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B-CELL GENERATION, ACTIVATION & DIFFERENTIATION

Overview:-

B-cell activation → Antigen-independent Phase
- → occurs in Bone marrow
- → before antigen encounter
- → matured B-cells formed are naive B-cells
- → V(D)J recombination takes place
- → First, μ chain gets attached to V(D)J sequence.
  ∴ In the bone marrow, only IgM will get expressed. [IgM^+ B-cells]
- → Travels to lymphoid organs.
- → Another maturation step, where δ chain gets attached to some of the V(D)J chain (Class-switching) [IgD^+ B-cells]

→ Antigen-dependent Phase
- → Upon Antigen encounter, they undergo activation.
- → Signal 1, 2, 3 are initiated
  - Signal 1: Activation by Antigens
  - Signal 2: Provided by T_H cells
  - Signal 3: Cytokines release
- → Affinity Maturation (Somatic Hypermutation)- Random mutation in B-cell receptor.
  There are B-cells that have low affinity against the antigens which undergoes Apoptosis.
- → Class switching – Affinity for the B-cells to the antigens will remain the same, but the effector function will vary.
  IgM, IgD → IgG, IgA, IgE

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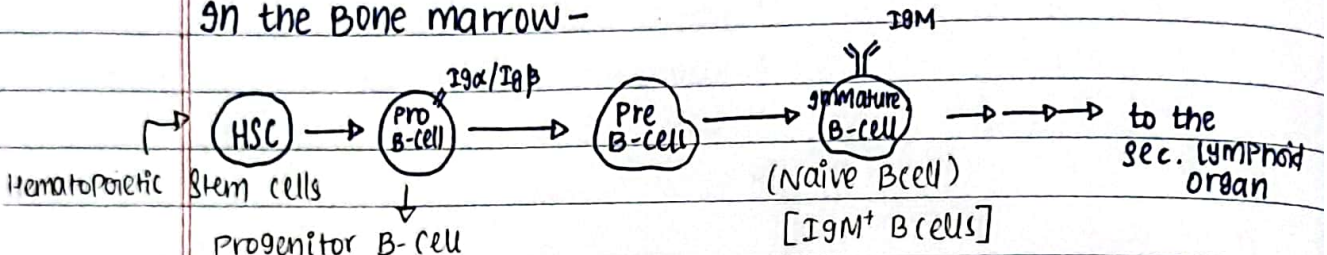
→ B cells (Effector cells) mature into: Plasma cells & Memory cells

Plasma cells → Release Antibodies

→ Memory cells have surface receptors that are often IgG (max. affinity)

In the Bone marrow –

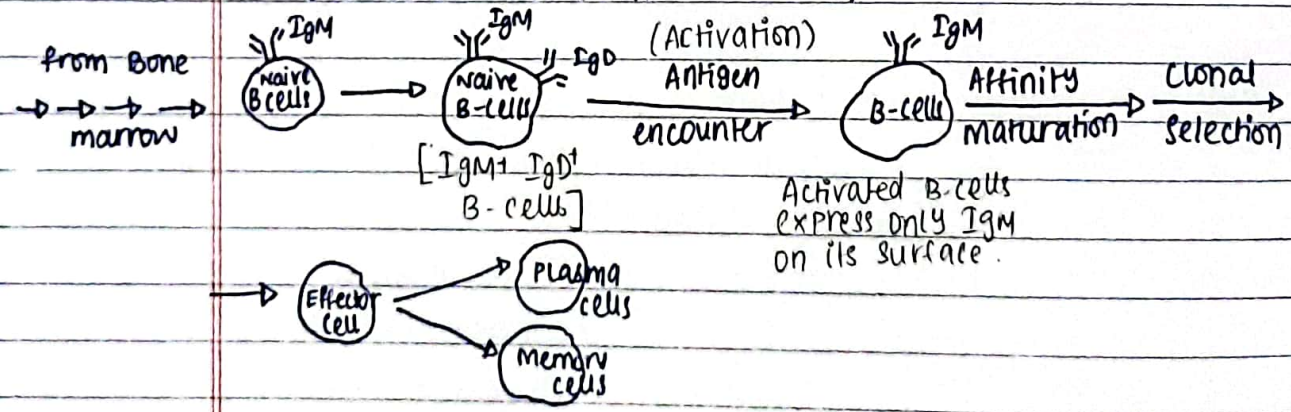


Recombination events:

$DJ_\mu \rightarrow VDJ_\mu$

$VDJ_\mu \xrightarrow{\lambda/K \quad VJ} IgM$

In the secondary lymphoid organ



NOTE:

- ~~cKit~~ cKIT [surface receptor] – helps the progenitor B-cells to bind to the stromal cells of the bone marrow.
  Lymphoid stem cells → Pro-B cells
- In addn. to Igα / Igβ, we have other receptors such as CD45R, CD19, CD24. These receptors are present throughout the B-cells (naive, mature, activated, differentiated).

Pro-B cells → End of B-cell maturation

Pro-B cells → Start of B-cell maturation

- Some markers like IL-7R (IL-7 cytokine receptor, IL-7 Provides signal for maturation of B-cells from HSC) are expressed only at the early stage of the B-cell maturation

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Development of immature B-cells from Pro-genitor B-cells:

- For B-cell maturation, it is imp. for ~~immature~~ Pro-genitor B-cells to come in contact with stromal cells.
- ↓ This initial contact results in IL-7 receptor expression on B-cell surface.
- IL-7 binds to the receptors on B-cells which provides signal for further B-cell maturation.
- Pro-genitor B-cells will mature to Pre-genitor B-cells and finally the immature B-cells (Naive B-cells).

There are 2 types of antigens based on how they active B-cells:

(i) Thymus-Dependent Antigen (TD): • requires a direct contact b/w B-cells and T_H cells.
- Signal (i): Antigen with B-cell receptor.
- Signal (ii): CD40 receptor on B-cells interacts with CD40L on T_H cell (Accessory receptor of B-cell with complimentary ligand of T_H cell)
- Signal (iii): Cytokines.

(ii) Thymus-Independent Antigen (TI): • no direct contact b/w B-cells & T_H cells required.
- Have conserved patterns on Pathogen
  - → eg: LPS ↳ TYPE 1
  - ~~Hint~~ Have highly repetitions molecules
  - → eg: Bacterial flagella ↳ TYPE 2
- Signal (i) & (ii): Antigen with BCR
  Signal (iii): cytokines

* TD ⇒ usually soluble proteins.
TI ⇒ present on cell surface

* TD ⇒ Humoral response: Isotype switching, Affinity maturation, immunologic memory are observed
TI ⇒ Humoral response: No ~~&~~ such observation.

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* TD ⇒ Mono clonal activation
TI ⇒ Poly clonal activation

B-cell Activation - Signal Transduction :

→ Antigen binds to ~~Ig~~ Ig receptor that leads to clustering of several B-cell receptors, Ig α/β units ~~the~~ to the lipid raft.
→ ITAM residues gets Phosphorylated. Phosphorylated ITAM creates docking sites for Adaptor molecules.
→ Finally, several transcription factors are activated.

~~Formation of TCR conjugate~~

B-cell Activation of TD antigen :-
[in sec. Lymphoid organs]

Signal 1 : Antigen ~~enters~~ interacts with BCR.
→ Once antigen is internalized (through Endocytosis), it will be Processed.
→ Antigenic Peptide - MHC complex will be expressed on the surface.
→ CD4 co-receptor recognised MHC-II.

Signal 2 : ~~CD40 co-receptor recognises MHC-II~~ Other Adhesion molecules interacts.
→ Once initial interaction becomes strong enough, B-cell will express CD40 receptor.
→ CD40 receptor interacts with CD40L on the T_H cell.
→ ~~This interaction will help B-~~

Signal 3 : Cytokine release upon signal (i) & (ii).
→ Activated B-cell will Proliferate into Effector cells.

NOTE : Interaction b/w CD40 & CD40L initiates class-switching.

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HUMORAL RESPONSE:

* Blood-borne antigens are filtered by spleen.
* Antigens from tissue spaces are filtered by lymph nodes.

Secondary lymphoid organs – Site of B-cell Activation, Proliferation & Differentiation.

matures into
Primary follicle : Site of Immature (naive) B-cells.
Germinal center : Site for B-cell activities such as class switching, Affinity maturation etc.

Differentiation :-

→ Takes place in Germinal center.
→ Germinal centers arise within 7-10 days after initial exposure to thymus.
→ 3 events take place in Germinal centers:

(i) Affinity maturation: Result of somatic hypermutation	(ii) Class Switching	(iii) Formation of Plasma & memory B-cells

In Germinal center, activated B-cells undergo somatic Hypermutation. Since its a random event, some cells can be high affinity for the antigen, while others low. The low-affinity/no-affinity B-cells for a specific antigen will undergo Apoptosis.
The high-affinity B-cells interacts with the Dendritic cells (follicular Dendritic cell) for B-cell selection. The selection process till now is called Affinity maturation.
Next, B-cells will undergo class-switching upon the release of cytokines that leads to B-cell differentiation into Plasma cells. Abs secreted by plasma cells have high affinity than the BCR which was present earlier in activated B-cells (due to Affinity maturation).