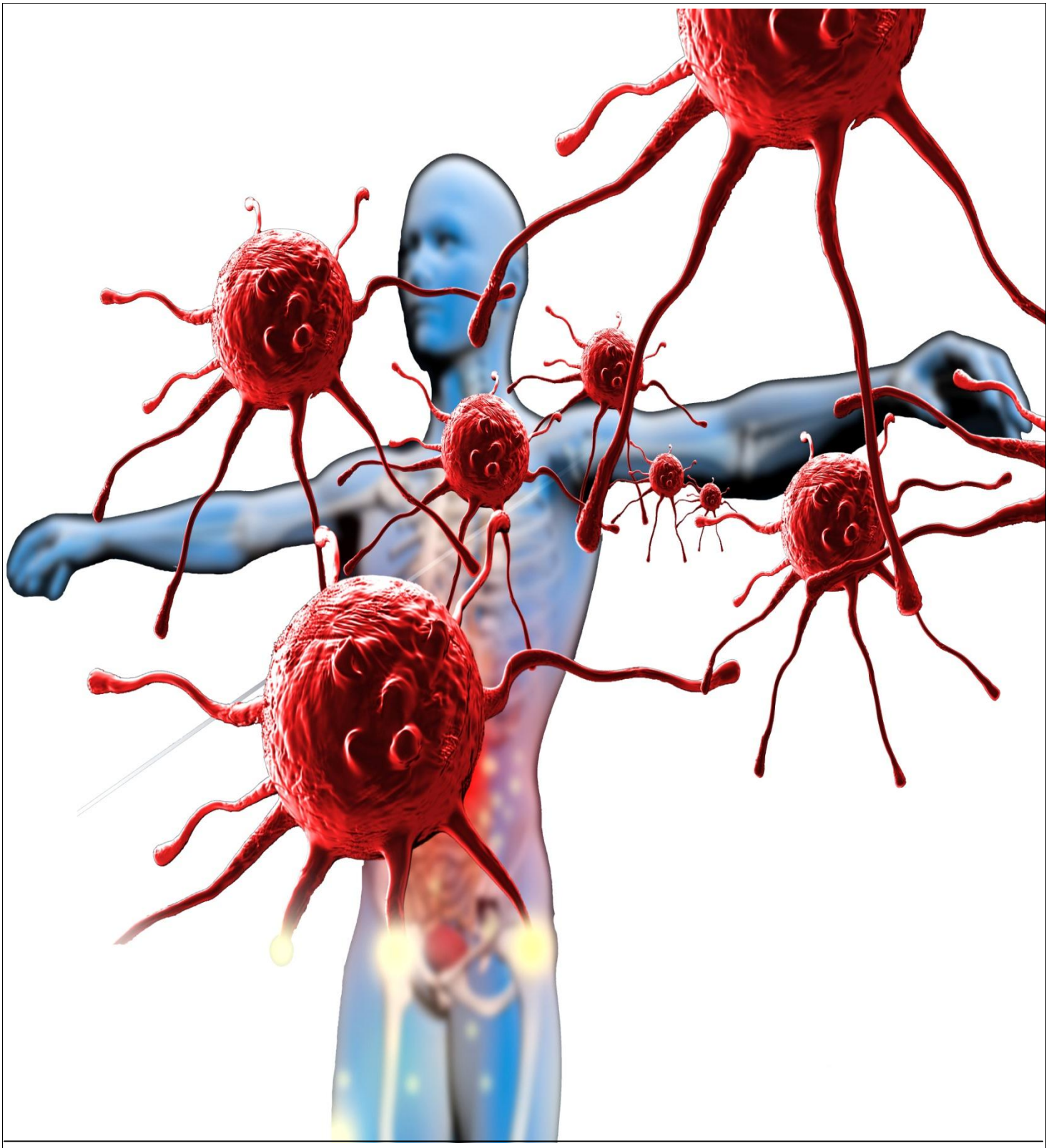

IMMUNOLOGY

Done By: Mohanned Momani

#3

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By Mohammed Nawasreh

INNATE AND ACQUIRED IMMUNE SYSTEM

♣ This sheet was written according to sec1

♣ I rearranged a lot of topics here and there and I've added some information from wiki for further clarification. So don't be confused when referring to the original recording

♣ Also, this is an easy lecture, enjoy.

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♦Types of immune reaction

We've mentioned in the last lecture that there are two types of the immune reaction;

1) Innate

2) Acquired

In this lecture we are going to talk about each one in more detailed

The innate immune system

•it is the first line of defense in the human body and it initiates an immune response immediately once the pathogen enters the body to limit the damage until the acquired immune response is ready to complete its work (since it needs longer time) but the actual remove of the pathogen is actually a function of the acquired immune system.

It can be;

1- Physical: like the skin which doesn't allow the bacteria to go into the body. If you cut skin, organs will get into your body and cause infection.

2- Chemical: like our sweat which provides an acidic environment. Also it's full of peptides which act as antibiotics that can kill bacteria by lyses.

3- Mucosa (mucus membrane): it's not a physical barrier, however it prevents pathogens from invasion by trapping and secreting mucus (such as mucosa of our respiratory system), eventually the cilia will sweep the mucus and then you get rid of the bacteria by swallowing or spitting it.

• The secretions of the glands in mucosa; tears, saliva and urine

Like the salivary glands that produce saliva that containing lysozymes which are enzymes that have the capability of degrading peptidoglycans, thus they are affective against gram positive bacteria, also the lacrimal glands that secrete tears.

These glands provide:

A) Continuous flushing which can help, as we can see in the urine, in getting rid of pathogens.

B) Different PH values:

The low PH in our stomach (high acidity) can also help in killing and digesting these nasty pathogens.

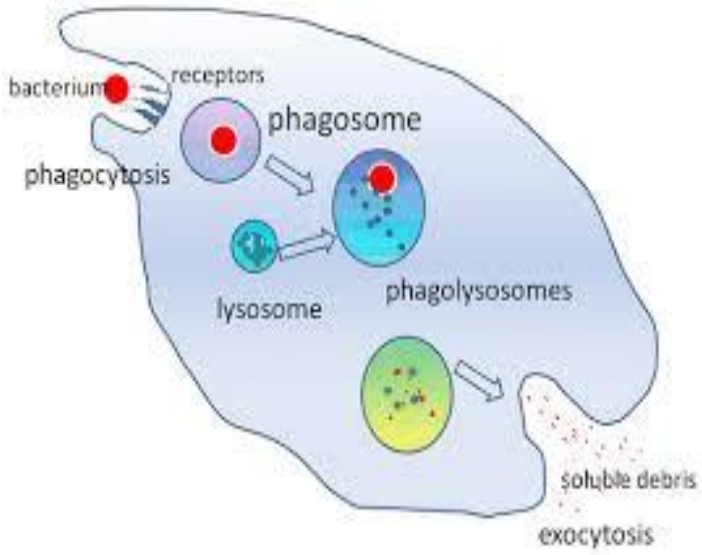
C) The hydrolytic enzymes in the small intestines can also help in killing bacteria.

4-Our normal flora

Can be considered as part of our innate system, even some types produce peptides that act as antibiotics killing other organisms, for example the acidic medium in the vagina produced by the lactobacillus (normal flora) can help in preventing bacterial and fungal infection there.

So those were the physiological barriers.

5-Phagocytes:



As we know macrophages and neutrophils are considered the first line of defense at the cellular level, they recognize bacterial antigens such as mannose sugar, lipopolysaccharides, bacterial DNA, RNA fragments, peptidoglycans and flagella on its surface by receptors sometimes known as PRR (Pattern Recognition Receptors) or what's known as Toll like receptors (TLR), they all are molecules present on the bacteria but not on mammalian cells. Then when recognition happens, you get adhesion between the membrane of the cell and the organism, then the plasma membrane takes the pathogen in to be inside the phagocytic cell forming a phagosome. Phagocytes actually act in both the acquired and the innate system; they don't only phagocyte the pathogens, they also present bacterial antigens on its surface.

<keep in mind phagosome is a vesicle formed around a particle absorbed by phagocytosis. The vacuole is formed by the fusion of the cell membrane around the microorganisms can be killed and digested. Phagosomes fuse with lysosomes in their maturation process, forming phagolysosomes>

Note form section 2 recording: phagocytes participate in both innate and acquired immune system as it participates as an antigen presenting cell.

6-Complement proteins

It is a collection of proteins that are activated in sequence like a cascade, (something similar to the coagulation system) the complementary system actually participates in both the innate and the acquired immunity. So there is an overlap just like the case in phagocytes. As these complement proteins are activated, you find that there is an induction of certain proteins that have specific functions: examples:

A) promote phagocytosis.
B) lyse the cell membrane of the poor pathogens by making holes in them.

7-interferons;

when cells are infected with viruses they produce a sort of cytokines called interferons (we have both α and β) and those stop the missionary (metabolism) of the cell, by doing this, the virus can't replicate any more leading to eradication of the virus and killing of the infected cell at the same time.

8-fever

In most times it means inflammation or bacterial infection, it has been thought that our body has adopted this mechanism so it can kill those pathogens with heat, but what really happens here is that, bacteria needs iron to make its required enzymes, they uptake them from the environment by producing **siderophores** which absorb iron from the environment to use it in the production of enzymes needed, anyway, with heat this process is stopped. Hah.

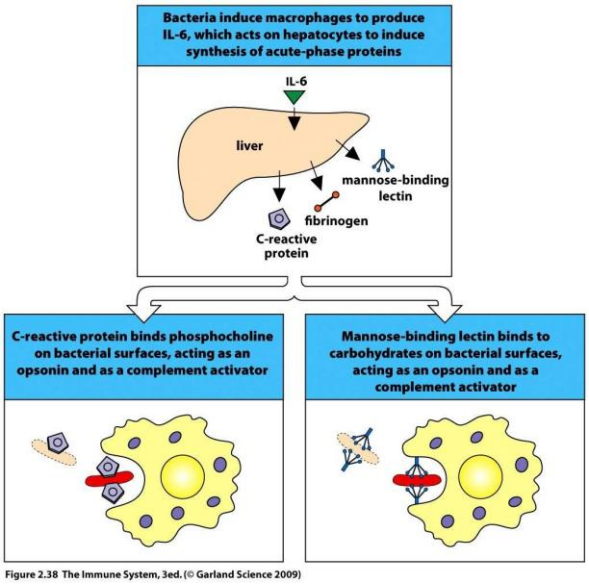


Figure 2.38 The Immune System, 3ed. (© Garland Science 2009)

9-Acute-phase proteins

- Are a class of proteins whose concentrations and synthesis increase in response after an infection. These proteins usually come from the liver .In response to injury, local inflammatory cells (neutrophil granulocytes and macrophages) secrete a number of cytokines into the bloodstream, most notable of which are the interleukins mainly IL5 and IL6, and TNFα. The liver responds by producing a large number of acute-phase reactants
- Those acute phase proteins are produced by both the liver and macrophages.

- Acute-phase proteins serve different physiological functions for the immune system. Some act to destroy or inhibit growth of microbes, e.g., C-reactive protein, mannose-binding protein, complement factors

- Just or your information, (not from the doctor) C-reactive protein; was so named because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the C-polysaccharide of Pneumococcus.

- Although it does react with many types of bacteria acting like immunoglobulin, but of course it's not an antibody because it's not specific. It is thought to activate complement protein binding to foreign and damaged cells and enhances phagocytosis by macrophages

- Another similar acute phase protein is mannose binding protein, again it's nonspecific binds to mannose sugar bacteria, by this is provokes the immune response, activate complement…

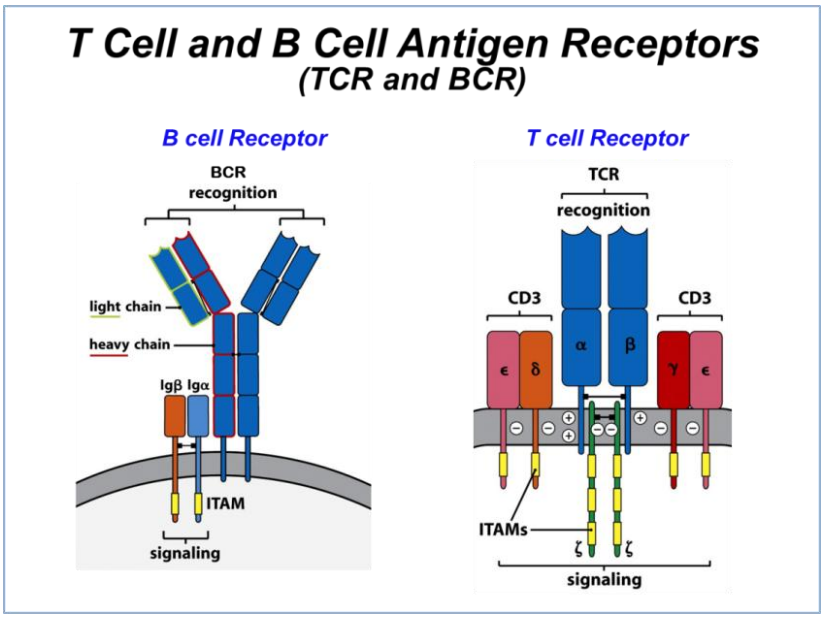
Previously, if we had an infection we tended to use ESR (erythrocyte sedimentation rate) test. But **now** we use the C-reactive protein test. Normally we have very little C reactive protein, almost zero but if we tested positive these level should be high indicating an ongoing inflammatory process in your body.

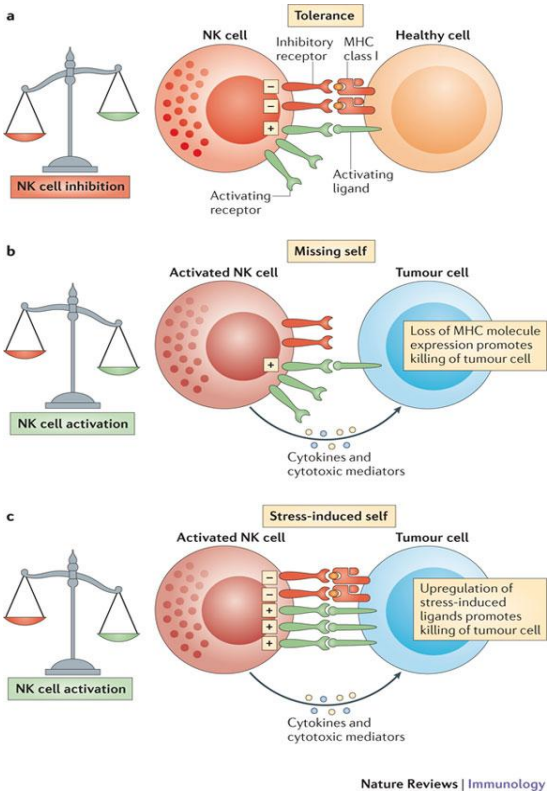
♦As we know defenses can be either inside the cell or excreted outside to the circulation and these are polypeptides that mainly work on membranes that don't contain steroid i.e. membrane of bacteria (make holes in them).

10- NK (natural killer) cells,

- these natural killer cells can recognize abnormal cell which could be viral infected cells, cancer cells or even foreign cells, this recognition occurs by their special receptors which recognizes other molecules on cell surfaces such as MHC 1 receptors, if present the NK holds its fire, otherwise it stigmatize them as a harmful subject and stick on them the "kill me" signal.

- Also when the cell is damaged by bacteria or by other means it starts expressing special molecules on their surface such as heat-shock proteins and MIC (MICA and MICB); which are proteins that are related to the MHC1 proteins but are considered to be markers of "stress" in the epithelium , they are expressed by the stressed cell and located on its surface, acting as ligands for natural killer-cell (NKG2D).





MHC1 and MHC2 are made of two polypeptide chains, the α chain and the β2 microglobulin whereas MICA and MICB consist of one α polypeptide chain only, So those two are related to MHC molecules and when expressed on the surface of the cell indicates stress.

Acquired immune system

It usually takes about a week to initiate an immune response.

When we talk about Acquired immune system the first thing cross our minds "antigens-antibodies interaction";

Talking about receptors, antigen receptors for B and T lymphocyte are BCR (B-cell receptor) and TCR respectively; they are responsible for recognizing antigens bound to (MHC) molecules.

TCR: is always cell-bound, always on the surface of cells.

BCR: we have two forms;

A)one is cellular (on membrane of B cells) which is also called BCR-proper that is bound to the cell surface just like the TCR,

B)and the other is secreted in the circulation and known as antibodies.

Haptens are small molecules that generate an immune response when they are attached to a large carrier molecule such as a protein. There are many different types of **haptens** occurring in nature and they all carry only one epitope.

A carrier: it is a protein that binds to hapten in order to make it an immunogen.

◘Antigens, antibodies and their receptors

First, let's talk about **Antigens**;

•It is a molecule that binds with its antibody with specificity.

•If this antigen develops an immune reaction then it's called an immunogen, because it initiated an immune response via an antibody.

•If this antigen is too small(less than 6kd) to be recognized by antibodies we call it **hapten** and in this case it is unable to bind to an antibody, and in order to do that, those haptens bind with other proteins –usually called a **carrier**- for them to be seen and interact with antibodies and be immunogens, because the bigger those antigens are, the better they'll be recognized -obviously- otherwise they can be there kept unseen.

***All immunogens are antigens but not all antigens are immunogens.

In order for an antigen to be called an immunogen it has to have the following characteristics:

1-it has to be foreign.

2-the size: The bigger the molecule the more likely it will produce an immune reaction. (Usually above 6 KDalton are immunogenic, from 1-6 is in between)

3-complexity:

If their structures are more complex they are more easy to get recognized, that's why polysaccharides can't be recognized well because they are made of repetitive units, I mean they can be recognized but not that well so they are not very good immunogens… unlike of course "proteins" which can be recognised easily because they will most likely have the epitope in their very long sequence of aminoacid structure so the best immunogens are actually proteins.

RNAs usually are not good immunogens but they can be immunogenic in certain cases such as Cushing's disease and SLE (systemic Lupus Erythromatosus)

Lipids are not immunogenic unless they are bound to proteins forming lipoprotein.

4-the genetic makeup of the person: not all people respond to antigens in the same way some of them may consider certain molecules as immunogens while others won't and that depends on immune response genes (the genes that are responsible for initiating immune responses and that usually code for the MHC-2). one example is when injecting mice with a foreign substance some of them will initiate an immune response (those are called responders) while others won't (those are called non-responders). Another example is that some people catch cold once a year while others get called 3 or 4 times a year.

5-way of exposure to the antigen:

A) if the antigen was presented orally it is more likely to develop tolerance rather than immune response that's why very few numbers of vaccines are given orally.

B) if it was presented intravenously it is also less likely that the body will develop an immune response because it will be cleared from the body in no time.

Epitope:

Is a short aminoacid sequence that specifies an antigen as an antigen

C)injecting the antigen intramuscularly or subcutaneously usually produces an immune response that's why we usually give vaccines in those two roots.

In order to increase the efficiency of injection we can do the following:
A)Some proteins called **"adjuvant"** may be added to vaccines, they have the power of dissolving the antigens and releasing it gradually allowing it to initiate a better immune response, also it might have an irritating response that will attract large number of macrophages to the site of administration.

**In animals we can use what is called as Freund adjuvant which is made (really toxic) of a suspension of a mycobacteria extracts with oil suspension and it is usually used alone or with aluminum hydroxide to absorb the vaccine and release it slowly in order to get a good immune response.
Don't confuse the carrier with the adjuvant!!:

-A carrier is a substance that is part of the antigen.

-An adjuvant is a substance added to the antigens (a vaccine mostly) to increase its absorption.

or it might be an i Other types are called "Freund's adjuvant" have an irritating effect and may be toxic, this irritation is needed to make sure large quantities of macrophages are there to eat up all these antigens, that's why some vaccine shots can be painful. However, Freund's adjuvant is not introduced in normal vaccine instead aluminum hydroxide is used in order to dissolve the antigen and release it gradually.

Vaccination

This antigen antibody thing can be implicated in the vaccination field, the thing is, if you want to produce an antibody for "X antigen", you simply inject that antigen in a human or animal so its immune system will create a

highly specific antibodies for the sake of destroying it. Later on these antibodies stay in their circulation hunting and looking for that X antigen in case if they appeared again.

We must make sure that the body has produced antibodies from those antigens in the vaccine shots, so we must administrate it slowly to make sure the body has reacted with it properly. Giving it orally can damage those antigens before our immune system can react with them, so we introduce it intramuscularly or subcutaneously to have our desired result.

•**Freund's adjuvant** is a solution of antigen emulsified in mineral oil and used as an immunopotentiator (booster). The complete form, Freund's Complete Adjuvant is composed of inactivated and dried mycobacteria.-wiki

Now let us talk about antigens and antibodies structurally.

We've talked about antigen previously, antibodies on the other hand are a Y shaped proteins because it has two binding sites for the antigen. The site of contact between the antigen recognition site and the antigen of them is only 7-8 amino acids called epitopes.

Epitope

Also known as antigenic determinant, is the part of an antigen that is recognized by the immune system, specifically by antibodies

antigens usually have more than one type of epitope, these are called **multivariate** antigens, so we can have an antigen with 100A epitope and 200X epitope and so on. Different types of antibodies can bind to the same antigen due to this variation. Unlike hapten, this poor thing only has one epitope so it is called a **monovariate**.

Based on their structure and interaction with the antibody We classify epitopes into:

A) **linear epitopes** if they have a specific linear sequence if you denature the antigen it will not be affected.

B) **conformational epitope (conformational epitope):** when an epitope is made of one bit of a molecule here and one bit of a molecule there. if you denature the antigen it will be affected and it won't act as an antigen.

Epitopes are divided into two categories;

Types of antigens:

- A **neoantigenic** determinant is an epitope on a **neoantigen**, which is a newly formed antigen that has not been previously recognized by the immune system. this occurs when the epitope is part of a globular protein and it is not exposed (it is hidden inside) then it will be exposed later and we call it a neoantigen.

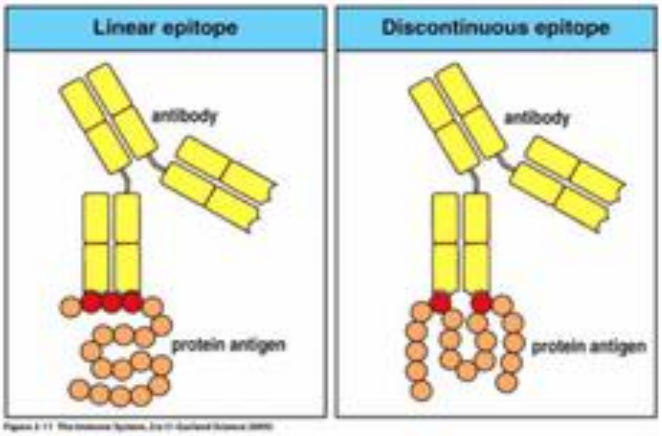
Epitobe has another name with is the antigenic determinant.

•Endogenous antigens

Are generated within normal cells as a result of abnormal cell metabolism, or because of viral or intracellular bacterial infection. The fragments are then presented on the cell surface in the complex with MHC class I molecules.

• Exogenous antigens

Are antigens that have entered the body from the outside, for example by inhalation, ingestion or injection



•Superantigens

Are a class of antigens that cause non-specific activation of T-cells resulting in polyclonal T cell activation and massive cytokine release.

SAgs are produced by some pathogenic viruses and bacteria most likely as a defense mechanism against the immune system.

Now what exactly determines the interactin between the antigens and their antibodies?

It's a non-covalent interaction (reversible); the affinity is caused by several types of bonds,

1) The shape of each one so they can fix on each other

2) Electrostatic force the charge of the epitope and the charge of the site where it should bind.

3) Hydrogen bonds.

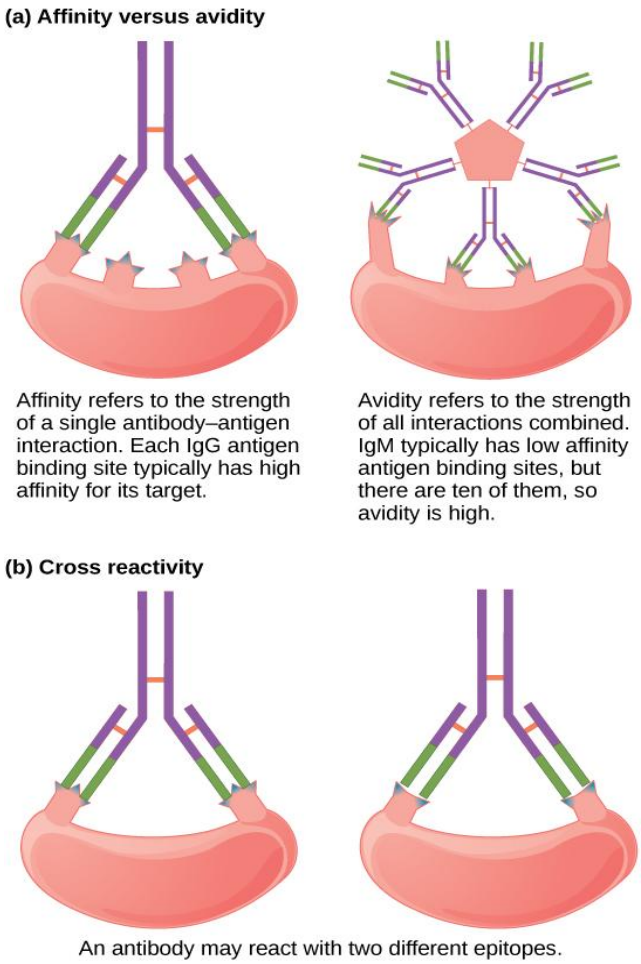
4) Van der waal forces.

5) Hydrophobic force.

Those 5 determine the AFFINITY of the antigen to its antibody

*

* Avidity: refers to the accumulated strength of *multiple* affinities of individual <u>non-covalent</u>



binding interactions, such as between a protein receptor and its ligand, and is commonly referred to as functional affinity. As such, avidity is distinct from affinity, which describes the strength of a *single* interaction. However, because individual binding events increase the likelihood of other interactions to occur (i.e. increase the local concentration of each binding partner in proximity to the binding site), avidity should not be thought of as the mere sum of its constituent affinities but as the combined effect of all affinities participating in the biomolecular interaction. Biomolecules often form heterogenous complexes or homogenous oligomers and multimers or polymers. If clustered proteins form an organized matrix, such as the clathrin-coat, the interaction is a described as matricity.-wiki

That's it! Good luck on your midterms ☺

Done by, Mohanned Momani

Dedicated to mazen hindi for not helping me at all :p. And a special thanks goes to tareq bushnak and hamzeh salameh

Corrected by: Qusai Sharief