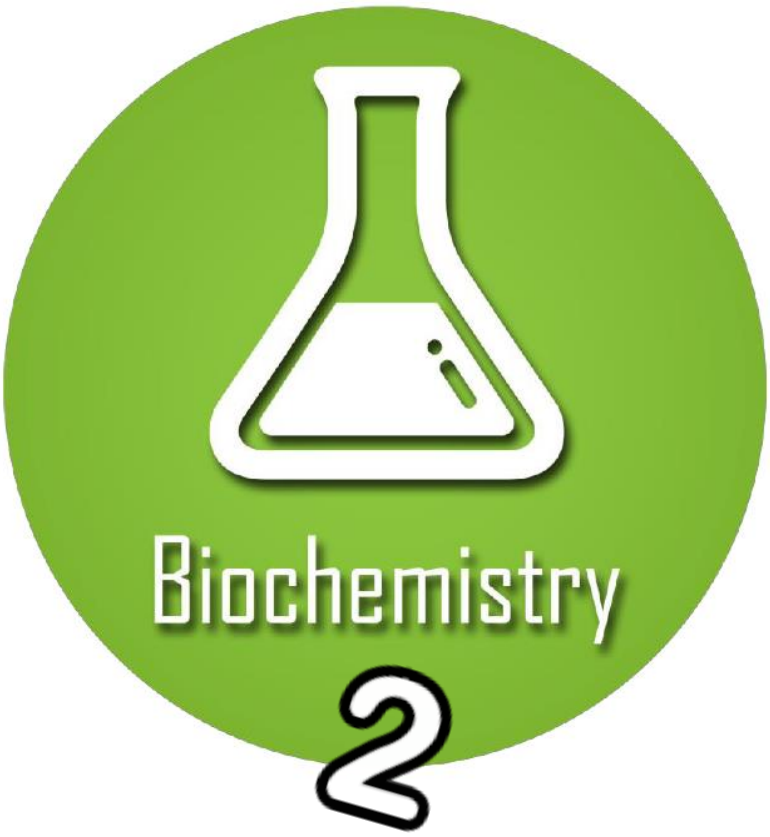

◉Sheet ○Slides

Number: 5

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Corrected by: Omar Khader

Subject: Immunoglobulins & Bioenergetics

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14/6/2015

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Quick revision:

- Plasma cells (also called plasma B cells) are white blood cells that secrete large volumes of antibodies (immunoglobulins).
- Immunoglobulins are quaternary Y-shaped glycoproteins, having two arms and a stalk. (2 F_{ab} & 1 F_c).
- All contain a minimum of 2 identical light chains (25 kDa) and 2 identical heavy chains (50 kDa).
- Total weight is 150 kDa, causing it to be the slowest band to travel in gel electrophoresis (Gamma band).
- Heavy chains are composed of 1 variable and at least 3 constant domains, while the light chains are composed of 1 variable and 1 constant domains.
- Loops are found between the first and the second constant heavy chain domains creating the hinge to ease movement therefore more flexibility.
- Maintained heavily by disulfide bridges (Intra-chain and inter-chain).
- The light chain maybe either kappa (κ) or Lambda (λ), and in one immunoglobulin they can never be a mixture.
- Every antibody is specific to one antigen.
- Antigens bind to variable heavy chains and variable light chains.

Class	Heavy chain	Chains structure	% in serum	T 1/2	Comp. fixation	Placental crossing
IgM	μ	Mono-, penta-, & hexa	5-10	5-10	++++	No
IgG	γ	Monomer	80	23	++	Yes
IgA	α	Mono-, di-, or tri	10-15	6	-	No
IgD	δ	Monomer	0.2-1	3	-	No
IgE	ε	Monomer	2	2	-	No

Immunoglobulin classes

Fragment crystallizable region (F_c) and hinge region differ in each class of antibodies. Classes IgA, IgD & IgG have free constant domains within their heavy chain while classes IgM & IgE have an extra domain located in the hinge region, that means flexibility is much less but it is not all gone (slightly flexible because of shorter hinge). Now we will talk about the different classes of antibodies.

IgM class {Primary immune response}

It can be present in different forms, monomer, pentamer (most common and in this form it can bind to 10 antigens) and hexamer. It is found in the circulation (intravascular), connected to the B lymphocytes by the F_c portion making the antigen receptor, and then it binds to the antigen presenting it to the immune cells (in this case it is in its monomer form). The main function of IgM is the primary immune response which is activated when you face the antigen for the first time (recognition response). This response is weak (because it has low affinity) and sometimes can be fatal (when large amount of antigens are present), as an example: when blood transfusion is not matched giving a patient blood different from his original blood type, in this case a large number of antigens is present in the patient's body (blood coagulation).

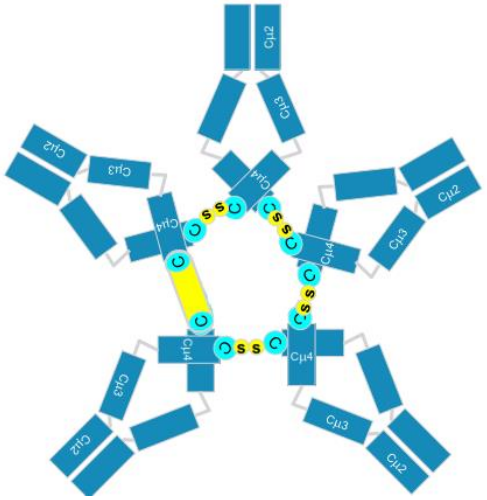
Any immunoglobulins are connected together by the crystallizable region, why?

-So the antigen binding site would stay free.

In IgM we have 4 constant domains, they are connected by constant region number 4 and also constant region number 3 participates in the connection process. This process is called multimerization. How is it done? 1 IgM molecule comes near another IgM molecule, a joining chain (j-chain) which is a piece of amino acids, gets the two molecules even nearer to each other, therefore two cysteines (which are found in large amounts in the immunoglobulins) are very close together initiating a disulfide bridge, then another IgM molecule comes near the molecules and so on until we have 4 disulfide bridges, when the last IgM molecule

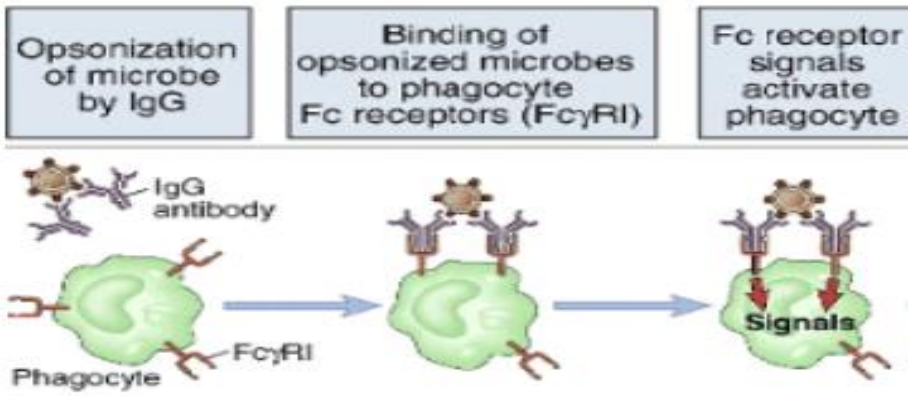
comes, the j-chain initiates a disulfide bridge but the this time the j-chain DOES NOT leave and it contributes in the last connection.

Pentamer → 4 disulfide bridges & 1 joining chain



IgG class {Secondary immune response}

Present only in the monomer form. Found in the blood, lymph and intestines. It is responsible for the secondary immune response (protective immunity), therefore it has the longest half-life between all of the classes and it is present in the highest concentration. It is the only one that can cross the placenta, providing immunity for the fetus and for the new born. Last but not least, IgG is responsible for the opsonization process, which is coating the antigen's entire surface by immunoglobulins to prevent any effect of the antigen.



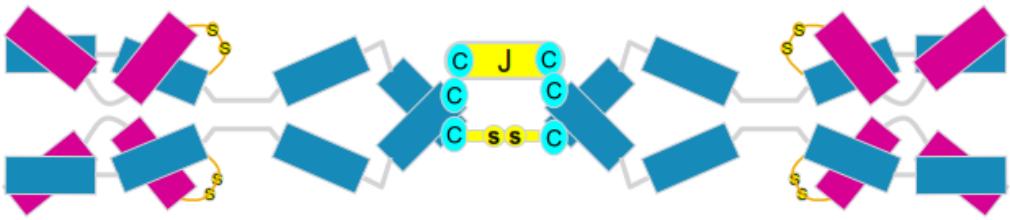
10:00

IgA class {found in the body secretions}

Present in 3 forms, monomer, dimer and trimer. In plasma it is found in all forms but in secretions only dimer form, such as in respiratory tract, tears, in the sputum , sweat, saliva, gastric juice, intestines, milk and urine. It provides the first line of defense before the antigen gets into the body, but, what is the problem when immunoglobulins are secreted? The answer is enzymes-almost proteases- (enzymes are found with all secretions because foreign bodies are found between the spaces), i.e. if the urinary tract in infected with some pathogens, it's better to fight them there before they get to the blood. To protect the immunoglobulins, a secretory component (piece of amino acids that will not be broken down by the enzymes) wraps around the immunoglobulins as an S-shape., leaving the tips of the Y-shaped molecule to be able to bind to the antigens. In the breast feeding of the baby, IgA is secreted with the milk and it enters the baby's body providing immunity.

How does the dimerization process occur?

-J-chain brings two IgA molecules close together initiating a disulfide bridge, and the j-chain DOES NOT detach and it is kept bonded to the two molecules.



Dimer →1 Disulfide Bridge & 1 joining chain

From where does the IgA get secreted (Transcytosis)?

-Any space in the body is surrounded by epithelial cells, under the epithelial cells mature B-lymphocytes are present that can synthesize IgA. The IgA is secreted in the dimer form and epithelial cells provide the

secretory component that is suspended from a stalk. IgA gets secreted from the B-lymphocytes then it binds to the secretory component and internalization occurs so both are now within the epithelial cells and then they get expressed to the outside. The enzymes degrade the stalk leaving the IgA wrapped with the secretory component and fully protected.

IgD class

It is found mainly as a monomer. Its main function is not well understood yet. It is found attached to the B-lymphocytes and it helps in initiating the immune response.

 20:00

IgE class {Allergy is mediated through the IgE class}

It is found only in the monomer form. It is found in the blood, and bound to mast cells and basophils. Allergy is what is special about the IgE class. When the allergen enters the body, it binds to the IgE, then the F_c portion of the IgE will bind to the receptors of the mast cells and basophils, which contain high content of histamine, heparin and other inflammatory molecules. This causes the secretion of the inflammatory molecules to the outside causing an inflammatory response.

Inflammatory response can be fatal. The body is going to respond in the following ways (allergic reactions):

1-Higher blood flow to the site of inflammation.

2-Constriction to the airways.

3- Generalized vasodilation, causing an increase in the spaces between cells (vascular permeability) so the plasma cells will escape the circulating system to the tissues causing edema or lowers the blood pressure causing coma.

4- Skin rashes.

5- Increased secretions from epithelium (watery eyes, runny nose).

Why the response for the allergy is always fast?

-When IgE binds to the receptors of the mast cells and the basophils, it binds with the highest affinity (km value for it is the lowest indicating a high affinity).

Diseases affecting immunoglobulins

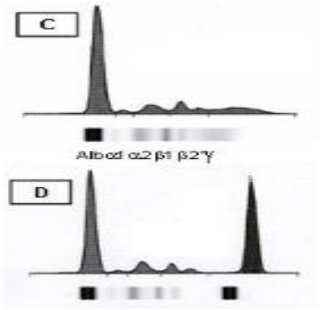
- Immunoglobulins either increase or decrease in concentration.

When a foreign molecule enters the body, this will cause an increase in the amount of immunoglobulins, this is normal due to an infection. But, if their number increased dramatically, it would be due to cancer; this cancer is affecting plasma cells which are producing immunoglobulins. The cancer may affect one cell type and accordingly one immunoglobulin class and it is called monoclonal, or it may affect more than one cell type and accordingly more than one immunoglobulin class and it is called polyclonal. The cancer affecting plasma cells is called multiple **myeloma**.

In gel electrophoresis, normally the gamma band must look faint because there is no high amount of immunoglobulins indicating a healthy case, but in the situation of cancer, the gamma band will be very dark (like albumin) indicating that there are an abnormal number of immunoglobulins.

In the densitometer representation, you can notice the sharp increase of gamma immunoglobulins. In the picture below, it is as increase in one cell type.

The decrease of production of immunoglobulins, would maybe due to genetic deficiencies or due to a disease ex: Aids (no secretion so no immunity), or maybe part of a treatment ex: leukemia and lymphoma, the treatment requires the killing of all immune cells that are not healthy through the use of radiation so the patient's healthy immune cells will be isolated at first and then returned back and this is called auto-transplantation, the patient can take cells from a relative and it is called hetro-tranplantation. During this period the patient must be Isolated in a special room because he has zero immunity.



30:00

In the case when there are no gamma immunoglobulins in the blood, it is called agammaglobulinemia (a= negative, aemia= related to the blood).

Easy way to remember:

IgM → primary immune response
IgG → secondary immune response
IgA → Secretions
IgD → not well understood yet
IgE →Allergy
==========

Extra info. (Not included...it's just to enhance your understanding :)

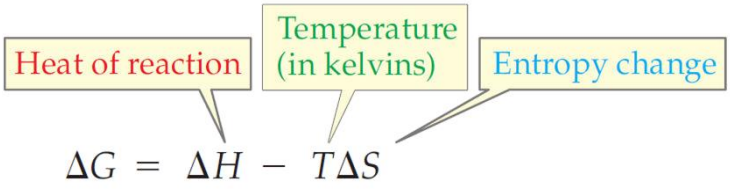
1- Heparin is a naturally occurring anticoagulant.

2- Receptors called Histamine H1 receptors occur in the smooth muscles surrounding the bronchi...during inflammation, histamine (derived from the decarboxylation of the amino acid Histidine) will bind these receptors and eventually will cause bronchoconstriction(the constriction of the airways in the lungs due to the tightening of surrounding smooth muscles, with consequent coughing, wheezing and shortness of breath).

Bioenergetics

We took a lot of information about this topic in the summer semester, so we are familiar with it. Please restudy what we took before because the dr. didn't explain some material. The slides are very important in this topic.

- Bioenergetics: capacity or ability to perform work
- Energy types:
  1-Kinetic energy: energy in the process
  Of doing work or energy of motion.
  2-Potential energy: energy stored in matter, and can be converted to a useful energy (Every material has potential energy).
- Why do reactions occur?
  - To achieve a situation of higher stability.
- Can a reaction go from a lower energy scale to a higher energy scale? Or -in other words- Can the energy of the reactants be higher than the energy of the products?
  -No, unless the reaction is provided with energy which is enough to exceed the energy of the products.
- Exergonic → reaction can proceed by itself
- Endergonic → reaction can't proceed by itself
- Exothermic → reaction results in heat
- Endothermic → in which the system absorbs energy from its surroundings, usually but not always, in the form of heat.



ΔG: free energy change (energy of products – energy of reactants), it tells you the bond energies within matter taking in consideration the disorder state of the matter.

ΔH: heat of reaction (heat of products – heat of reactants)
ΔS: entropy change.

T: temperature in Kelvin.

ΔG = the free energy difference (potential energy) of a system at any Condition.
ΔG^{o}=the free energy (potential energy) difference of a system at standard conditions (25Co, 1 atmospheric pressure, 1M Concentration of reactants & products, pH = 7).

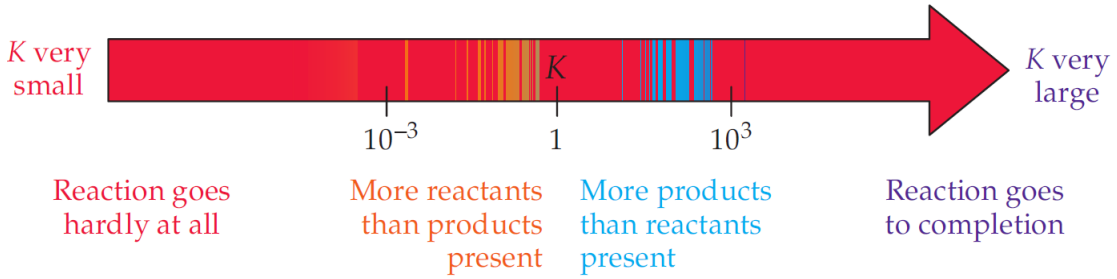
- ΔG doesn't give us information about what happens during the reaction, it is only concerned with the reactants and products.
- Do all favorable reactions happen at room temperature?
  -No, because of the energy barrier (activation energy).
- Why is the activation energy present in our lives?
  -So reactions will not occur all the time and life can exist.
- Enzymes lower the activation energy.
- Equilibrium= rate of forward reaction equals the rate of backward reaction.
- Rate does not mean concentration and will never be.
  Ex: If there is a big hall that fits 150 students and another smaller hall that fits 100 students, if 10 students exit from the big hall to the small hall per minute and at the same time 10 other students exit from the small hall to the big hall per minute, the rate of students exiting the room is what? The answer is 10 students per minute (same rate for both halls regardless of the concentration).

- Equilibrium constant (K) = Product conc. / Reactant conc.

<u>Important note</u>: at equilibrium, it is not important for the equilibrium constant to be equal to 1, because we are concerned about the rate not concentration, so the following situations can occur at *EQUILIBRIUM:*

- If the equilibrium constant is equal to 1, it means that concentration of the products equals the concentration of the reactants.
- If the equilibrium constant is greater than 1, it means that concentration of the products is greater than the concentration of the reactants.

- If the equilibrium constant is less than 1, it means that concentration of the products is less than the concentration of the reactants.
- If the equilibrium constant is equal or less than 10^{-3} it means that the reaction is hardly going. (conc. of reactants is 1000 and conc. of products is 1)
- If the equilibrium constant is equal or greater than 10^{3} it means that the reaction is almost completed. (conc. of reactants is 1 and conc. of products is 1000)



ΔG = ΔGº' + RT ln (conc. of products / conc. of reactants)

ΔG at equilibrium = 0

ΔGº'= -RT ln (K)

This formula connects ΔG with K equilibrium.

40:00

Sorry for any mistake

Good luck everyone: D