Antibodies as Therapeutics

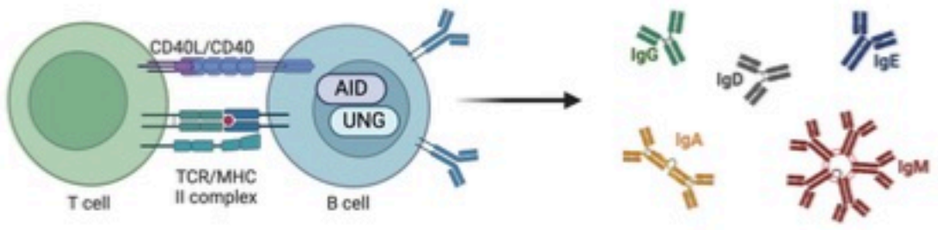
Learning Outcomes

1. Outline the steps in B-cell development and antibody gene rearrangement
2. Describe selected primary immunodeficiencies that arise from problems with B-cell development
3. Describe the steps involved in the B cell response to antigen, including how this affects antibody diversity
4. Describe primary immunodeficiencies that arise from problems with the B cell response to antigen
5. Suggest therapies available for selected primary immunodeficiencies, including the basis for the mechanism of action

Overview of Hyper IgM Syndromes

Hyper IGM syndromes are characterized by defects in B cell activation and differentiation, resulting from four key mutations. These mutations include:

- CD40 ligand deficiency (X-linked, most common)
- CD40 deficiency (autosomal recessive, rare)
- AID mutations (autosomal recessive or dominant)
- UNG mutations (less common, affects somatic hypermutation and class switch recombination)



CD40 Ligand Deficiency

CD40 ligand deficiency is the most prevalent cause of hyper IGM syndrome, stemming from inborn errors in the CD40 ligand gene. This X-linked, cellular, humoral, innate condition affects the surface expression of CD40 ligand on activated CD4 T cells, leading to:

- Defects in B cell activation
- Impaired T cell function
- Inability to form germinal centers in secondary lymphoid tissue; defective B cell proliferation
- Absence of switched memory B cells and antibody-secreting cells

Patients experience significant challenges due to the lack of T cell help and interactions.

CD40 Deficiency

CD40 deficiency is an exceptionally rare autosomal recessive condition that prevents B cells from receiving T helper signals. This results in:

- Complete block in germinal center formation
- Absence of switched B cells
- Almost complete lack of B cell memory

Only about five cases have been documented worldwide.

AID Mutations

Mutations in the AID gene lead to defects in class switch recombination and somatic hypermutation. The severity of these defects varies based on whether the mutation is:

- Autosomal recessive (2 copies mutated gene): complete loss of function
- Autosomal dominant (1 copy, mutation in C-terminus): partial defect, some AID expression and function

In both cases, GC can form. No CSR also occurs with both, however SHM can still occur with autosomal dominant mutations.

UNG Deficiency

UNG deficiency is another cause of hyper IgM syndrome. UNG is an enzyme that acts downstream of AID, and its deficiency results in significant impairments in both class switch recombination and somatic hypermutation.

Pathogenic Mechanisms of Disease:

- CSR defects:
    - Signalling or enzymatic defects that block Igμ H chain replacement by other downstream H chain isotypes
    - T cell defects: lack of T cell help
- SHM defects
    - Blocks in signalling or enzymatic effectors that prevent introduction of mutations in V region of actively transcribed Ig genes à lack of high-affinity Abs
    - T cell defects: lack of T cell help

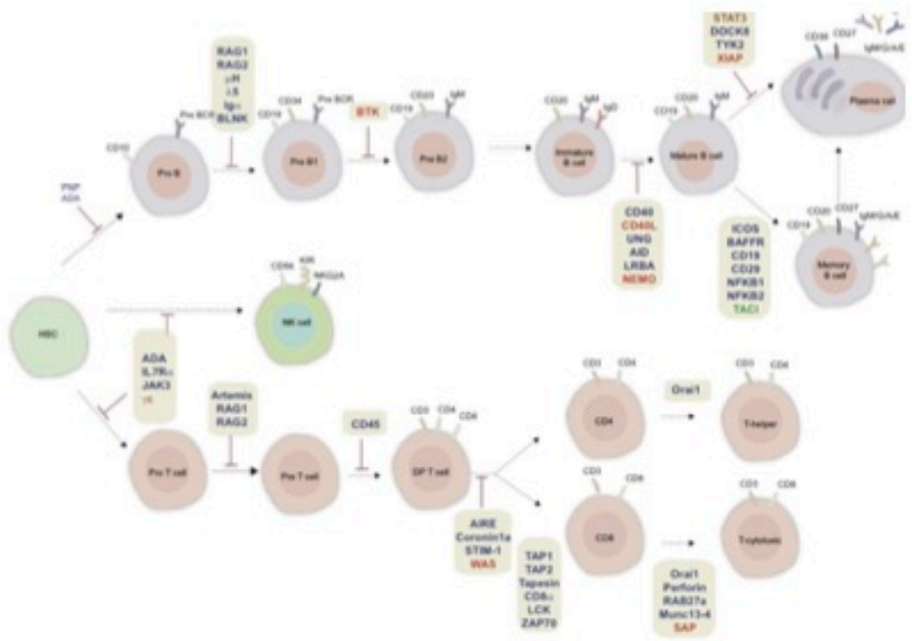
Consequences of Hyper IGM Syndromes

Hyper IgM syndromes lead to defects in producing high-affinity isotype-switched memory and plasma cells. While IgM production remains normal, patients lack IgG, IgA, and IgE memory cells.

Pathways Impacted by Genetic Mutations

Mutations can impact B cell and T cell development and activation, leading to varying severities of antibody deficiencies. Key points include:

- **Intrinsic B Cell Defects:** Can result in complete or partial blocks in B cell function.
- **T Helper Signals:** Essential for generating high-affinity switched antibodies and memory responses.



Antibody Structure

Understanding the structure of antibodies is crucial. Key components include:

- **Variable Regions:** Contain antigen binding sites; composed 7 amino acid regions
    - 4 framework (FW) regions (=scaffold)
    - 3 hypervariable CDR; specificity is determined by CDR1, 2, 3 on each chain.
        - CDR1, CDR2 encoded in germline, CDR3 created during rearrangement
- **Constant Regions:** Direct antibody functions such as complement activation and neutralization.
- **Class Switching:** Changes the isotype of antibodies, affecting their functions and tissue distribution.