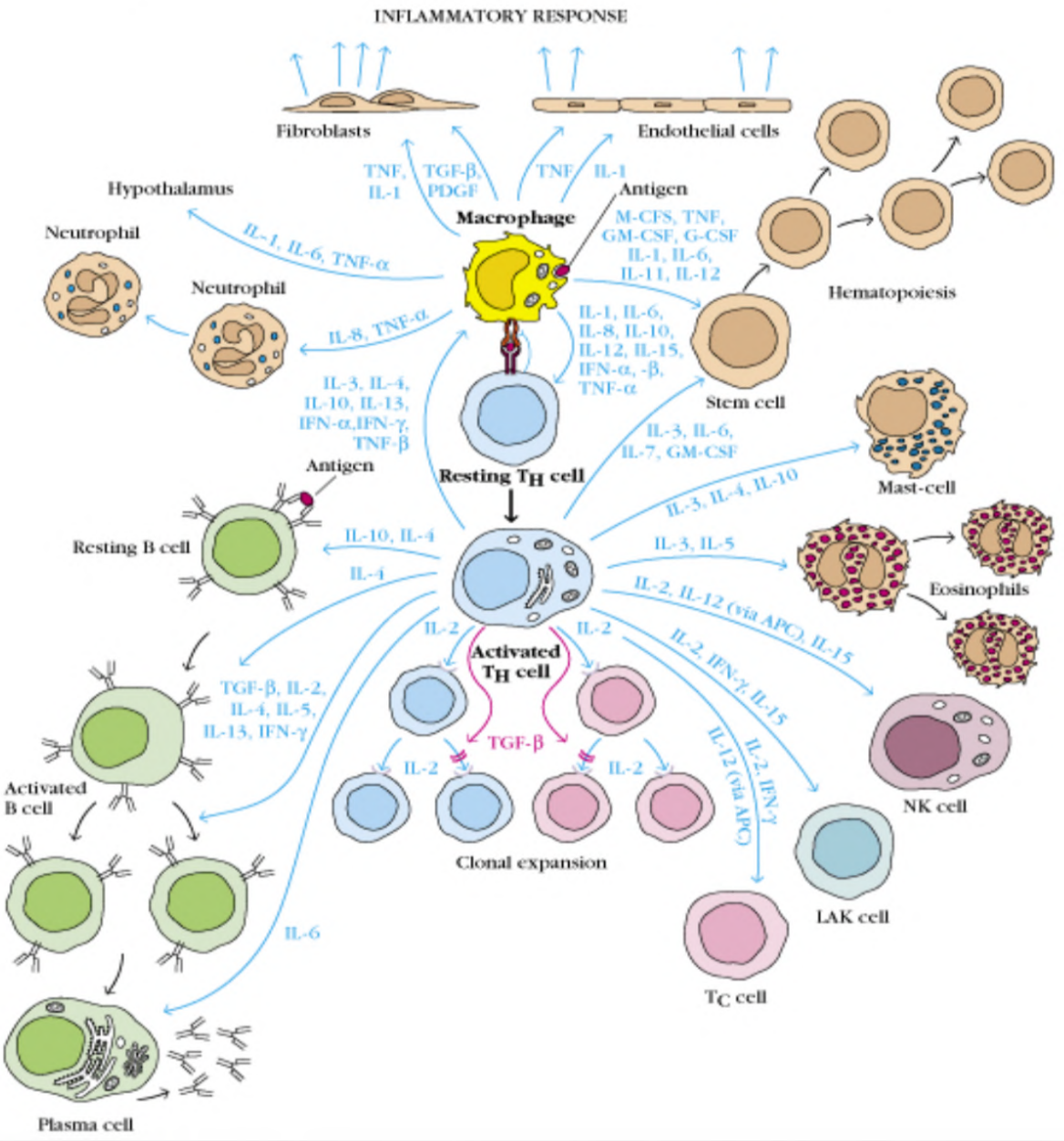
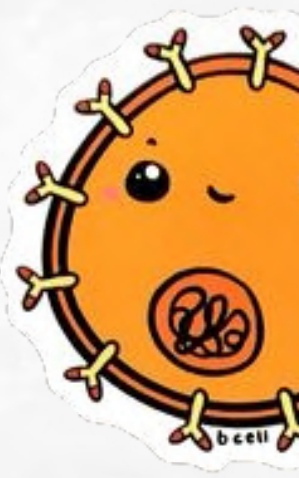


Complex image illustrating role of cytokines





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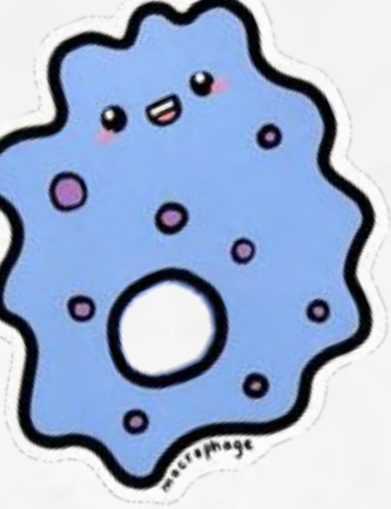


6. Complement System

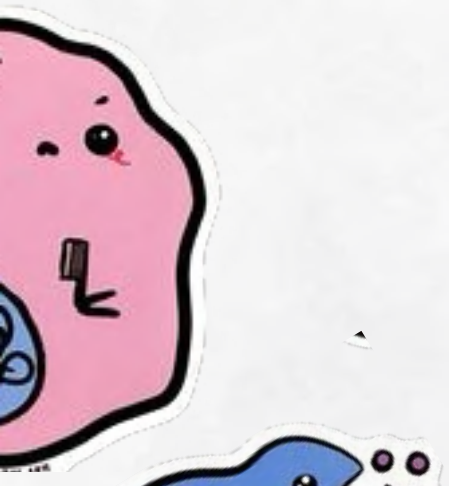
• The complement system is a collection of circulating and membrane associated proteins that are important in defense against microbes

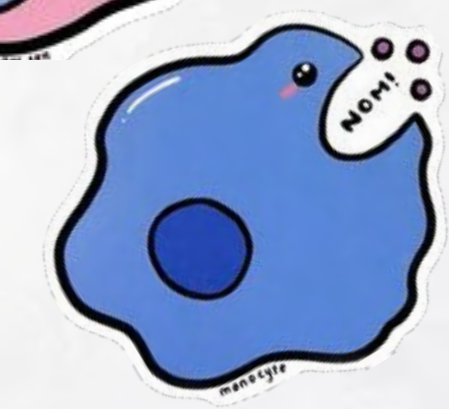
• Many complement proteins are photolytic enzymes and complement activation involve the sequential activation of these enzymes called the enzymatic cascade

• Three pathways to activate the complement system
– Classical: activated by antibody binding to microbes or antigen (adaptive part)
– Alternative: directly activated by microbes (innate immunity) no need for antibodies
– Lectin pathway (binding to mannose-containing carbohydrates) (innate immunity- no need for antibodies) ie: salmonella, candida, neisseria.

• Host cells have complement regulatory proteins on their surface that protect them from spontaneous activation of C3 molecules while microbes can activate the complement pathway but it have no regulatory proteins

• When pathogen activates the complement system this initiates innate immunity response by three main mechanisms:
– Inflammation
– lysis
– Opsonization and Phagocytosis





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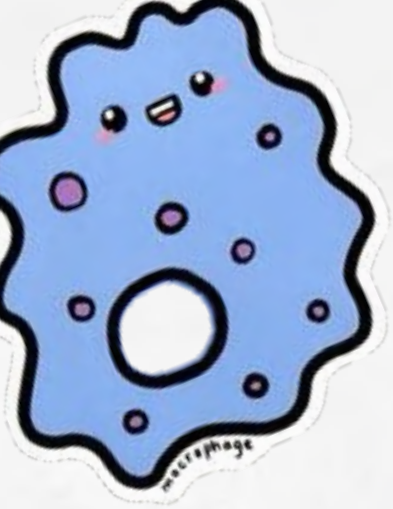

CLASSICAL PATHWAY

Antigen-Antibody Rxn

C1

C4

C4a C4b

C14b

C2 C2a C2b

C14b2a C3 CONVERTASE

C3

C3a C3b

C14b2a3b C5 CONVERTASE

C5

C5a C5b C6 C7 C8 C9 C5b6789 MEMBRANE ATTACK COMPLEX (MAC)

C3a
C5a > Chemotaxis

C3a
C4a
C5a > Induce acute inflammation by activating mast cells and neutrophils.

ALTERNATIVE PATHWAY

Spontanous hydrolysis
Factor C3
↓ H_2O
Factor B + C3b
Factor D
Ba Bb
Factor C3bBb
C3 CONVERTASE

LECTIN MANNOSE PATHWAY

Mannose binding lectin (MBL)

Neisseria
Candida
Salmonella

Recognise

Mannose and glucose

activate MASP

MBL associated SERINE PROTEASE

bind to MBL

activate

C4 and C2

C4a C4b C2a C2b

C4b2a

C3 CONVERTASE

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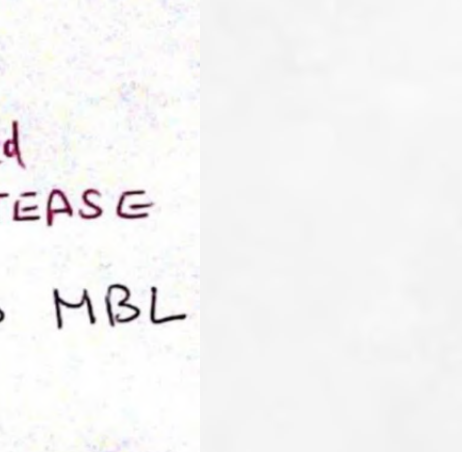
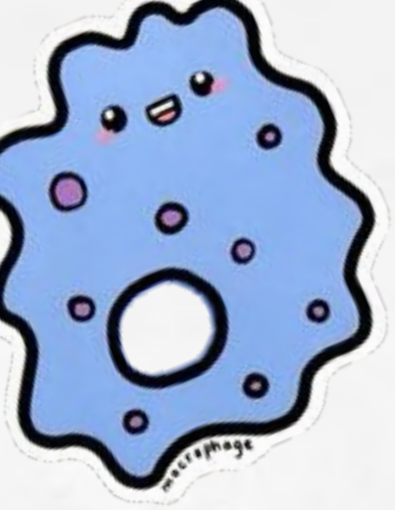




Complement System

من الكتاب

The complement system is a collection of circulating and membrane-associated proteins that are important in defense against microbes. Many complement proteins are proteolytic enzymes, and complement activation involves the sequential activation of these enzymes. The complement cascade may be initiated by any of three pathways :

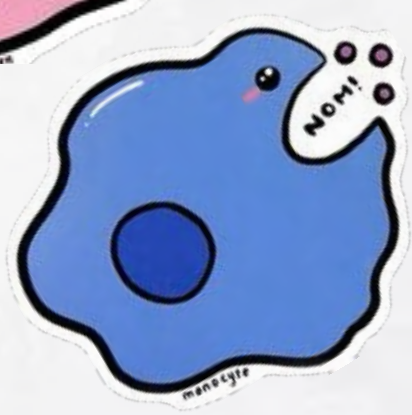
• The alternative pathway is triggered when some complement proteins are activated on microbial surfaces and cannot be controlled, because complement regulatory proteins are not present on microbes (but are present on host cells). The alternative pathway is a component of innate immunity.

• The classical pathway is most often triggered by anti-bodies that bind to microbes or other antigens and is thus a component of the humoral arm of adaptive immunity.

• The lectin pathway is activated when a carbohydrate-binding plasma protein, mannose-binding lectin (MBL), binds to its carbohydrate ligands on microbes. This lectin activates proteins of the classical pathway, but because it is initiated by a microbial product in the absence of antibody, it is a component of innate immunity.

Activated complement proteins function as proteolytic enzymes to cleave other complement proteins. Such an enzymatic cascade can be rapidly amplified because each proteolytic step generates many products that are themselves enzymes in the cascade. The central component of all three complement pathways is a plasma protein called C3, which is cleaved by enzymes generated in the early steps. The major proteolytic fragment of C3, called C3b, becomes covalently attached to microbes and is able to recruit and activate downstream complement proteins on the microbial surface. The three pathways of complement activation differ in how they are initiated, but they share the late steps and perform the same effector functions.

The complement system serves three main functions in host defense:
• Opsonization and phagocytosis. C3b coats microbes and promotes the binding of these microbes to phagocytes by virtue of receptors for C3b that are expressed on the phagocytes. Thus, microbes that are coated with complement proteins are rapidly ingested and destroyed by phagocytes. This process of coating a microbe with molecules that are recognized by receptors on phagocytes is called opsonization. Inflammation. Some proteolytic fragments of complement proteins, especially C5a and C3a, are chemoattractants for leukocytes (mainly neutrophils and monocytes), and they also are activators of endothelial cells and mast cells. Thus, they promote movement of leukocytes and plasma proteins into tissues (inflammation) at the site of complement activation.
• Cell lysis. Complement activation culminates in the formation of a polymeric protein complex that inserts into the microbial cell membrane, disturbing the permeability barrier and causing osmotic lysis.



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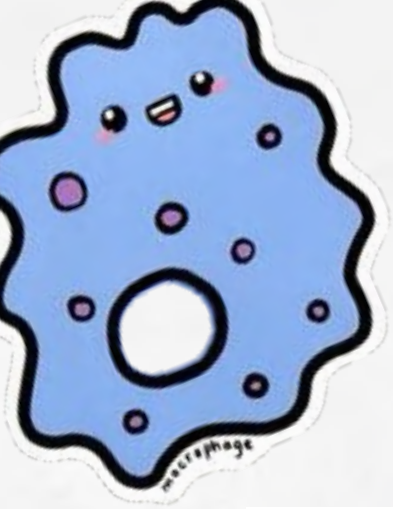


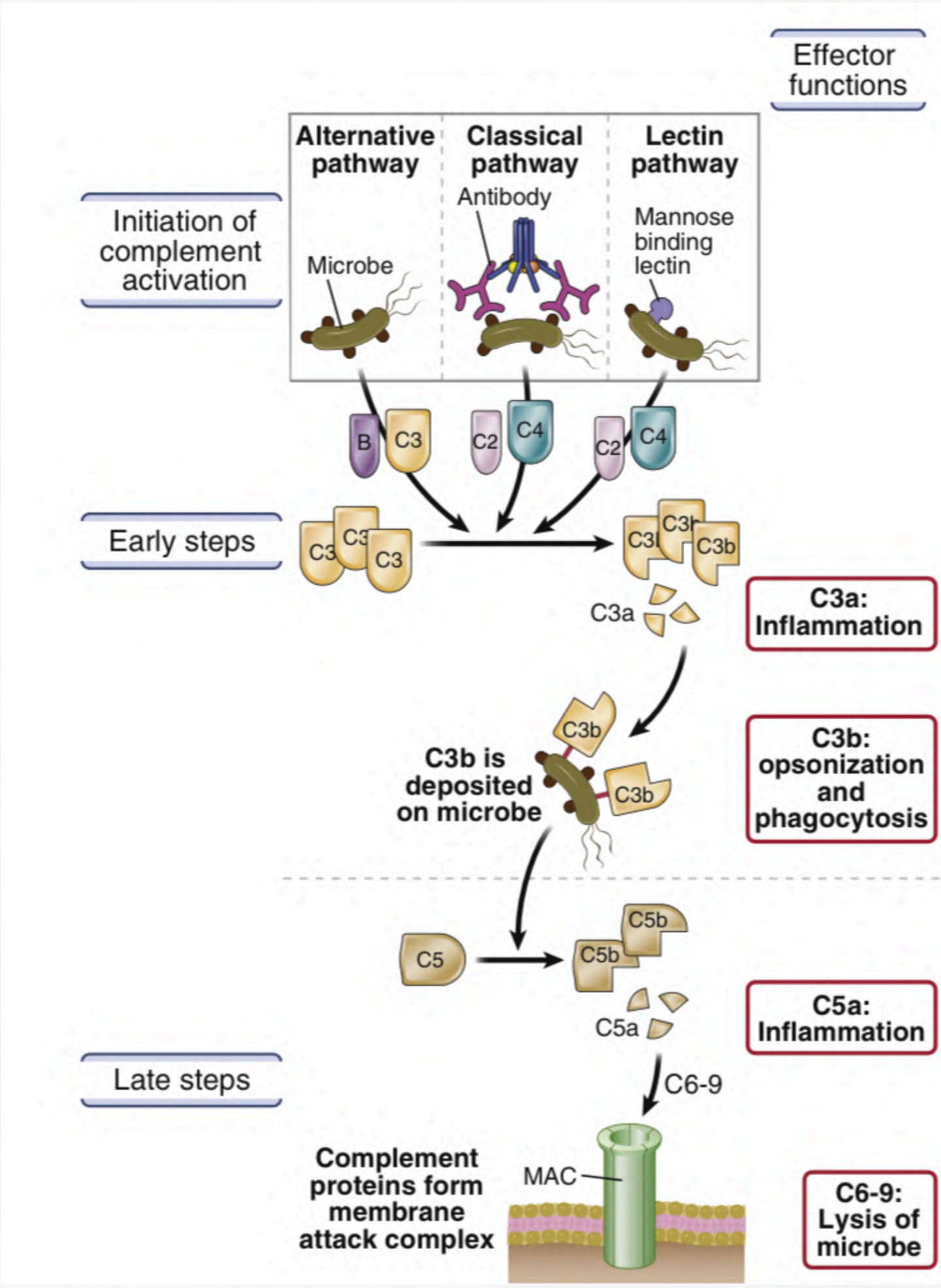
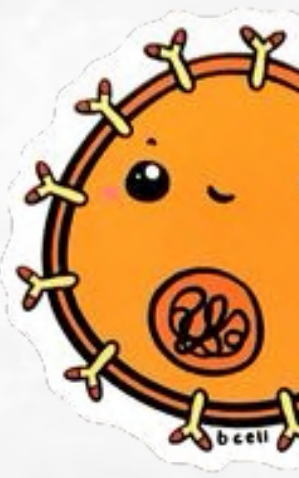
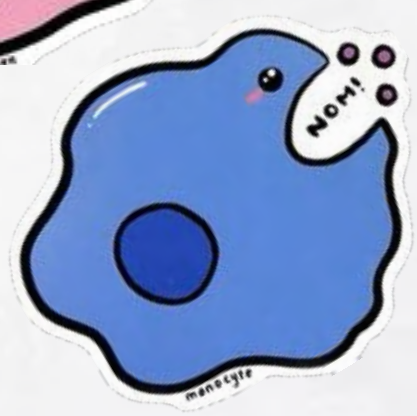


Fig. 2.14 Pathways of complement activation. The activation of the complement system (the early steps) may be initiated by three distinct pathways, all of which lead to the production of C3b. C3b initiates the late steps of complement activation, culminating in the formation of a multiprotein complex called the membrane attack complex (MAC), which is a transmembrane channel composed of polymerized C9 molecules that causes lysis of thin-walled microbes. Peptide by-products released during complement activation are the inflammation-inducing C3a and C5a. The principal functions of proteins produced at different steps are shown.





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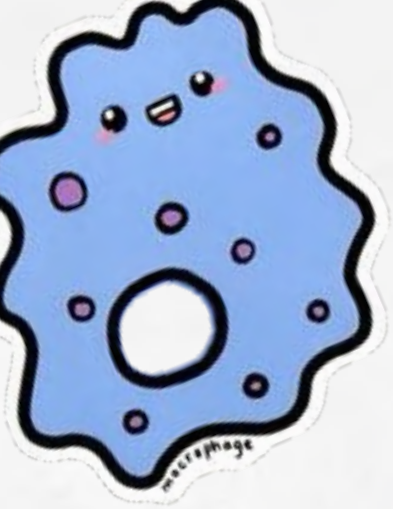
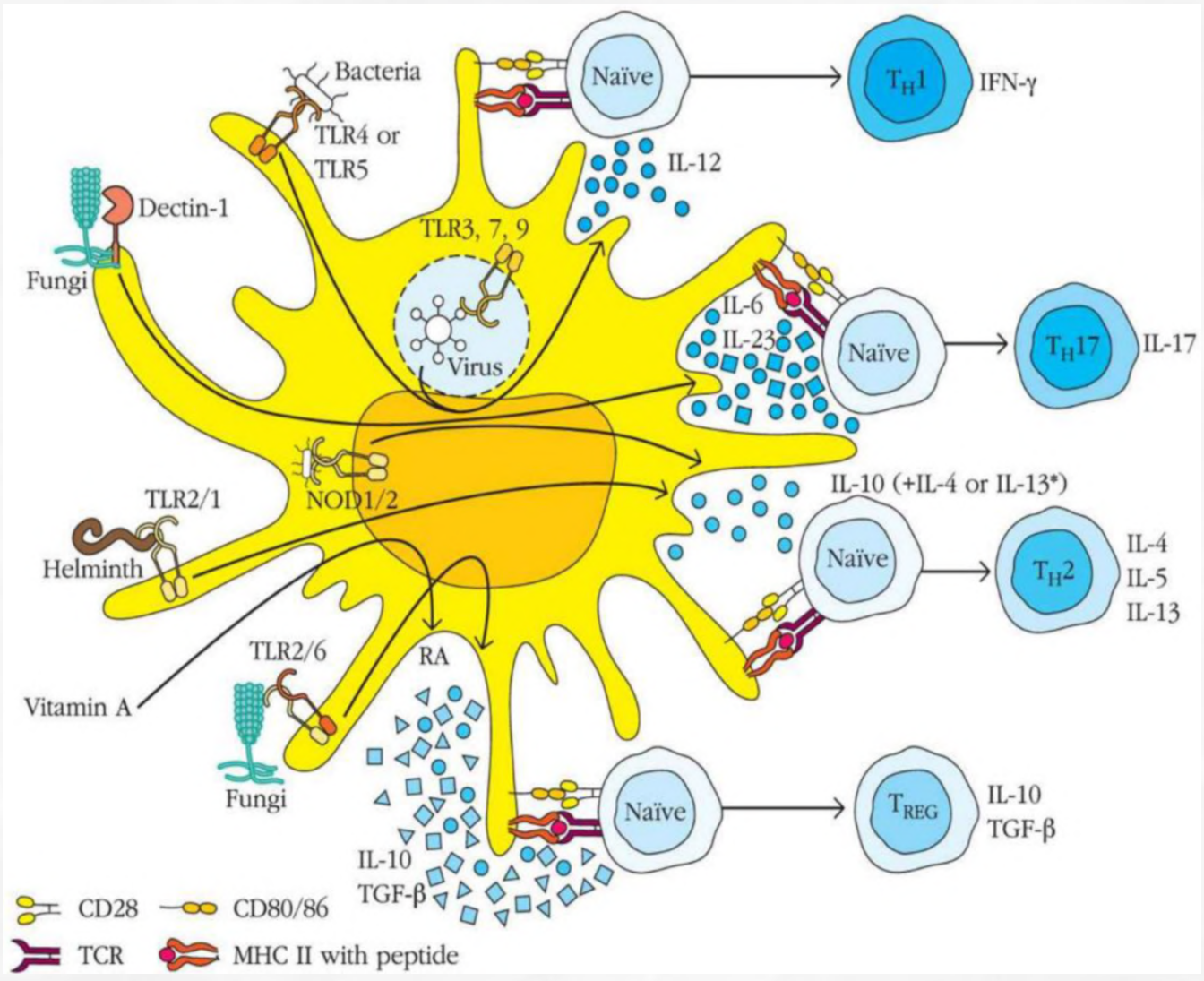


Role of innate immunity in stimulation of adaptive immune response

- Adaptive immune system activation (T or B-cells) need two signals for activation:

– First signal: antigen recognition
– Second signal: derived by innate immunity



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