IMMUNOLOGY - 4 - ☺

What is an ANTIGEN? It is a molecule that can be recognized by a receptor and combine with it specifically… and the receptor here is the one either produced by B cells or T cells:

♦ Receptors of T cells are TCR – T Cell Receptors – which are present on the cell surface of T lymphocytes.

♦ Receptors of B cells can be present as cell bound surface molecules on the B lymphocytes, in the same time, they can also be secreted as immunoglobulins in the serum.

Now, the antigen is a big molecule, and definitely not all of it will be in contact with the receptor, only a small part of the antigen (8-10 amino acids in size) will be in contact with the receptor which is the EPITOPE.

ANTIGENIC DETERMINANT: Another name of the epitope itself, it's named so because it determines the antigenicity of an antigen.

If there is a big antigen, then definitely it is made of thousands of amino acids & since one epitope is made up of 6-9 amino acids, then for sure there will be more than one epitope on that antigen:
♦ MULTIVALENT ANTIGEN: The antigen that has more than one epitope of the same amino acid sequence i.e. **identical epitopes**, which will interact with the same antibody/receptor type since they have the same specificity.
♦ There are other antigens that have **more than one epitope of more than one different variety** i.e. epitopes with different amino acid sequence & thus of different specificity.
♦ Also, you may have an antigen that has multiple epitopes, some are identical & some are different.

What is a Paratope? It is the part of the antibody which interacts/contacts with the epitope.
The interaction between the antigen & the antibody is:
♦ Specific, i.e., the epitope must be complementary to the paratope & vise versa in order to combine with each other.
♦ Non-covalent, it is a very loose interaction mediated through 4 forces: electrostatic forces (+,-), hydrophobic forces, van der waal's forces & hydrogen bonding.
♦ Reversible; since it's not covalent & the strength of the interaction depends on the previous 4 forces in a way that the stronger the attractive forces are, the stronger are the forces required for separation.

The attraction between one epitope and one paratope is known as AFFINITY (it is the sum of the 4 forces that are responsible for the attraction between the two)… you may have high affinity antibody .or low affinity antibody against a specific antigen depending on the forces of attraction mentioned before.
Usually antibodies have 2 paratopes; one on each arm of the Y-shaped antibody & each stick to one epitope… but IgM is different; it is made of 5 molecules, each molecule has 2 arms & thus the IgM has 10 paratopes/ combining sites, so the total sum of affinity between paratopes and epitopes in the whole immune complex // the attraction between the antigen and the antibody due to the sum of all the combining sites will give you AVIDITY… IgM avidity is more than IgG although the affinity of IgG might be higher than the affinity of IgM, why? Because IgG has got 2 arms only, so the summation of the affinity will be less than that of IgM with its 10 arms (10 combining sites)

Q: Do the 5 molecules in one IgM have the same specificity? YES
Q: Which is more important for a better interaction between the epitope & the paratope, affinity or avidity? You can't tell; because if you have 1 IgM & one epitope, then IgG would be better because of its high affinity, but if you have more than one epitope, then IgM would be better.
Q: Is avidity related to multivalent antigens? Of course, because if you don't have a multivalent antigen i.e. 1 single epitope is present on the antigen, you won't have avidity & you'll only have affinity for that single epitope.
Note: if we have a multivalent antigen, the IgM will interact with its epitopes, but not all the 10 combining sites will be occupied; because the conformation of the IgM doesn't allow it to bind to 10 epitopes of that multivalent antigen.

Types of antigens regarding the immune response:

1) IMMUNOGENs: The antigens that are able to produce an immune response on their own when they are injected into animals, i.e. specific antibodies are produced against these antigens.

2) HAPTENs: The antigens that are very small & they are unable to produce an immune response when they are injected alone into animals, i.e. no specific antibodies are produced against them … if so, then how antibodies are produced against such antigen? The hapten must be coupled with a protein molecule known as a CARRIER to make it bigger; in this case, if you inject the hapten with the carrier into the animal, it will produce an immune response with specific antibodies against that hapten.
   Q: If we change the carrier, would the antibodies change against the same hapten? NO, the carrier has other functions but has nothing to do with the specificity of the antibodies against the hapten.

Bottom line: All immunogens are antigens, but not all antigens are immunogens.

What is an ADJUVANT: A substance which is incorporated with the antigen/vaccine to increase the immunogenicity & the likelihood of producing an immune response… how is that achieved?

EITHER by adsorbing the antigen & then releasing it slowly OR by producing irritation to attract the macrophages & dendritic cells to the site of injection in order to take up the antigen & then present it on the surface –remember, macrophages & dendritic cells are antigen presenting cells – for T-lymphocytes and by this the adjuvants will make the process of immune response much easier.

One of these adjuvants is known as FREUND, it is used in experimental work and is made of mycobacterial extracts in oil suspensions; it increases the immunogenicity of the antigen but is not used for humans because it's toxic.
The only adjuvant that is used for humans in vaccinations is Aluminum Hydroxide, which produces slow release of the antigen at the site of injection, so you get a very good immune response.

DON'T confuse between *the adjuvant* & the carrier, the carrier plays a part in the immune response, by becoming part of the antigen & then producing an immune response, whereas *the adjuvant doesn't play a part in the immune response, it only slowly releases the antigen or causes irritation to make the immune response more effective.*

What are the requirements of immunogenicity – to be immunogenic -?

1) The antigen has to be foreign, so that the immune system can recognize it & react to produce antibodies against the foreign antigen (if you inject yourself with your own proteins, they won't be recognized as foreign antigens & there won't be an immune response).

2) The size, the bigger the antigen is, the better is it's immunogenicity (molecules < 1000 in m.w are usually non immunogenic, molecules of 1000-6000 m.w can be immunogenic or maybe not, molecules > 6000 m.w are most likely to be immunogenic).

3) Complexity, the more complicated the antigen is, the more immunogenic it is.

   Note: The size of the antigen is important, but the complexity is more imp. , for example, polysaccharides are large molecules made of *repetitive* units so they are less immunogenic than proteins which are very immunogenic; because they are made of amino acids which are *different* in type and sequence.

4) Genetic makeup of the person: this is more demonstrated in animals; they found that there are animals that respond to a certain antigen (Responders) & other animals do not respond to the same certain antigen (Non-Responders), why? MHC molecules are the ones responsible for such variation in responding, some people respond better than others according to the variety of MHC molecules that they have on their immune cells … to be discussed later.

5) Method of administration: if you inject antigens intravenously, they are very unlikely to produce an immune response, because they are taken up very quickly by the spleen & then disappear… if you eat antigens, also immunogenicity isn't that good and that's why oral vaccination isn't a good way to produce immunity against an antigen.
   The best methods of administration of antigens for producing an immune response (as in vaccinations) are through intramuscular & subcutaneous injections, but exceptions can be made for live polio vaccine which is given orally to mimic the natural infection (multiplying in GI) – if it's killed polio vaccine, then it's administered IM or SC - & there are NO vaccines administered IV.

6) High doses & low doses of the antigen are not immunogenic… in case of low doses, the response is negligible and there won't be an immune response, in case of high doses, you are more likely to become tolerant to the antigen; rather the immune cells respond & form antibodies, they actually become tolerant… so there is some sort of intermediate optimal dose of the antigen that will produce an immune response.

CROSS REACTIVITY: It is when the antibody produced by an antigen interacts with another antigen which is similar to the one that caused its production (similarity between these 2 antigens is due to the presence of similar epitopes on both of them).

Clinical Application on cross reactivity: DPT vaccine is a toxoid which means that it is a toxin that has been inactivated by formalin, so what we are injecting is a toxoid, but due to cross reactivity, the antibodies that are formed against this toxoid will neutralize the active toxin when it comes back (since the active toxin is similar to the toxoid).

Note: Proteins are the most excellent antigens that produce an immune response with the best antibodies, polysaccharides can produce antibodies which are most likely IgM with low affinity, lipids are non-immunogenic unless they are coupled to proteins, that's why lipoproteins are immunogenic, nucleic acids as a rule are not immunogenic, but they can be as in autoimmune diseases where there are lots of antibodies formed against the DNA.

The antigens themselves – specially the protein antigens – can be classified into different varieties:

♦ T – Dependent antigens: are the antigens that B cells can't produce antibodies against them without the help from T cells, usually protein antigens are of this type.
♦ T – Independent antigens: are the antigens that B cells can produce antibodies against them without the help from T cells, usually polysaccharide antigens are of this type.
♦ Exogenous Antigens: are the antigens that come from outside the cells and then are phagocytozed and broken down then presented on the surface of the cells.

♦ Endogenous Antigens: are the antigens that are produced inside the cells, e.g.: viral antigens produced inside the cell using the cellular machinery.
♦ Super Antigens: are antigens that can activate lots of cells at the same time nonspecifically, e.g.: TSST which is a toxin produced by staphylococcus aureus is a super antigen that produces an intense immune response causing shock… WHEREAS the other antigens –non super- activate T & B cells specifically by combining with their receptors… the whole classification will be further discussed later.

Epitopes are divided according to their structure into:

♦ Linear epitopes: they have a primary structure of a continuous sequence of amino acids.
♦ Conformational epitopes: they have complicated enfolding tertiary structure of discontinuous sections of amino acid sequence.

What happens to the linear & conformational epitopes if we denature the protein which has them? The linear epitopes stay as they are (but if we digest them with enzymes, then they will disappear), but the conformational epitopes will disappear.

Now, the surface epitopes on a protein are present for the benefit of B cells (for recognition), but if we take the protein and process it by cutting it into pieces, then the resulting small pieces – epitopes – will be useful for the activation of T cells.

There are epitopes that are buried inside (between the folding of the protein) if the protein is globular for example, and those buried/hidden epitopes could be linear or conformational, but upon denaturing the protein, those hidden epitopes will be exposed and by that we have produced new antigenic epitopes … so NEOANTIGENS: are antigens - along with their epitopes - that are present on a protein molecule but are hidden & upon unfolding of the protein they will be exposed.

HAVE A NICE DAY WARRIORS ☺