SHEET NO.

6

IMMUNOLOGY

DOCTOR 2019 | MEDICINE | JU

DONE BY : Doctor 2018

SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

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In this lecture we will revise a few points discussed previously and we will continue talk about molecules of innate immune system, such as soluble PRR, the complement system and interferons.

Molecules of the immune system

They orchestrate everything in the immune system; response and interactions:

1. Between cells of the immune system
2. The invading foreign microbes

We have been talking about the innate immunity, which is hard to separate and differentiate from adaptive immunity because they're intertwined due to the presence of common cytokines and APCs.

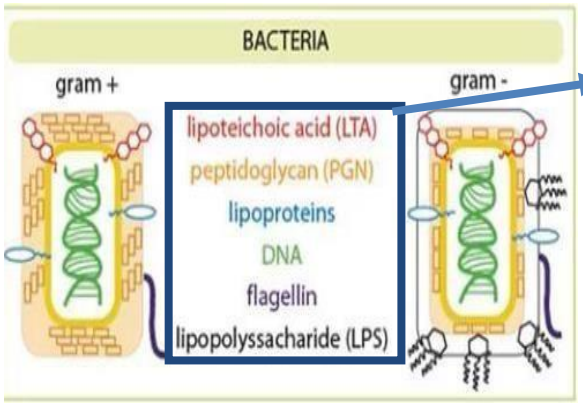
1. Pattern Recognition Receptors(PRR)

They recognize specific patterns such as PAMPS and DAMPS.

PAMPs

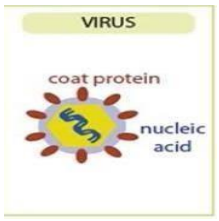
Pathogen associated molecular patterns; antigens coming from pathogens that is recognized by the body.

They're found in microbial pathogens but not mammalian cells and they're essential for survival of microbe because during co-evolution the pathogen can't change. It is difficult for the microbe to change its entire cell wall if other proteins were the target it would be easy to keep shifting the antigens but these would be recognized by the adaptive but innate immunity has a few patterns for which it can recognize.

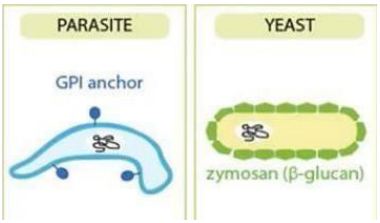


All of the following are part of the cell wall and are considered PAMPs.

DNA is found in both prokaryotes and eukaryotes, so how is it considered as a PAMP? Basically, there is differences between them (e.g. methylation of CPD sequences).



Viruses have dsRNA, that isn't commonly found in eukaryotic cells.

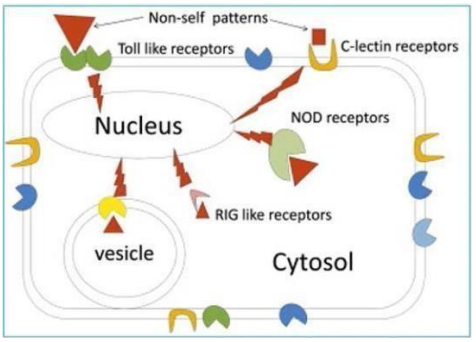


Have similar PAMPs.

DAMPs

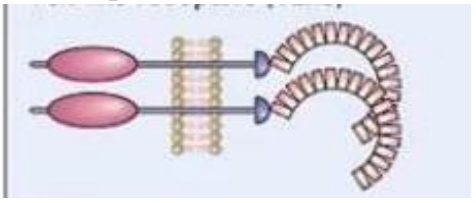
Damage associated molecular patterns: endogenous molecules found in the nucleus, such as transcription factors, to be located extracellularly indicates that there's damage going on. Example: Nuclear proteins such as HMGB1, a transcription factor when located outside; initiates an immune response.

These receptors can also be viewed as danger sensors; they must be located everywhere.



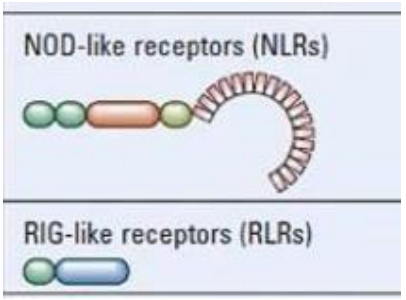
- **Cell bound PRR**: transmit signals to nucleus & are located:

1. On the cell surface:
    a. TLRs recognize none self-patterns and send signal inside the cell. They have an EC domain that senses the pattern, another domain transmits signals and an IC domain that is bound to a protein which sends signals to the nucleus, where the transcription factors are located, and start to transcribe genes associated with the inflammatory response.



    b. Lectin receptors, recognize carbohydrates.

2. Inside the cell (endosome or cytoplasm, some bacteria replicate intracellularly):



   a. NOD; inflammasome accumulates and cleaves proteins into their active form.
   b. RIG.

- **Soluble PRR:**

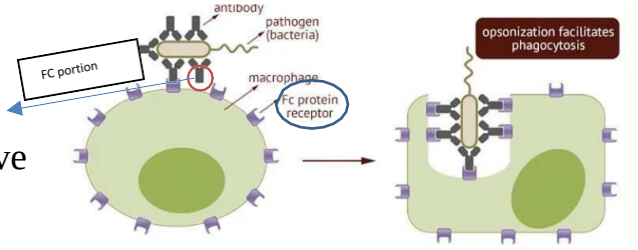
They are also called effector molecules; (recognize and restore) phagocytosis, promotion of inflammation, release of cytokines and killing of microbial cells.

They aren't located on the cell surface or IC. Thus, they work as:

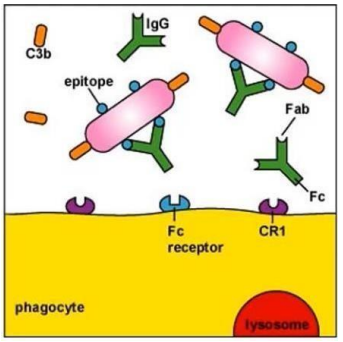
1. Opsonins

   Opsonization is the mechanism that enhances phagocytosis by covering the pathogen with opsonins that are basically antibodies or complement proteins.

   a. Phagocytes have receptors which recognize these antibodies, the unbound antibody (FC portion) have their own FC receptors.



   b. C3b protein, which deposits on surfaces of the pathogens and have specific recptors on phagocytes which facilitates phagocytosis.



2. Promote inflammorty responses, they can kill certain microbes.

Examples:

1. **Natural antibodies**; are part of innate, subsets of B-cells, formed without being exposed to any antigen (as seen with germ free mice) unlike the specific antibodies produced by B-cells after being exposed to antigens.

    - Their specificity is similar to PRR, recognize a few and common PAMPs and DAMPs.
    - Mostly of IgM class.

2. **Pentraxins**; composed of five parts including and the long pentraxin PTX3 and C-reactive protein (CRP), and serum amyloid protein (SAP) that recognize specific DAMPs and PAMPs. CRP is important clinically because it is increased *1000 in the blood during infection and inflammation in general, it is one of the acute phase proteins.

- Acute phase proteins: class and group of proteins that increase in concentration during inflammation and are used clinically to diagnose infection because they're released quickly and in huge amounts; making it easy to recognize if they're elevated or not.
  During inflammation, cytokines are secreted by inflammatory cells like IL-1, IL-6 & TNF-a (most important ones).
  These cytokines accumulate in the blood and have systemic effects that are typically seen in infection:

    - Brain; have an effect on the hypothalamus causing fever.
    - Liver; induce hepatocytes to release acute phase proteins.

3. **Collectins and ficolins:** recognize sugars and activate complement system
    - MBL **:**
        - Mannose-binding lectin, which isn't usually found in mammalian cells.
        - Activates lectin pathway of complement system.
    - Ficolin:

  are plasma proteins that are structurally similar to collectins, possessing a collagen-like domain, but instead of a C-type lectin domain, they have a fibrinogen-type carbohydrate recognition domain.

2. The complement system

Definition: a group of proteins that circulate in the blood in an inactive form and once they sense danger and recognize a certain pattern by a PRR, they start the activation process; by cleaving proteins in the system.

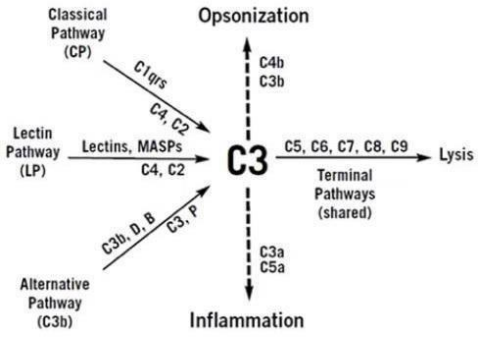
- It has functions that go beyond the borders of innate immunity, it has a general role in homeostasis (which is also a function of the immune sys.).
- One protein activates the other and so on, in some cases two proteins form an enzyme in order to become more efficient in cleaving downstream proteins, these cleaved and activated proteins are the effectors; opsonization, promote inflammation and induce lysis.

This system was in early multicellular microorganisms but was simpler; one protein sensed the danger, activates another and opsonize the microbe. When such a system has been conserved through many years of evolution, this emphasizes its important role.

Mechanism:

3 pathways of complement activation depend on different PRR but converge at C3 activation, the general mechanism of all the pathways is to generate C3 convertase which cleaves C3 into:

- Heavier fragment **C3b**, which goes to cell surface and works as an opsonin.
- Lighter fragment **C3a**, attracts WBCs, increases permeability of blood vessels and potentiates the immune response and inflammation in general.



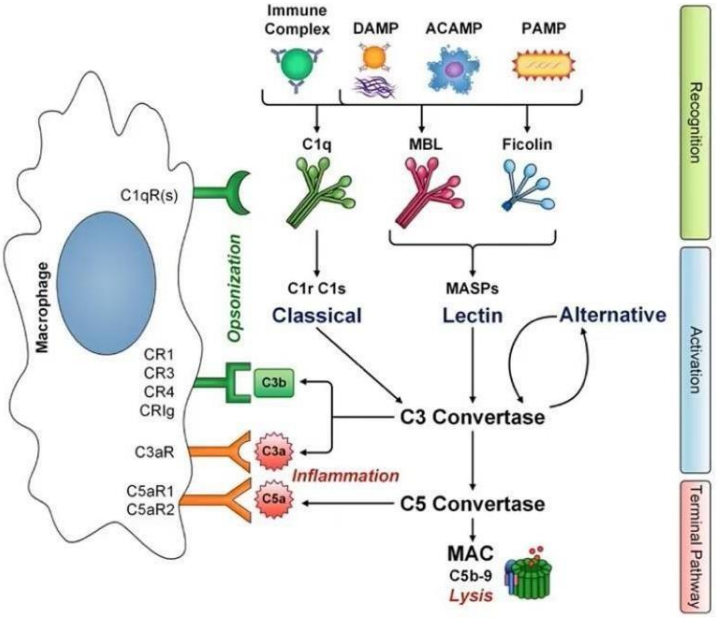
C3 is the heart of the complement system

When the system senses danger through PRR, each receptor initiates a specific pathway:

- Classical pathway

i. PRR: C1q (part of C1 complex), lectin receptor
ii. Activates C1r & s , which are also part of the complex
iii. The activated C1rs, cleaves downstream proteins C4 & C2 which together form an enzyme C3 convertase.
iv. This C3 convertase cleaves C3, which is an important part of the cascade.

From what can be viewed from the following picture (another point of view): PAMPs and the other proteins associated work together to activate C1q, MBL &Ficolin (all structurally similar).



- C1q binds to FC portion of the antibody, activating C1r & s that cleave C2, C4 forming C3 convertase (classical pathway).
- MBL and Ficolin detect PAMPs & DAMPs, activating MASPs (associated serine proteases) forming the C3 convertase.

1. Pattern recognition
2. Pro-inflammatory signals
3. Opsonization
4. Pore formation

As mentioned earlier, the C3 convertase cleaves C3 into 2 fragments. If the pathway continues after C3, a C5 convertase will be formed which cleaves C5 into 2 fragments as well:

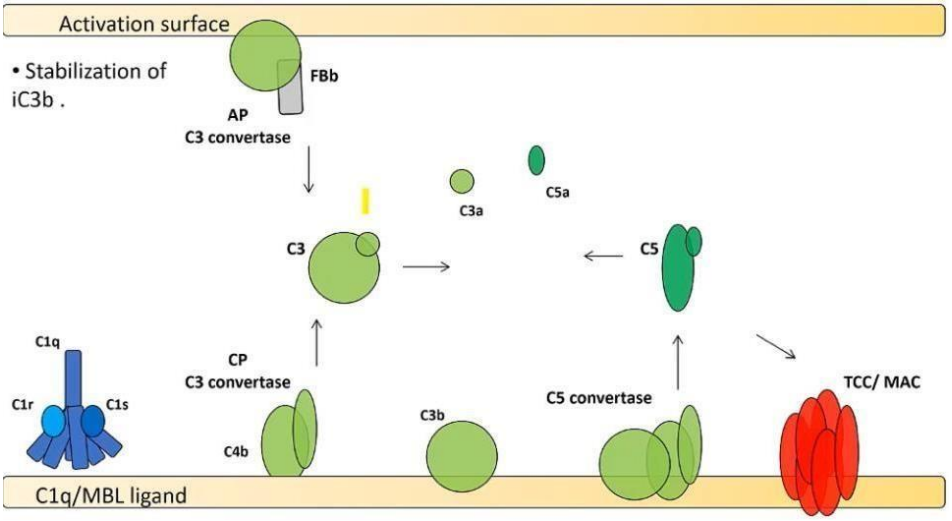
- **C5a**, lighter fragment involved in inflammation
- **C5b-9**, heavier fragment which binds to cell surface forming a scaffold (+C5,C6,C7,C8) for C9 proteins attachment which form a pore inducing lysis. TCC or MAC, membrane attack complex.

The doctor showed a video of the process minute 28:58 - 32:37

- Alternative pathway:

i. It works if another pathway works.
   i. C3b formed can attach to blood factor B
   ii. Form C3 convertase, differs in composition from the one formed in classical pathway.

ii. It can work independently by the unstable form of C3b, iC3b, (differs from the inactive form) which doesn't attach to normal host cells but to bacterial or any activated surface which stabilize it. The iC3b in some way is a pattern recognition molecule since it recognizes different surfaces.



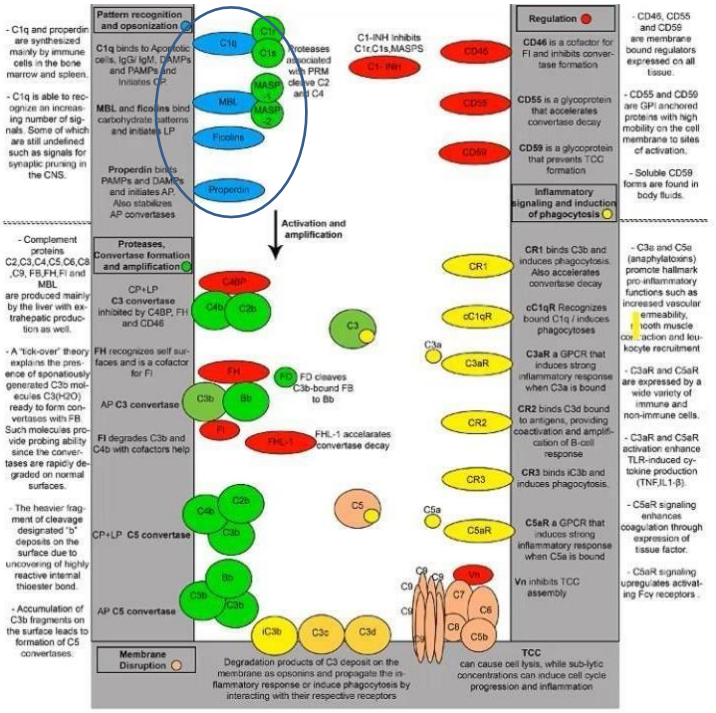
The previous 2 pathways keep activating themselves by C3b and convertases formation on bacterial surfaces but if they occur on host surface, complementary regulatory proteins will be found.

Regulators are very important in the immune system

C3 and C4 are considered acute phase proteins; mainly synthesized in the liver so in cases of inflammation they will increase. However, in some inflammatory diseases they will be decreased due to consumption and activation.

The following is used as a reference:

- PRR circled around them.
- The red circles are the regulators of comp. sys. : **CD46** (receptor for entry of certain viruses) and **CD55** both inhibit convertases, **CD59** (cell bound) **Factor H**, inhibits convertases and involved in other inflammatory diseases
- The yellow circles (on right side) are the receptors involved in inflammation: C5a, C3a and C3b for phagocytosis since it is an opsonin.



iii. Cytokines

They're all the molecules that through which cells communicate with each other (chemokines, interleukins, lymphokines and TNF).
The important ones are **IL-1, IL-6** and **TNF**.

- **Interferons(IFN)**

They interfere with:

a) Viral replication and <u>produce an antiviral state.</u>
   i. Sensors sense the infection (inside or outside the cell), which induce transcription factors producing IFN in response to viral infections.
   ii. IFN attach on neighboring uninfected cells (too late for the infected cell) in order to block the viral replication and to reach the antiviral state (immune to the virus) by upregulating certain proteins involved in inhibition of viral protein synthesis, viral gene expression and virion assembly and degradation of viral RNA.

b) Increase the cytotoxicity of NK cells and CD8+ CTLs (more potent).

c) Upregulate expression of class I MHC; IC proteins will presented on their surface with the viral being one of them, which will be recognized and phagocytosed by CD8+ CTLs.

d) Increase the sequestration of lymphocytes in lymph nodes, thus maximizing the opportunity for encounter with microbial antigens.