مقدمة في علم المناعة الطبّي

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Medical Committee
The University of Jordan

IMMUNOLOGY

Lec# 3 ,Date(29/6 /2014)

Subject: Handout #3

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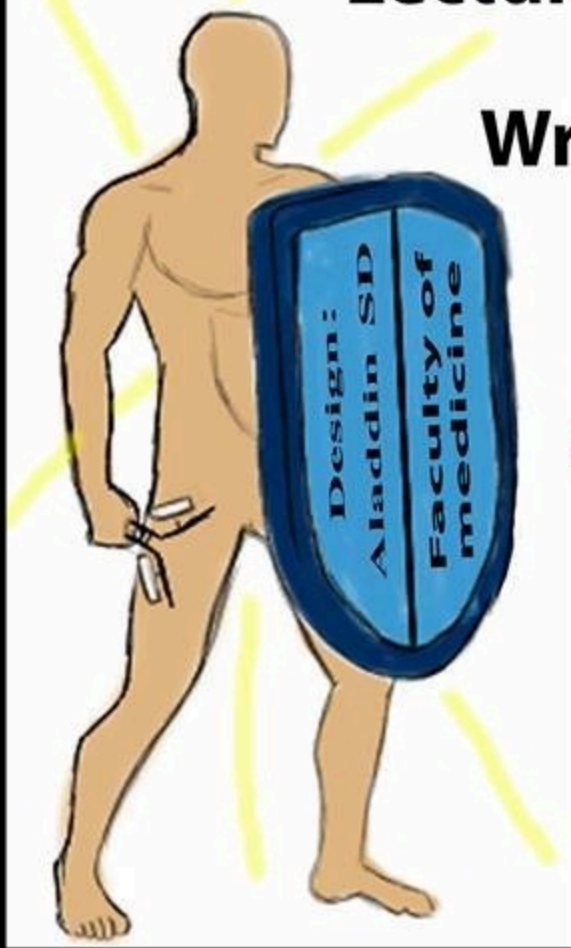

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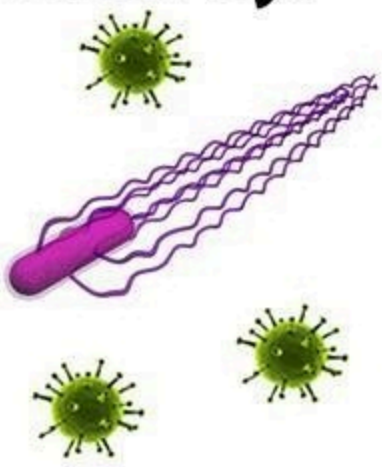

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Immuncgens.

An immune response is evoked by a foreign agent called antigen or immunogen. The distinction between these two terms is functional, an antigen is a compound that is capable of binding with Ig or T-cell receptor, but does not necessarily evoke an immune response, an immunogen always does. Thus not all antigens are immunogens but the converse is true.

This is apparent with low molecular weight compounds known as haptens, the hapten can bind antibody but does not produce an immune response unless it is conjugated to a high molecular weight compound called carrier. The carrier provides the antigen to be processed and presented to T-cells which will provide help.

Requirements for immunogenecity :

1)- Foreigness. Exception auto-immune disease.
2)- High molecular weight : < 1kDa is not.
1-6 kDa may or may not be immunogenic.
> 6kDa are generally immunogenic.
3)- Chemical complexity : polymers of the same unit structure although of high m. w. are usually not immunogenic.

A compound must have all three properties to be immunogenic.

Other factors that affect an immune response are :

1)- The genetic make-up of the animal : responders and non-responders to a particular antigen is controlled by Ir genes which are autosomal dominant (these in fact are MHC genes).

2)- Method and dose of administration of antigen : I/V, very high and low doses are not efficient. They may even lead to tolerance. (ORAL)

Adjuvants :

An adjuvant enhances the immunogenecity of an antigen, importance in immunisation. Distinguish from the carrier of a hapten. It does this through slow release and attraction of cells involved in the immune response e.g. macrophages.

Freund's adjuvant : water in oil emulsion with killed Mycobacteria tuberculosis. The most widely used one in humans is alum precipitate $Al(OH)_3$ suspension on which the antigen is adsorbed, it has an irritant effect which attracts and enhances ingestion by macrophages.

The antigen binding site to the antibody is called an antigen determinant or epitope. This is equivalent to about 5-7 amino-acids.

Epitopes may be linear or conformational.

Modification of an antigen can produce new epitopes, these are called neoantigenic determinants.

An antigen can have several epitopes. These epitopes may be different or identical, when identical the antigen is said to be multivalent.

The corresponding combining site on the antibody is called a paratope.

Epitopes may be exposed on the surface and combine with antibodies. Other epitopes may be buried within the structure of the antigen and may be presented after processing by macrophages, these combine with TcR.

+H BONDING

Binding between antigen and antibody is non-covalent, electrostatic and hydrophobic and Van der Waals interactions which are usually weak forces, thus the FIT is very important in the affinity of antibodies.

Cross-reactivity :

An antibody may bind two different molecules that share the same epitope. This is important in immunisation Toxoids.

Major classes of antigens :

1)- Proteins : virtually all are immunogens. Multi-epitopes.
2)- Polysaccharides : potentially but not always. Glycoproteins.
3)- Lipids are usually non-immunogenic unless coupled to proteins.
4)- Nucleic acids : poor immunogens, exception SLE.

Antigens that illicit an immune response usually do so with the help of helper T-cells and thus are called T-dependant antigens. There are also T-independent antigens which trigger B-cells without Helper T-cells, they are usually polysaccharides of repeating units, they result in IgM mainly and there is no memory produced.. The mechanism is not clear.
Superantigen : non-specific activation of T cells. Polyclonal.

Endogenous and exogenous antigens in connection with MHC. SUPER ANTIGENS

Affinity is a measure of the strength of binding of paratope to epitope.
Avidity is an overall measure of antigen antibody binding, this depends on the total number of epitope paratope binding i.e. multivalent antigen and pentameric antibody would produce high avidity even if the affinity is low. Thus IgM has potentially 10 combining sites which provide great avidity even if the affinity may not be very strong.

Immunoglobulins :

Antibodies are soluble protein molecules called globulins, due to their globular structure. On electrophoresis, they are predominantly found in the gamma region (γ globulins) furthest away from the anode. They are collectively called immunoglobulins.

Structure of immunoglobulins :

An immunoglobulin molecule is made of two identical heavy chains (m.w. 53000) and two identical light chains (m.w. 22000), these are mirror images of one another.

These chains are connected together by means of S-S bonds. One part of the molecule (Fab) combines with antigen i.e. has the specificity of the antibody, while the rest (Fc) is the effector part responsible for the biological activity.

The enzyme papain cleaves the Ig molecule into three fragments : two Fab (antigen binding) and Fc (crystalline).

The bond between antigen and antibody is non-covalent, affinity is the measure of this bond. Avidity.

The light chain can be of two classes : Kappa and Lambda, in humans, 60% of Ig contain kappa and 40% contain lambda chains.

The heavy chain can be of five different classes : μ, δ, γ, α, ε corresponding to IgM, IgD, IgG, IgA and IgE respectively, these are present in all individuals and are called isotypes. The class of the heavy chain determines the biological activity of the immunoglobulin.

There are also subclasses of IgG and IgA, due to small changes in amino-acid sequences in the H domains of H chains.

Each heavy or light chain is divided into segments of compactly folded globular structure 100-110 amino acids in length with an intra disulphide bond, these segments are called domains. This is the immunoglobulin fold and all molecules containing this structural fold are called members of the immunoglobulin superfamily.

All these domains show a great deal of homology or resemblance in sequence indicating that all came originally from a common ancestral gene. The end (-NH_2) domains are called variable domains on both light and heavy chains, all the rest are constant domains.

Light chain : one variable and one constant domains : VL and CL.

Heavy chain : one variable and 3-4 constant domains : VH and CH.

Hinge region :

Except in IgM and IgE which also happen to have 4 constant domains, a short additional segment is present between CH1 and CH2 domains known as the hinge region. It affords flexibility between the two Fab fragments of the Ig molecule. It is probably the remnant of a domain.

Structure of a domain :

Special pleated structure called the immunoglobulin fold, 7 pleats and folds.

The variability in the V domain in the amino acid sequence is mainly found in three regions called hypervariable regions, they are responsible for the repertoire and because they are complementary to the antigen with which they combine, they are called complementarity determining regions or CDRs.. There are 3 CDRs on each variable domain. The CDRs from light and heavy chains form the cleft whose fit determines the epitope with which it is to combine and with which affinity.

Allotypes : Classes of Ig and subclasses are found in all individuals of a species and are called isotypes. Some allelic variation in AA sequences lead to allotypes of Ig in certain individuals, there are allotypes of gamma and kappa chains as well as alpha chains.

Idiotypes : the specificity regions of an Ig molecule i.e. paratope is immunogenic due to its heterogeneity, this is known as the idiotype. Antibodies can be raised to this and are called anti-idiotypes.

Biological properties of immunoglobulins :

1)- Agglutination : clumping together of particulate antigen e.g. bacteria.
2)- Precipitation : linking soluble antigen to form a precipitate.
3)- Opsonisation : facilitating phagocytosis.
4)- Complement activation : opsonisation and cell lysis.
5)- ADCC : through NK cells and eosinophils.
6)- Crossing the placenta : only IgG subclasses (except IgG2).
7)- Immobilisation of bacteria : binding of flagella and cilia.
8)- Neutralisation of viruses : inhibiting of binding sites to cells.
9)- Neutralisation of toxins : binding to active site.

IgG : this is the most abundant Ig in serum. MW 150,000. Has 3 constant domains. It is the least anodic i.e. least negatively charged of all serum proteins and belongs to the γ region of serum zone electrophoresis, hence the term gamma globulins as equivalent to immunoglobulins. It has 4 subclasses. The half life is 23 days, thus it is suitable for passive immunisation. IgG aggregates readily by heating or with alcohol treatment, and then act as an immune complex. It is important that passive immunisation is not carried out with aggregated IgG.
IgG causes agglutination and precipitation, which results in immune complexes that are easily phagocytosed and removed from the circulation.
It is the only Ig to cross the placenta (except IgG2), the newborn does not produce IgG up to 2 months after birth : important in defense but a drawback in Rh haemolytic disease.
It is a good opsonin, Fc receptors on macrophages. ADCC through Fc receptors on NK cells. It activates complement, neutralizes viruses and toxins, it immobilizes bacteria, hence its versatility as an immunoglobulin.

IgM : m.w. 900,000 it has 4 C domains in the heavy chain. It exists as a pentamer with S-S bonds with Fc and J chain. Contrary to expectation, IgM has only five binding sites instead of 10 because of conformational constraints.
It has a half life of 5 days. It can be present on the surface of B cells.
It is the main Ig in the foetus and the newborn. The main Ig of the primary immune response and with T-independent antigens.
IgM is a very efficient agglutinating agent, the pentameric structure helps bridge wider distances. The isohaemagglutinins of the ABO system are IgM.
It is efficient at activating complement one molecule being sufficient for that..
It does not cross the placenta. It is a poor neutralizing antibody.

IgA : m.w. 165,000. Dimeric 400,000. Half life is 5.5 days.
Two isotypes, IgA1 more in serum , IgA2 more in secretions.
IgA in secretions is dimeric, has J chain and secretory component from the epithelial cell across which it passes.

IgE and **IgD**.