Disease module 1: B Cells and Disease

1: Major steps in B-cell development & Ig gene rearrangement

Primary immunodeficiencies (PIDs)

- >350 rare disorders characterised by impaired ability to produce normal immune response that typically result in recurrent or severe infections
- are not caused by other diseases, treatments, or environmental exposure to toxins (i.e. not secondary or acquired immunodeficiencies)
- Mostly genetic disorders and most are diagnosed in children under 1 year
- Variable disease onset, severity, etc.
- There are 10 warning signs of primary immunodeficiency, e.g. two or more pneumonia within 1 year
- ~400 genes found as monogenic causes of PID

Most PIDs are antibody disorders.

Antibody deficiencies

- Refers to loss of some or all humoral (i.e. antibody) immunity with cellular immunity intact
- Absent B cells (or reduced, or normal but dysfunctional)
- X-Linked agammaglobulinaemia (XLA) – due to developmental defects in B cells
- Common variable immunodeficiency (CVID) – differentiation defects
- Hyper IgM syndromes (HIGM) – differentiation defects

Combined immunodeficiencies (CID)

- Includes Severe Combined Immunodeficiency (SCID)
- Refers to combined loss of humoral (ie. B-cell) AND cellular (i.e. T-cell) immunity

Since CD4+ T cells regulate B cells (T cell help), intrinsic T cell defects can also lead to antibody deficiency (no help, no antibody)

How to treat PIDs?

Curative treatment: Replace the whole immune system if completely missing in most severe forms (e.g. SCID, XLA)

- Haematopoietic stem cell transplantation (HSCT)
- Gene therapy

Can be a risky procedure for many antibody deficient patients (old people, who often have multiple infections) with *some antibody* (so we must increase conditioning to prepare them for a transplant). But, increasingly considered.

- e.g. Hyper IgM Syndrome (HIGM), X-linked lymphoproliferative Disease (XLP), Common Variable Immunodeficiency (CVID); Immunosuppression, Graft vs Host Disease

Lifelong treatment: Replace antibodies Intravenous Ig (IVIG) Sub-cutaneous Ig (SCIg)

B Cells: precursors to plasma cells/antibody secreting cells

To make antibody, a B cell must:

1. Recognise antigen via immunoglobulin on the surface
   Surface membrane Immunoglobulin (SmIg) = B-cell receptor (BCR)
2. Break down Ag and re-present to T-cells as peptides on surface MHC class II
3. T cells then provide activation signals or 'help' (CD40L, ICOS, cytokines)
4. Allow B-cell to differentiate to antibody secreting cells (ASCs) and memory B cells

Role of B cells:

- main role is to differentiate into plasma cells
- Help direct other B cells by releasing cytokines

B Cell development, activation, differentiation

All lymphocytes descend from a common lymphoid progenitor (CLP)

- NK cells develop in fetal liver
- T cells develop in thymus
- B cells develop in bone marrow throughout life.

B cells exit bone marrow as immature B cells and circulate in periphery as naïve/mature b cells that have not yet been exposed to antigen. When they interact with a specific antigen, the naïve b cell becomes a memory b cell or plasma cell.
Genetic defects in development, activation or differentiation can cause complete or partial block in process → unable to produce sufficient antibody.

Antibodies ≡ immunoglobulin ≡ Ig ≡ gamma globulin

- Globular proteins produced by differentiated B cells (plasma cells) found in serum, interstitial fluids, mucosal secretions
- Identify and neutralize foreign pathogens e.g. bacteria and viruses
- Each antibody binds a specific antigen

Has 4 chains: 2 identical Heavy and 2 identical light chains

- L chains (variable + constant) = 25 kDa
- H chains (variable + constant) = 55 kDa (but can be variable)

- L + H chains paired by disulfide bond in each dimer
- H + H paired by disulfide bond(s) in each tetramer
- Heavy chains give 'Y' structure of Ab molecule

2 regions:

Variable: 'antigen binding site' that grabs hold

- Small region at the tip of the protein
- Extremely variable, allows millions of antibodies with different antigen binding sites to exist (hypervariable region at the very tip)

Constant: class/isotype of antibody that does stuff

- Each class of constant region differs in sequence and number of domains, hinge region & valency
- Each class has distinct distribution & effector functions

Both heavy and light chains contain constant and variable regions.

Ig isotypes

IgG:

- most abundant in plasma (70-85% Ig pool)
- major antibody of secondary immune response, has 4 subtypes

IgM:

- major antibody of primary immune response, has an extra constant region and?
- usually a pentamer (5-10% circulating Ig)

IgA:

- major antibody of mucosal surfaces, has two subtypes
- usually a tetramer dimer (5-15% Ig pool)

IgD:

- Function is unknown: absence of IgD has no phenotype
- <1% total Ig.

IgE:

- major antibody for infections, innoculous environmental triggers (e.g. pollen)
- has 2 additional C regions instead of hinge region

For IgG, in the average adult human (5L fluid), contains at least 10^{20} circulating IgG molecules at any time.
Not all IgG circulating in the body are the same though – differences between IgG subtypes are variable regions.

Immunoglobulin variability

If variable region of every IgM, IgG, IgA and IgE is unique, Ig variability achieved by:

1. A separate gene for every different Ig (remember 10^{20} just for IgG)
2. Clonal Selection Theory = A special mechanism that generates huge protein diversity from limited genetic diversity; a single cell and its progeny are called a clone

Clonal Selection: theory by Burnet

- Rare B lymphocytes (B cells) are 'selected' by the antigen
- Recognition is by surface bound antibodies/B-cell antigen receptor
- Huge diversity of antigen receptors amongst otherwise identical B-cells (you have B cells able to recognise very possible antigen in the universe)