A study material for M.Sc. Biochemistry (Semester: III) Students
on the topic (CC-12; Unit II)

Antibody

Types and Functions I

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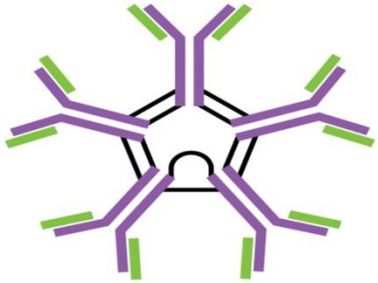
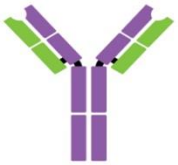
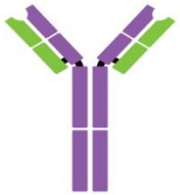
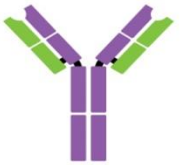
HUMAN IMMUNOGLOBULIN CLASSES, SUBCLASSES, TYPES AND SUBTYPES

- **Immunoglobulin classes**
  The immunoglobulins can be divided into five different classes, based on differences in the amino acid sequences in the constant region of the heavy chains.
- All immunoglobulins within a given class will have very similar heavy chain constant regions. These differences can be detected by sequence studies or more commonly by serological means (*i.e.* by the use of antibodies directed to these differences).

  - IgG - Gamma heavy chains
  - IgM - Mu heavy chains
  - IgA - Alpha heavy chains
  - IgD - Delta heavy chains
  - IgE - Epsilon heavy chains

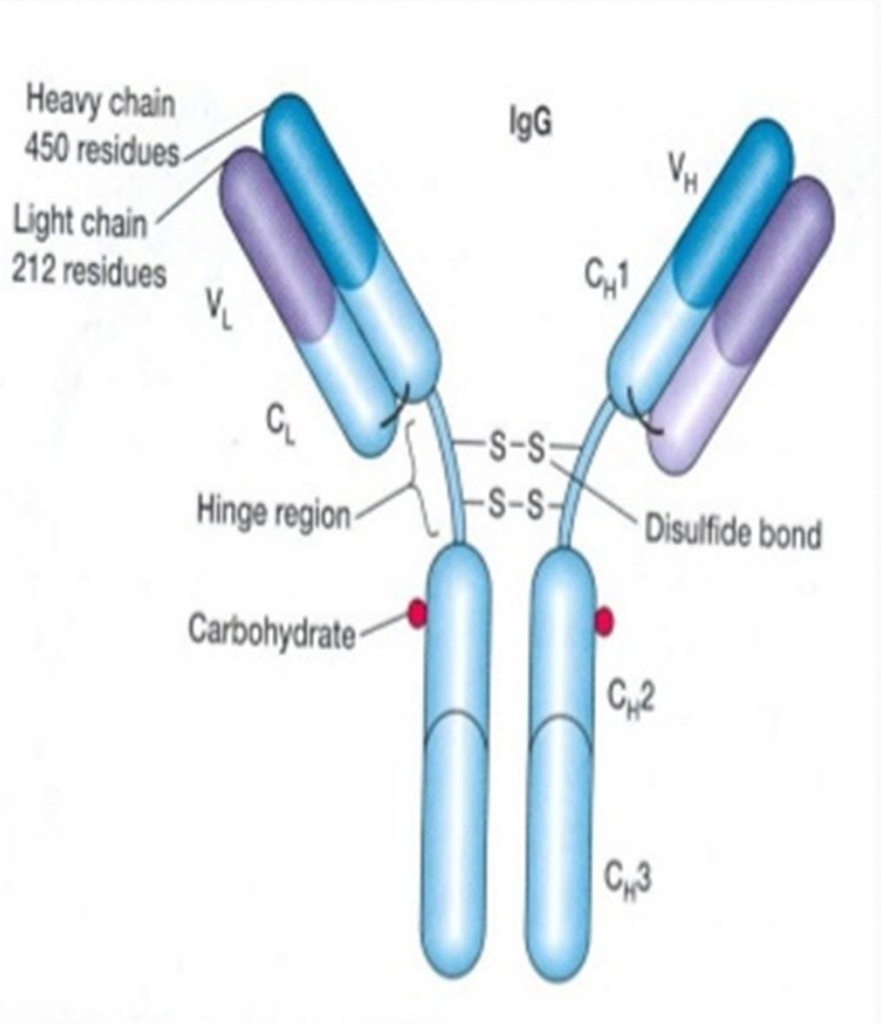
The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

Class of Antibody	Serum levels	Structure	Biological functions
IgM	5%	Monomer Pentamer	Membrane-bound immunoglobulin on the surface of immature and mature B cells First antibody produced in a primary response to an antigen First antibody produced by the fetus Efficient in binding antigens with many repeating epitopes, such as viruses Classical complement activation
IgD	0.3%	Monomer	Membrane-bound immunoglobulin on the surface of mature B cells No biological effector function known
IgA	7-15%	Monomer Dimer	Predominant antibody class in secretions (saliva, tears, breast milk) and mucosa First line of defence against infection by microorganisms
IgG	85%	Monomer	Most abundant class with four isotypes - IgG1, IgG2, IgG3, IgG4 Crosses the placenta Opsonization
IgE	0.02%	Monomer	Defence against parasite infections Associated with hypersensitivity reactions (allergies) Found mainly in tissues

The most abundant Immunoglobulin is Ig G > Ig A > Ig M > Ig D > Ig E

Immunoglobulin G (Ig G)

- Most abundant class of Ig in serum
- Constitutes 80% total immunoglobulin
- Present in blood, plasma and tissue fluids
- Contains less carbohydrate than other immunoglobulins
- It has a half life of 23 days: the longest of all of the immunoglobulin isotypes



IgG Subclasses

- *Functions of the IgG Subclasses*
  - IgG1 and IgG3
    - rich in antibodies against proteins
  - IgG2
    - predominantly antibodies against the polysaccharide (complex sugar/carbohydrate) coating or capsule of certain disease producing bacteria
  - IgG4
    - function is largely unknown possibly due to it's limited prevalence in the total IgG serum
    - generally accepted that IgG4 works with IgG2 to bind to carbohydrate antigens

Four IgG subclasses;
relative serum concentrations: IgG1 > IgG2 > IgG3 [a] IgG4

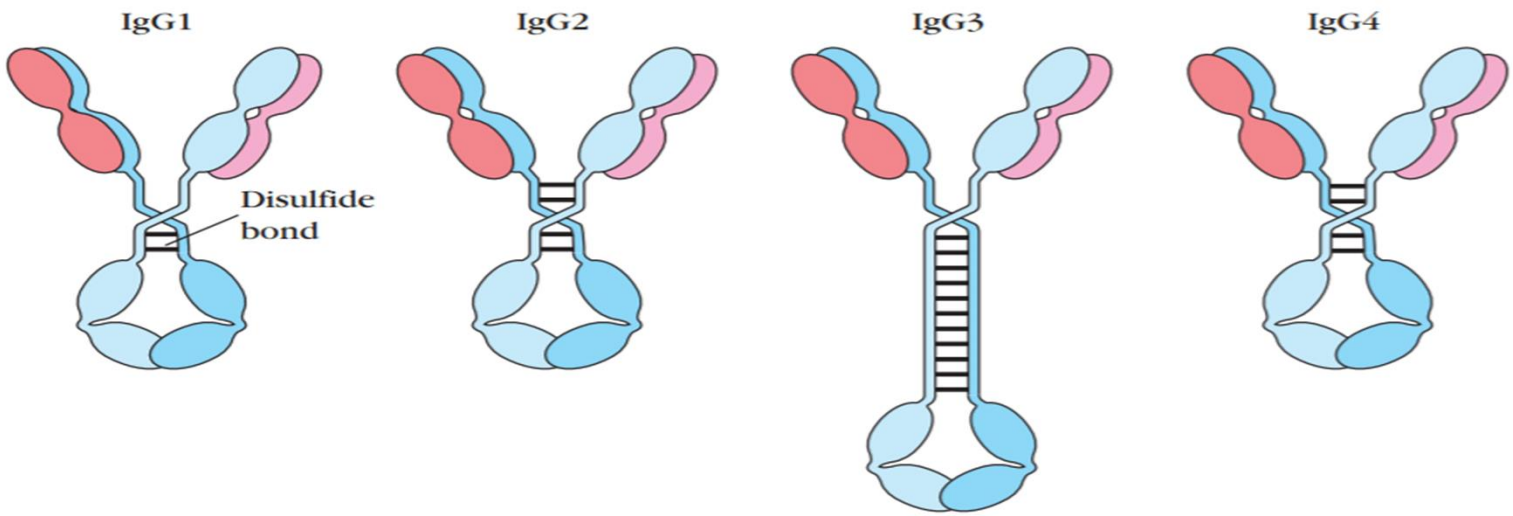
Differences in physicochemical properties
Differences in structure of the 'hinge region':
- length: number of amino acids
- number of inter-heavy chain disulfide bridges

Differences in the flexibility
of the IgG molecule: IgG3 > IgG1 > IgG4 > IgG2

Differences in biological properties
'Fab-part' of the IgG molecule + antigen R triggering effector functions mediated via the 'Fc-part' of the IgG molecule.
- Activation of complement: IgG3 > IgG1 > IgG2 > IgG4
- Induction of phagocytosis (opsonisation)
  Binding to Fcγ R of effector cells:
  Fcγ RI: IgG3 > IgG1 >> IgG4
  Fcγ RII: IgG3 > IgG1 > IgG2
  Fcγ RIII: IgG3 ≈ IgG1

IgG Antibody Isotype Comparison

Property	IgG1	IgG2	IgG3	IgG4
Molecular Weight (kDa)	150	150	170	150
Amino acids in hinge region	15	12	62	12
Inter-H chain disulfide bonds	2	4	11	2
Half life (days)	14-21	14-21	7	14-21
Mean adult serum level (g/l)	6.98	3.8	0.51	0.56
Relative abundance (%)	60	32	4	4



IgG3	IgG1	IgG2	IgG4
Ligation of all Fc receptors, including FcγRI in monomeric form (IgG3 > IgG1)		Restricted ligation of Fc receptors and only when complexed, particularly large complexes	Restricted ligation of Fc receptors and only when complexed, particularly large complexes
		Weak complement activation	No complement activation
		Most resistant of all IgG isotypes to proteolytic degradation	Produced after chronic immune stimulation, particularly parasite infections
Potent complement activation through the classical pathway (IgG3 > IgG1)		Predominant IgG subclass in plasma IgM-IgG complexes	Regulated similarly to IgE
		Only IgG subclass to undergo covalent dimerization	May form bispecific antibodies
		Predominant IgG subclass in phagocytic antibodies to polysaccharide antigens	

	IgG3	IgG1	IgG2	IgG4
Antigen binding	High flexibility of hinge region, which is about four times longer than the equivalent region in other subclasses (34)		Opsonization of antigens with a high epitope density (35) Conformational variation resulting from rearrangement of disulfide bonding of the hinge region with the light and heavy chains (37, 38)	Monovalent bispecific antibodies resulting from exchange of half molecules between IgG molecules (36)
Effector function	Potent complement activation and binding to all Fcγ receptors (FcγRs) as monomers or multimers (39) Lower affinity binding to tripartite motif containing-21 than other IgG subclasses (39)	Complement activation and binding to all FcγRs as multimers only (39)	Low complement activation, sufficient for opsonophagocytosis of bacteria (40) Binding only to "low affinity" FcγRs, particularly FcγRIIa (39)	Absent complement activation. Binding to all FcγRs but with lower affinity than for IgG3 or IgG1 (39)
Other	Substantial genetic variation (13 immunoglobulin Gm allotypes) Shorter half-life (7 days) than other IgG subclasses (21 days) Least resistant to human proteolytic enzymes (cathepsin G) (42)	Moderate genetic variation (4 immunoglobulin Gm allotypes)	Low genetic variation (1 immunoglobulin Gm allotype) Covalent dimerization (41) Most resistant to human proteolytic enzymes (cathepsin G) (42)	No genetic variation (no immunoglobulin Gm allotypes)

Acknowledgement and Suggested Readings:

1. Kuby Immunology; Sixth Edition; Kindt, Goldsby and Osborne; W. H. Freeman and Company
2. Fundamental Immunology; 5th edition; William E., Md. Paul (Editor) ; Lippincott Williams & Wilkins Publishers
3. Roitt's Essential Immunology; Tenth Edition; Roitt and Delves; Blackwell Science
4. Cellular and Molecular Immunology; 6th Edition; Abbas, Lichtman and Pillai; Saunders Elsevier

Thanks