Theories of antibody formation

**Instructionist hypothesis**

There is only one common receptor encoded in the germline and that different receptors are generated using the antigen as a template. Each antigen would cause the one common receptor to be folded to fit the antigen. It could not explain why the one common receptor did not fold around self antigens.

**Clonal selection hypothesis**

the germline encodes many different clones of immunologically competent cells (ICC) bearing antigen receptors (Abs) against all possible antigens. Antigen selects those clones of cells that have the appropriate receptor (Ig). Any cell or clone of cells bearing receptors for self molecules are destroyed during embryonic life.

**Immunoglobulin genes & synthesis**

- **Immunoglobulin Genes & Generation of Diversity**
  
  For each type of Igs there is a separate cluster of genes located on different chromosomes:
  
  - Kappa light chain gene clusters located on chromosome 2
  - lambda light chain gene clusters located on chromosome 22
  - heavy chains genes on chromosome 14
  - The variable region of each L chain is encoded by two gene segments: V + J.
  - The variable region of each H chain is encoded by three gene segments: V+ D+ J.
  
  The segments are united into one functional V-variable gene by DNA rearrangement. Each assembled V-variable gene is then transcribed with the appropriate C-constant gene to produce mRNA that encodes for the complete peptide chain.

- **Antibody diversity**

  To produce the very large number of immunoglobulin molecules, about $10^6$-$10^9$, without requiring excessive numbers of genes, Special genetic mechanisms are used like:

  1. **A large number of V genes (in human and mouse)**
  2. **DNA rearrangement and gene recombination**, occur at both the DNA and RNA levels in germline.
  3. **Junctional diversity**, mostly occurs in heavy chain, the addition of new nucleotides at the splice junctions between V-D & D-J gene segments (inaccurate), this occurring in the third hypervariable region & directly affecting the combing site of Ab.
  4. **Somatic hypermutation**

    when memory B cells are stimulated by subsequent exposure to the same epitope (Ag), point mutations are occurring in the $V_L$ & $V_H$ genes of Ab during rapid proliferation that follows re-stimulation, result in improve antibody binding to its Ag.
Heavy chain genes; \( V_n = 1000, D_n = 15 \)

Lambda light chain genes; \( n = 30 \)

Kappa light chain genes; \( n = 300 \)

DJ rearrangement

V(D)J rearrangement

Transcription
**Affinity Maturation**
The binding of antibodies to a given antigen becomes better over multiple exposures. It caused by the accumulations of small mutations that affect Antigen-binding sites and the positive selection (by Ag) of clone of plasma cells carrying mutations that result in tighter binding.

**Immunoglobulin Class Switching**
When responding to subsequent restimulation by an Ag & interaction with helper T cells, B cells undergo further DNA rearrangement of different heavy chain C region genes, thereby altering the Ig isotype (IgG, IgA, or IgE), but has the same specificity as the original IgM.
ISOTYPES
Isotypes are antigenic determinants that characterize classes and subclasses of heavy chains and types and subtypes of light chains. Heavy chain isotypes are found on the Fc portion of the constant region of the molecule while light chain isotypes are found in the constant region.

ALLETOPES
Allotypes are antigenic determinants specified by allelic forms of the immunoglobulin genes. Each class of Ig may vary among individuals of the same species. The allotypic differences are localized to the constant region of the heavy and light chains.
Importance: Forensic medicine, Paternity testing

IDIOTYPES (Id)
Unique antigenic determinants present on individual antibody molecules or on molecules of identical specificity. Idiotypes are the antigenic determinants created by the hypervariable regions of an antibody and the anti-idiotypic antibodies are those directed against the hypervariable regions of an antibody.
Importance: Vaccine, Treatment of B cell tumors,

B. Lymphocytes and the Antibody Response
The Response to T-Dependent Antigens
1. B.cells present antigen to effector T-helper cells for inspection. If an effector T-helper cell recognizes the antigen, it will deliver cytokines to the cell, initiating the process of clonal expansion, which ultimately forms plasma cells that produce antibody.
2. Under the direction of effector T-helper cells, the expanding B-cell population will undergo affinity maturation and class switching, and form memory cells.

Central role of T helper cell
Cell-cell interactions in 1° Ab response
Cell-cell interactions in Ab responses

Kinetics of antibody responses to T-dependent Antigen (primary and secondary immune response)

1) Primary immune response: when the Ag is first encountered

   i. **lag phase**: is longer, until Ab detected in serum (7-10) days
   ii. **IgM**: is first Ab
   iii. appear and followed by IgG (after 2 weeks), the total Ab concentration increased exponentially (log phase) for weeks and then drop to very low level.

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**Diagram:**

- **1.** Hapten binds BCR, Endocytosed Ag presented
- **2.** CD80 expressed
- **3.** CD80/86 expressed, Th activated, express CD40L, cytokine release
- **4.** Cytokine binds R, CD40L binds CD40, B cell activation
- **5.** B cell proliferate, differentiate, secrete Ig

**Graph:**

- **Total Ab**
- **IgM Ab**
- **IgG Ab**

**Axes:**

- **Ab Titre**
- **Days After Immunization**
2) **Secondary (2°) response**: when there is 2nd encounter with the same Ag, memory cells are responsible for the rapid and effective secondary response, eliminating invaders before they cause noticeable harm.

   i. Short lag period (3-5)
   ii. Higher titer of Ab in serum*(due to presence of memory cells)
   iii. IgG appear earlier and produced at higher titer & persist for longer time than in the primary response.
   iv. IgM amount is similar to that after first contact.

**Ab response to T-independent antigen**

T-independent antigens include polysaccharides that have multiple identical evenly spaced epitopes and LPS. Responses to T-independent antigen are characterized by the production of almost exclusively IgM antibody and no secondary response. Secondary exposure to the antigen results in another primary response to the same antigen

- Cell-cell interactions do not occur
- Activation of Bs without class II self MHC-restricted T help
- Polymeric nature of these Ags allows for cross-linking of Ag receptors on Bs
- No 2° response, affinity maturation, or switch
- Response dominated by CD5+ Bs (B1 cells)