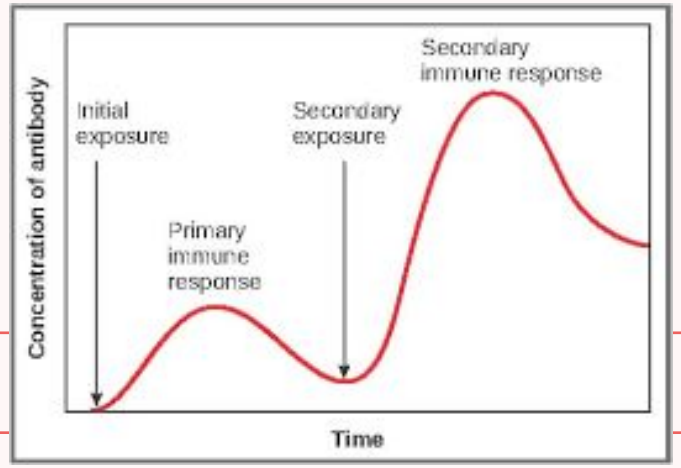
Immunology

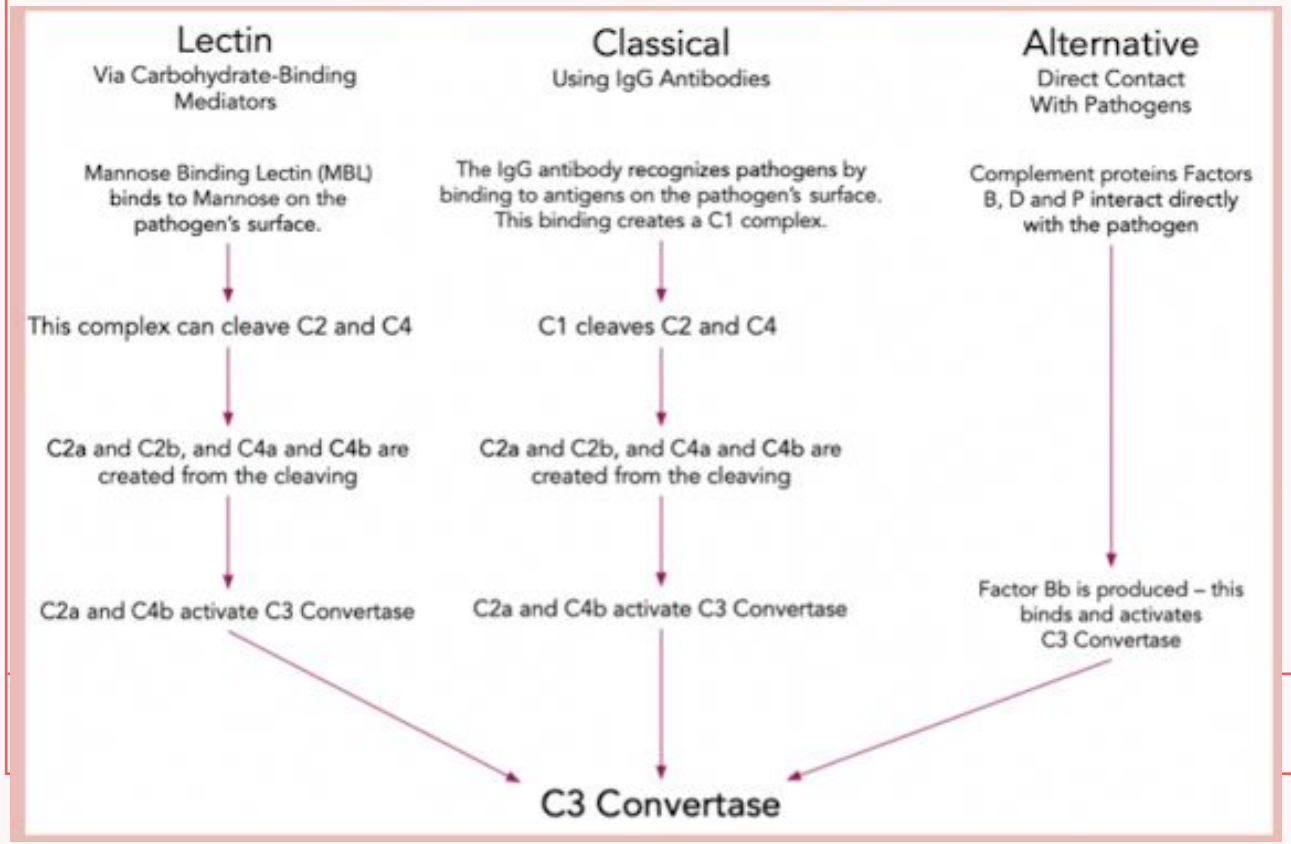
Types of Immunity

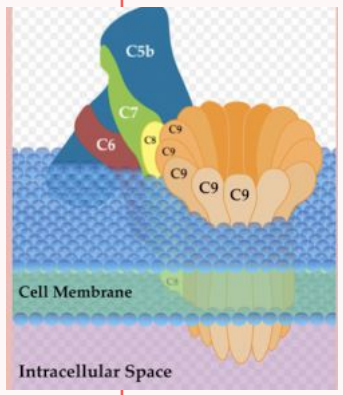
Innate Immunity	Adaptive Immunity
Non-specific	Specific
Rapid	Delayed but after repeated exposure is rapid
No memory	Memory response by B cells
Effectiveness doesn't increase with repeated exposure	Effectiveness increases with repeated exposure
Always on	Needs priming by a specific antigen



Complement Cascade

- MAC (membrane attack complex) -> punch holes in membrane by inserting itself allowing free diffusion of substances in and out of cells leading to cell death
- c5B, c6, c7, c8 & c9 form membrane attack complex





C3 convertase converts C3 into C3a and C3b.
C3b cleaves C5 into C5a and C5b

C3a and C5a are anaphylatoxins = bind to mast
Cells causing them to release histamine increases
vascular permeability and phagocytic recruitment

Innate Immunity

- **Granulocytes** (Neutrophils, Basophils, Eosinophils and Mast cells):
  - Kill pathogens via degranulation which releases cytotoxic compounds, pro-inflammatory molecules and cytokines from granules inside their cytoplasm
- **Sentinel/APCs** (Macrophages, Dendritic cells, Monocytes)
  - They detect, engulf and display remnants on surface for recognition by other immune cells
  - Monocytes can form either Dendritic cells or Macrophages
- **Lymphocytes** (e.g Natural Killer cells):
  - Kill infected cells by releasing perforin and granzymes
  - They produce cytokines too

	TYPE		
Macrophage*	Sentinel / Phagocyte / APC	Central round nucleus with a vacuole	**Phagocytoses pathogens** and may present the digested antibodies to stimulate the rest of the immune system
Dendritic Cells	Sentinel / Phagocyte / APC	Large with branch-like projections coming off the body	Phagocytoses pathogens and presents the digested antibodies to **trigger the adaptive immune response**
Natural Killer Cell	Lymphocyte	Single-lobed nucleus; very little cytoplasm	**Kills tumor** and **virus infected cells** by releasing perforin
Mast Cells	Granulocyte (APC)	'Fried-egg' appearance of nucleus and cytoplasm; granules	Causes **vasodilation** and **inflammation** degranulation to release **heparin** and **histamines.** (Can phagocytose and present antigens too.)
Neutrophils	Granulocyte	Multi-lobed nucleus; granules	The most abundant (70%) granulocyte. First responder at the site of infection □ **degranulates**, **releasing toxins** which kill pathogens. Can also phagocytose
Basophil	Granulocyte	Two-lobed nucleus; purple-staining granules	Defends against **parasites** □ causes allergic **inflammation** by degranulation to

Extracellular mediators of innate immunity

Cytokines - substances such as interferon, interleukin and growth factors which are secreted by immune cells and have an effect on other cells

Acute phase proteins - proteins released by the liver in response to inflammation, these may be involved with clotting cascade complement cascade or inflammation

Complement proteins - proteins which are released at the end of complement cascades to cause cell death

Soluble innate mediators which can activate the complement system includes:
- acute phase proteins
- complement proteins
- collecting 's new line
- C-reactive proteins

Mechanism

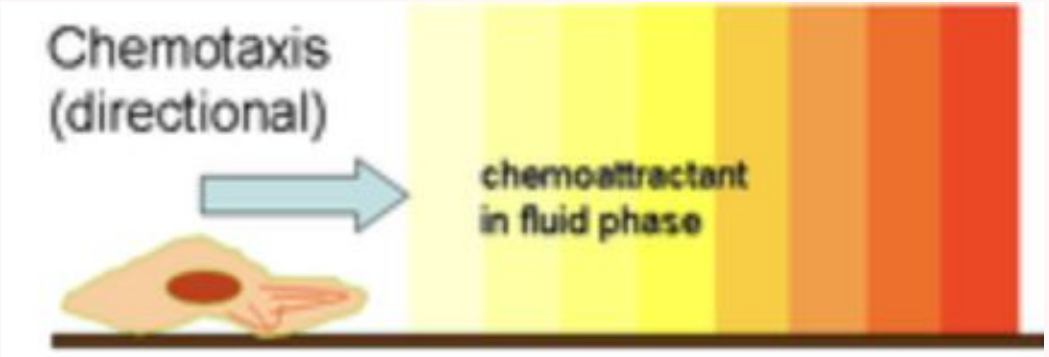
Detection:

- Macrophage and dendritic cells will use PRRs to bind to DAMPs to recognize host is getting damaged

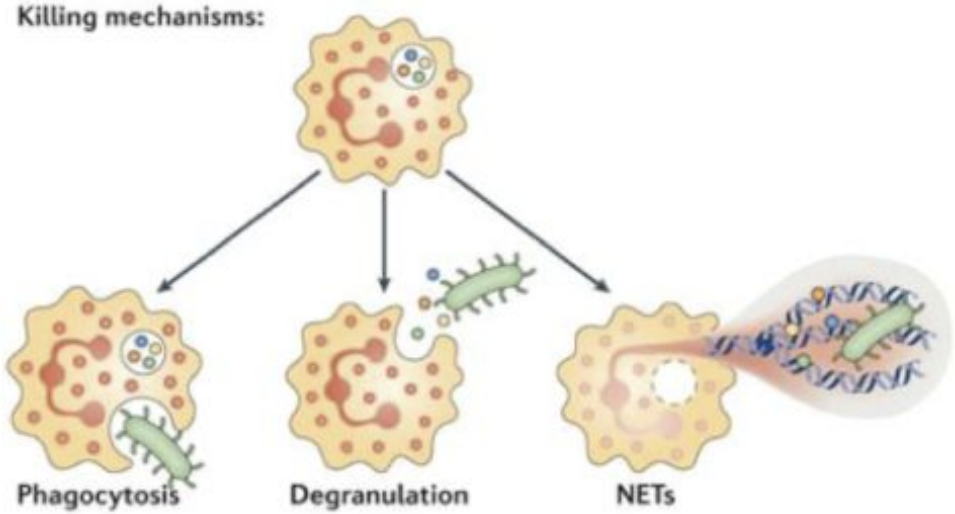
- PAMPs → Proteins on surface of pathogens which are not commonly found on host cells
- DAMPs → Molecules released by damaged tissue
- PRR → Pattern Recognition Receptors, these are receptors on dendritic cells and macrophages that will detect PAMPs and DAMPs
  - Examples of PRR →
    - TL-2 = Gram-positive bacteria
    - TL-4 = Gram-negative bacteria
    - TL-3,7,9 = Viral Nucleic Acids

Chemotaxis

- Sentinel Cells release chemokines (type of cytokine) when encountering infection
- Immune cells have chemokine receptors which chemokines will bind to causing immune cells to move up a concentration gradient to site of infection
- Anaphylatoxins like c5a and c3a increase chemotaxis



Killing Mechanisms

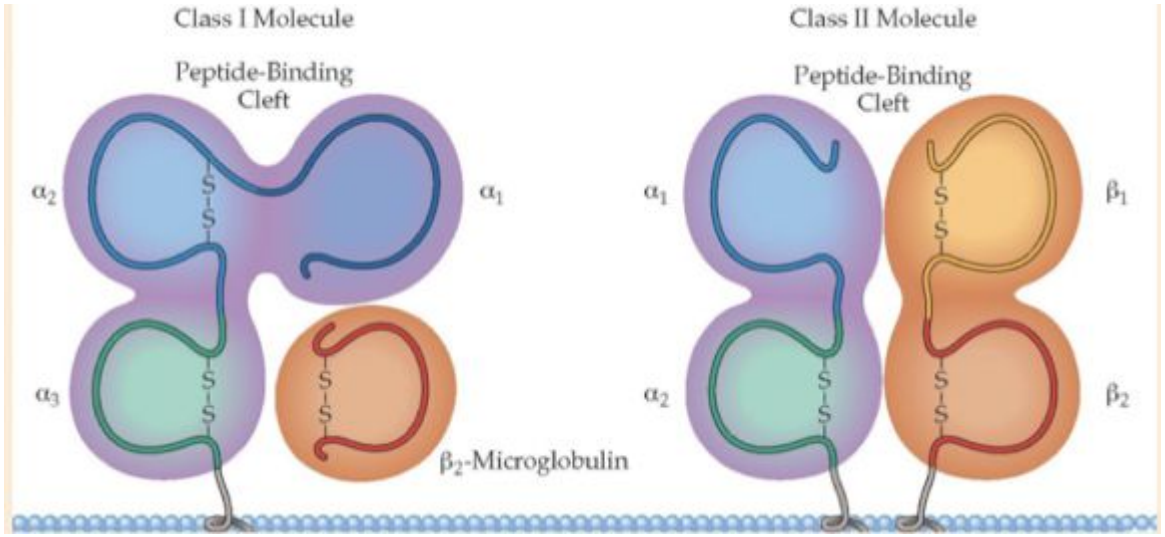


Phagocytosis ? Ingestion of pathogens followed by presenting the antigens on their cell surface. This is the link to the adaptive immune response.

NETosis ? Neutrophil Extracellular Traps.
Neutrophils can release their chromatin in a web of fibers to trap the pathogen and kill it

Degranulation ? Release granules which will kill the pathogen (usually by creating holes in their cell membrane so they leak out)

MHC



Structure of MHC-I one alpha chain with 3 domains and a b2 macroglobulin
MHC-2 one alpha and one beta chain with 2 domains each

Genes for MHC are on **Chromosome 6**
MHC is polygenetic and polymorphic
Polygenetic made up of multiple genes
Polymorphic presence of different alleles of a gene
- This makes it so within a population there is resistance against rapidly mutating pathogens

- Major Histocompatability Complex
- These are proteins on cell surface which present antigens to T cells
- MHC Class I found on all **nucleated** cells (so excludes erythrocytes) and it presents endogenous antigens to CD8+ T (cytotoxic) cells
- MHC Class II found on APCs only (so macrophages and dendritic cells and B cells)
- MHC Class II presents exogenous antigens to CD4+ T (helper) cells

Weird way to remember which MHC goes to which T cell: 1 x 8 = 8, 2 x 4 = 8

Adaptive Immunity

T cells

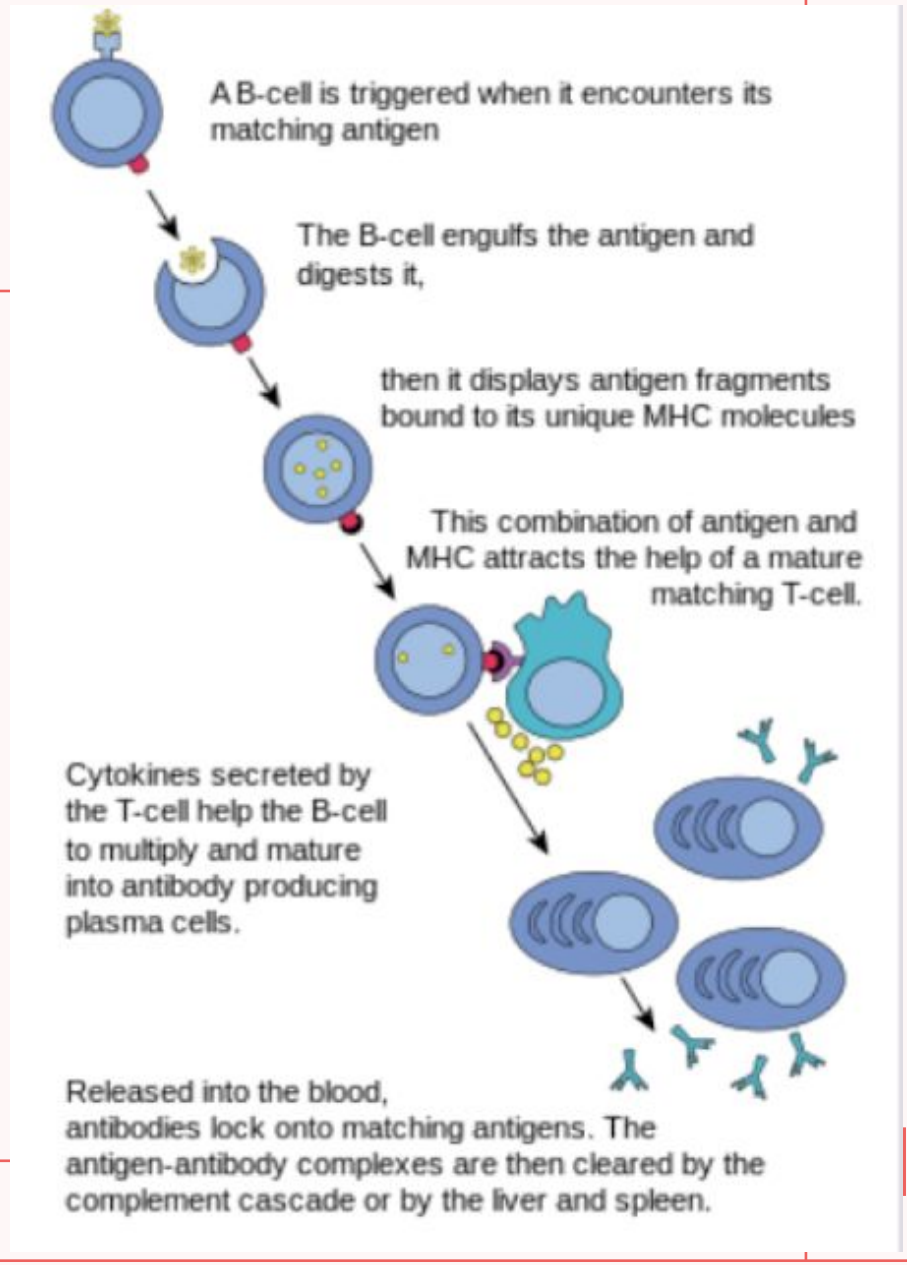
- +selection of immature T cells that bind firmly with MHC-I and these will become CD8+ T cells and same goes for MHC-II and CD4+ T cells
- -selection of self peptides and receptors means that they will undergo apoptosis preventing attack on self-cells
- T cells made in bone marrow but mature in Thymus

Subset	Function	Cytokines
T_H1	Cell-mediated immunity	Interferon-γ Interleukin (IL)-2 IL-12
T_H2	Help for antibody production; eosinophil activation	IL-4 IL-5 IL-10
T_H17	Neutrophil activation	IL-17
Treg	Immune regulation	IL-10 TGFβ

Humoral Immunity

- Mature B cells circulates in the blood and lymph. When they encounter an antigen, they bind to it using B cell receptor on their surface.

  B cells then digest antigens into smaller fragments and with MHC-II displays this complex on its surface and now B cell acting as APC
- CD4+ T cells will bind to and recognize MHC-II complexes on APCs
- CD4+ cell releases **IL** causing B cells to proliferate into plasma cells
- **Plasma cells** can secrete antibodies which can bind to the antigen and **memory B** cells also produced by this activation



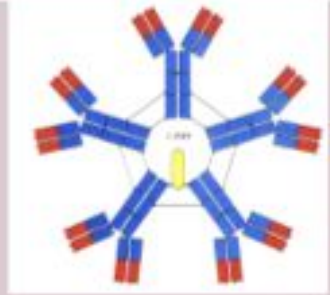
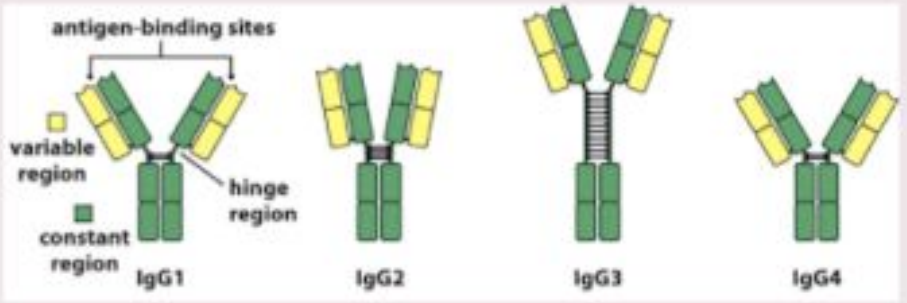
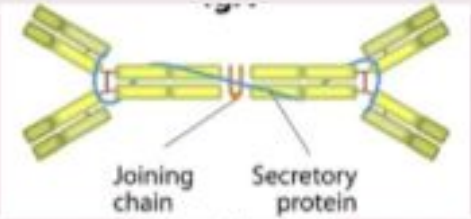
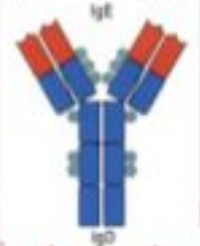
Antigen Processing

ENDOGENOUS □ MHC-I

- Pathogen inside cell (e.g viruses)
- Proteases break down endogenous pathogens down into antigen fragments □ transported to ER where fuses with MHC-I
- Presented on surface where it will bind to CD8+
- Kills pathogens directly as CD8+ will release perforin and granzymes which perforate and kill cell

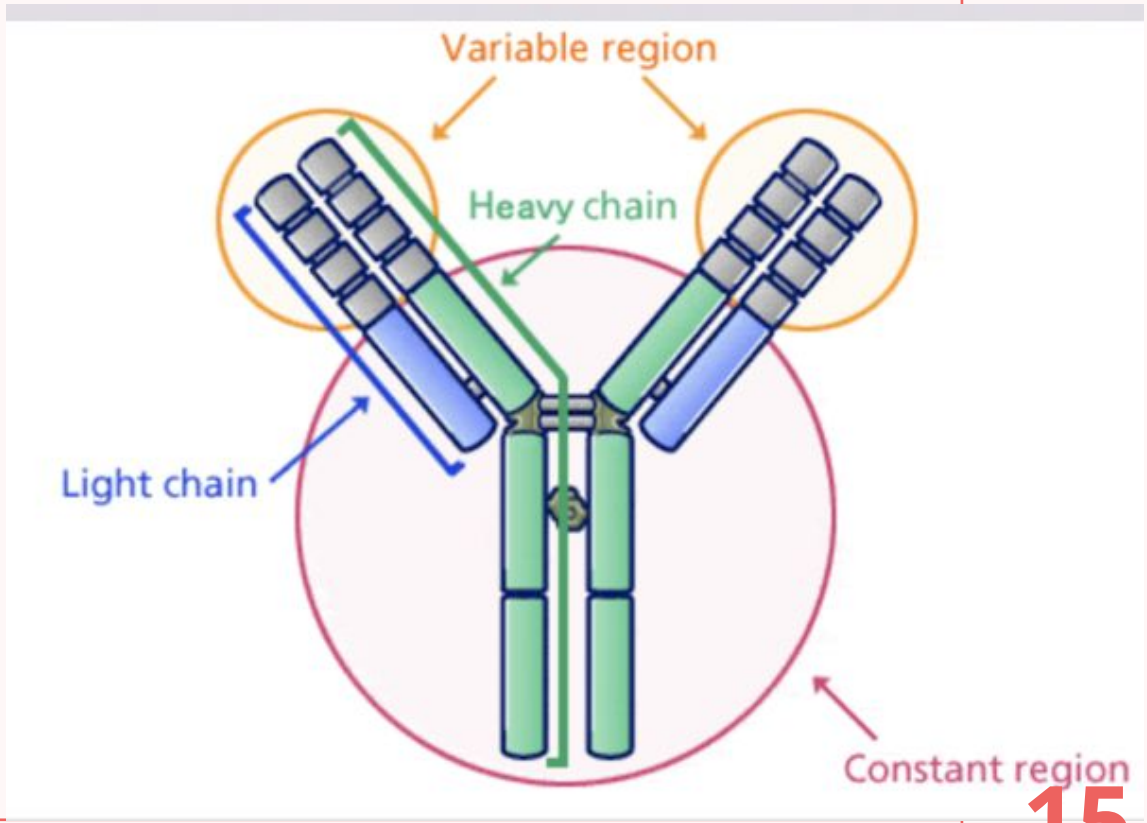
EXOGENOUS □ MHC-II

- Pathogens from OUTSIDE APCs are internalised by phagocytosis □ broken down by proteases resulting in antigen fragments
- Combined with MHC-II which is presented on surface
- CD4+ cells bind to and recognize MHC-II complex
- CD4+ (helper) cells then activate other immune cells such as B cells and others

Class	Description	Function	Image
IgM	Largest in *size* – pentameric structure. Predominant antibody in the **primary antibody response.** First antibody detected in the blood after infection. Pentameric structure allows it to bunch lots of pathogens together for phagocytosis – this is **agglutination**	**Agglutination** Neutralization Opsonization	
IgG	Largest in *number* (75%) – 4 varieties. Predominant antibody in the **secondary antibody response.** *Only* antibody which can pass through **placenta**. Same basic structure → a **variable F_{ab} region** which will bind onto the pathogen, and a **constant F_c** region which will bind to WBCs, to carry out **opsonization** (optimizing phagocytosis)	**Opsonization** Neutralization Agglutination	
IgA	Predominant antibody found in mucous / secretion → **breast milk, mucous** (respiratory and GI tract). Produced by epithelial cells.	Neutralization / **Blocking**	
IgE	Low in quantity, but important for defense against **parasites.** Also important for **allergic reactions**, by binding to and activating mast cells.	**Parasite** defense **Allergic** response	
IgD	Is found on the **surface of B-Cells** as the receptor for antigens. Antigens bind to the IgD antibody, activating the B-Cell	**B-Cell Receptor**; allows the adaptive immune response to progress	

Antibody Structure

Antibodies:
- Can activate the complement system (Classical pathway via IgG)
- **Agglutination** □ clumping lots of pathogens together
to make it easier for WBC
- **Opsonisation** □ process of which pathogen is marked for phagocytosis
- **Neutralisation** □ neutralize pathogenic toxins



Extra

- Tapasin, Calreticulin and ERP57 □ makes sure MHC-I folds correctly
- TAP transporter □ they pump the digested antigen from cytoplasm into ER so it can be loaded on MHC-I

•IFN-gamma (interferon-gamma)
- **induces class switch to IgG**
- **promoter of CD8+ development**

•IL-2
- **stimulates immune response (T cells)**

•IL-4 and IL-21
- **B cell maturation and T cell response**
- **IgG class switch**

•IL-5
- **Eosinophil activation**

•IL-6
- **Acute phase protein release**

•IL-7
- **mucosal immunity**

•IL-10
- **anti-inflammatory and immune inhibition**

•IL-12
- **T cell and NK cell activation**

•IL-17
- **Neutrophil activation**

•IL-21
- **B cell activation and antibody class switch**

•TGF-beta
- **tumour suppressor**

Part of the immune system	Cellular Mediators	Extracellular mediators	Mechanism of immune response?	How do they kill pathogens?
PHYSICAL	epithelial cells- eg, respiratory epithelium, GI epithelium, skin	Mucous + antimicrobial factors	N/A	N/A
INNATE	Granulocytes- neutrophils, eosinophils, basophils Sentinel cells- dendritic cells and macrophages Lymphocytes- NK cells	cytokines, acute phase proteins, collectins, defensives, acute phase proteins	Detection -PAMP's and DAMPs are detected by PRRs on sentinel cells -Release of vasoactive molecules (increased inflammation)... increased vascular permeability, activates the complement cascade, immune cell recruitment	Complement Cascade- Membrane Attack Complex
ADAPTIVE	Lymphocytes- B-cells, T-cells (CD4+ CD8+)	antibodies IgM,IgG, IgA, IgE, IgD	cell-mediated response (T-cells) humoral response(MHC, T cell selection, plasma cells produce antibodies, memory cells etc)	antibody action -opsonisation, agglutination etc T-cell and MHC processing (exogenous or endogenous processing)

Questions

- Which cell of innate immunity kills by releasing perforin and granzymes?
  - A) Natural Killer cells
  - B) Mast cells
  - C) Basophils
  - D) Neutrophils
  - E) Cytotoxic T cells

- Answer:
  - A □ Natural Killer Cells

Note: T cells also kill via perforin and granzymes but T cells are part of adaptive immunity

Question

- Which pathway works by binding to Mannose receptors on pathogens:
  - A) Classical
  - B) Alternative
  - C) Lectin
  - D) Common
  - E) None of the above

- Answer: C) Lectin
- MBL binds to Mannose receptors

- What cells can differentiate into Dendritic cells?
  - A) Macrophages
  - B) Phagocytes
  - C) Reticulocytes
  - D) Monocytes
  - E) Granulocytes

- Answer D) Monocytes
- Note: Monocytes can differentiate into both Dendritic cells and macrophages

- Which Toll-like receptor is for gram-negative bacteria?
  - A) TL-2
  - B) TL-3
  - C) TL-4
  - D) TL-7
  - E) TL-9

- Answer □ C) TL-4

- What is NETosis and which cell does this?
  - A) Granules released which kill pathogen and done by neutrophil
  - B) Web of chromatin released to trap and kill and done by neutrophil
  - C) Engulfing pathogens and done by neutrophil
  - D) Granules released which kill pathogen and done by macrophage
  - E) Perforin and granzymes released and done by NK cells

- Answer: B) Web of chromatin released to trap and kill and done by neutrophil

- Which antibody is a pentamer?
  - A) IgA
  - B) IgG
  - C) IgM
  - D) IgD
  - E) IgE

- Answer □ IgM