B cell Generation, Activation & Differentiation

Overview:
- An immature B cell possesses IgM in its membrane.
- Leave the bone marrow & matures to express both membrane bound IgM & IgD, with single antigenic specificity.
- These naive B cells that have not encountered Ag, circulate in blood & lymph & carried to secondary lymphoid organs (spleen & lymph nodes).
- If B cell is activated by interaction with an Ag by its membrane bound Ab, cell proliferates (clonal expansion) & differentiates to generate a population of Ab-secreting plasma cells & memory cells.
- B cell undergoes affinity maturation, as a result of activation, which is nothing but "The progressive increase in the average Ab-pro affinity of the Abs produced as the response to activation proceeds."
- They also show "Class Switching" - that is, the change in the isotype of the antibody produced by the B cell from μ to k, α or ε (IgM → IgG/IgA/IgE).
B cell Activation & Proliferation:

After export of B cells from bone marrow, activation, proliferation & differentiation occur in the periphery in response to Ag. Ag-driven activation & clonal selection of naive B cells leads to generation of plasma & memory B cells. In the absence of Ag-induced activation, naive B cells in the periphery have short life span & may die in few weeks by apoptosis.

Thymus Dependent (TD) & Thymus Independently

B cell response to TD Ag requires direct contact with Th cells & not merely cytokines. Some Ags that can activate B cells in the absence of such direct participation by Th are called as TI Ags.
**Contrast**

**TD**

1. Chemically TD Ags are generally soluble Prtn.
2. Response to TD Ag is Stronger
3. Memory cells are produced.
4. Isotype switching is observed to occur.
5. Affinity maturation occurs.
6. TD Ag provides signal 1 by cross linking of mIg but a separate interaction between CD40 on B cell and CD40L on an activated Tp cell is required.

**TI**

1. TI 1 Ag - Bacterial cell wall components (LPS)
2. TI 2 Ag - highly repetitive prtn. (flagellin), bacterial cell wall polysaccharides
3. Response to TI Ag is generally weaker
4. No memory cells formed.
5. No isotype switching happens.
6. No affinity maturation observed.
B cell receptor

BCR is composed of a membrane Ig molecule associated with a disulfide linked heterodimer of Ig-α & Ig-β.

Antigen is recognized by extracellular portion of the complex & signal transduction is initiated by cytoplasmic tails of Ig-α & Ig-β.

Phosphorylation of tyrosines in the ITAM motif in Ig-α & Ig-β form docking sites for the assembly of multimolecular signal transduction complexes. (Same as TCR).

BCR is a transmembrane protein complex composed of mIg & disulfide-linked heterodimer Ig-α/Ig-β.

The Ig-α chain has a long cytoplasmic tail composed of 61 amino acids, the tail of Ig-β has 48 amino acids. Both these tails are long enough to interact with intracellular signaling molecules.

Membrane Ig mol. (mIgM/mIgD), however has very short cytoplasmic tails containing only 3 aa's. mIgA tail has 14 aa.

mIgG & mIgE has 28 aa's. All these are
short to be able to associate with intracellular signaling molecules. (Fig. 11.8).

B cell signaling is initiated by Ag binding & similar to TCR-signaling pathways using Src kinases, PLCγ.

B cell co-receptor
Stimulation through Ag receptors can be modified significantly by signals through co-receptors.
B cell co-receptor provides stimulatory modifying signals & another membrane protein CD22 provides inhibitory signals. The B cell co-receptor is a complex of 3 proteins: CD19, CR2 (CD21) & TAPA-1 (CD81). CD19: Long cytoplasmic tail that has docking sites which provide additional signal delivered by BCR complex for Adv. (Fig. 11.11).

CR2: Component is receptor for C3d (complement product) & transmembrane protein TAPA-1.
Role of Th cells in B cell response.

Th cells play essential role in most B cell responses. (Fig 11.12).

After binding of Ag with mIg on B cells result in internalization by receptor-mediated endocytosis to process it to form peptides. It also initiates signaling through BCR that induces B cell to upregulate the expression of MHC-III costimulatory ligand B7. (Processing & expression of processed peptides req. 30-60 min).

As BCR-Ag interaction is specific, the processed peptides req. are 100-10000 times lower than req. for mϕ/DC.

Once Th recognizes processed peptide-MHCII on mem. of B cells. The two cells interact to form T-B conjugate with which Golgi apparatus, cytoskeleton, organizing junction migrate towards the junctions. This facilitates release of cytokines toward the Ag-spec. B cells.
It also upregulates CD40L that interacts with CD40 on B cells to provide essential signals for T-cell dependent B cell activation, after which protein kinases get activated to activate finally signal transduction cascade.

It also results in immunological synapse & result in polarized release of cytokines towards the interacting B cell.

Activated B cell then start expressing membrane receptors for IL2, IL4 & IL5 the interact with these receptors with cytokines support B cell proliferation & differentiation into plasma & memory B cells, class switching & affinity maturation.