Adaptive Immunity to Bacteria Second line of Defense.

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The Immune System

- **Innate Immunity**
  - Antimicrobial Peptides
  - Phagocytes
    - Macrophages
    - Monocytes
    - PMN
    - DCs
  - Complement System
  - Innate signals: TLR and cytokines
- **Adaptive Immunity**
  - B Lymphocytes
  - T Lymphocytes

Major principles of immunity

- 1. Highly specific recognition of foreign antigens with potent mechanisms for pathogen elimination.
- 2. A vast universe of distinct antigenic specificities.
- 3. The capacity to display immunological memory.
- 4. Tolerance to self-antigens.

Why get adaptive?

- **Specificity:**
  - Pathogen A versus B
- **Memory:**
  - Re-infection
- **Fine-tuning :**
  - Speed
  - Magnitude
  - Affinity
  - Efficiency

Adaptive Immunity
Lectures

- B Lymphocytes- Humoral immunity
  - The role of Antibody in immunity.
- T Lymphocytes - cell-mediated immunity
  - CD4+, CD8+ □/□ T cells
  - Antigen Processing and Presentation
  - T cell activation and differentiation
  - Cytokines and inflammatory signals
  - T effector functions in infection
- How does the immune system control T and B cell responses?
  - Regulatory T cells

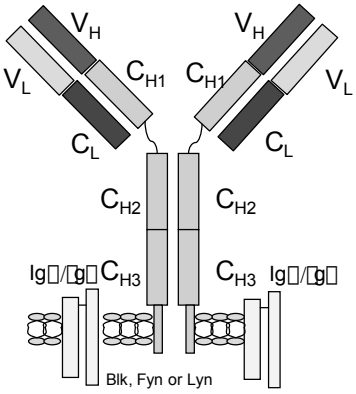
Antigen characteristics
Implications for vaccines.

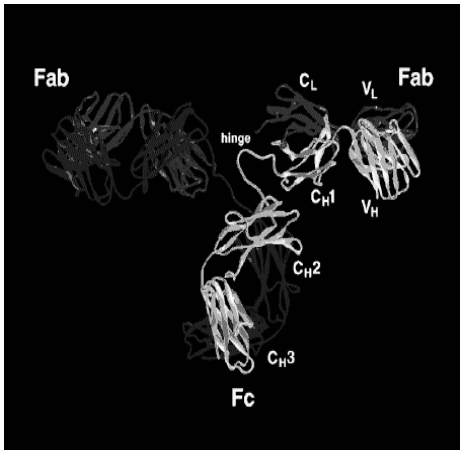
- **Antigenic:** Protein epitope can be recognised by immune system (Ab).
  - However, does not necessarily lead to a productive immune response.
- **Immunogenic:** Protein epitope is recognized and leads to productive response.
  - Problem with cryptic antigens?
- **Types of bacterial antigens**
  - Lipids
  - Polysaccharides
  - Lipopolysaccharides
  - Glycoproteins

Roles of antibodies in bacterial response:

1. Block attachment (I.e. fimbriae, lipoteichoic acids)
2. Block proliferation of bacteria (block transport of nutrients, I.e. iron)
3. Lyse bacteria via triggering complement pathway
4. Contribute to phagocytosis opsonized bacteria by C3 or Fc receptors.
5. Neutralize immunorepellents which bacteria use to avoid phagocytosis.
6. Neutralize toxins, spreading factors used for invasion (I.e. hyaluronidase).

B Lymphocyte Antigen Receptors





5 isotypes: IgG, M, A, D, E.

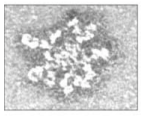
2 light chains (□ or □)
2 heavy chains 2 Binding sites (Divalent)
Secreted into circulation
Binds Soluble Antigen

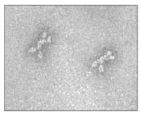
Human Serum Ab and protection

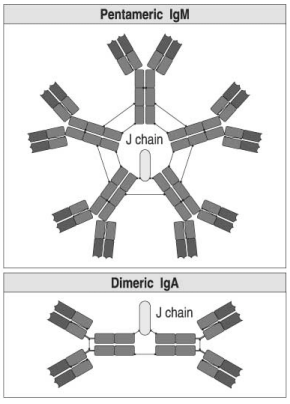
Role	IgG1	IgG2	IgG3	IgG4	IgM
Neutralize toxins	+	+	+	+	+
Prevent binding to host cell	+	+	+	+	+
Opsonize for PMNs	+	-	+	-	-
Opsonize for macrophages	+	-	+	+	+
Activate complement	+	+	+	-	+
Cross placenta	+	+	+	+	-

Dimeric and Pentameric antibodies

Electron micrographs







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Antigen-antibody interaction

- Strength of interaction of one Fab and the antigen = **affinity**
- When multiple arms of the antibody interact with the antigen this overall strength of interaction increases = **avidity**

Affinity and avidity depend on:

- Type of antigen
  - repeating epitopes can lead to higher avidity interactions
- Type of antibody
  - polymeric such as IgM have higher avidity interactions
- Number of somatic hypermutations in the CDR's
- High affinity is important (k_{on}/k_{off} rates) important for IgG and memory response

Antibody response to bacteria

- Structure /function of antibodies:

  Variable region genes

  – diversity of response

  Constant region - Isotype

  – Mucosal versus Systemic response

  – Role of T cells

  – Class switch

  – Affinity and avidity

  Types of Antigens

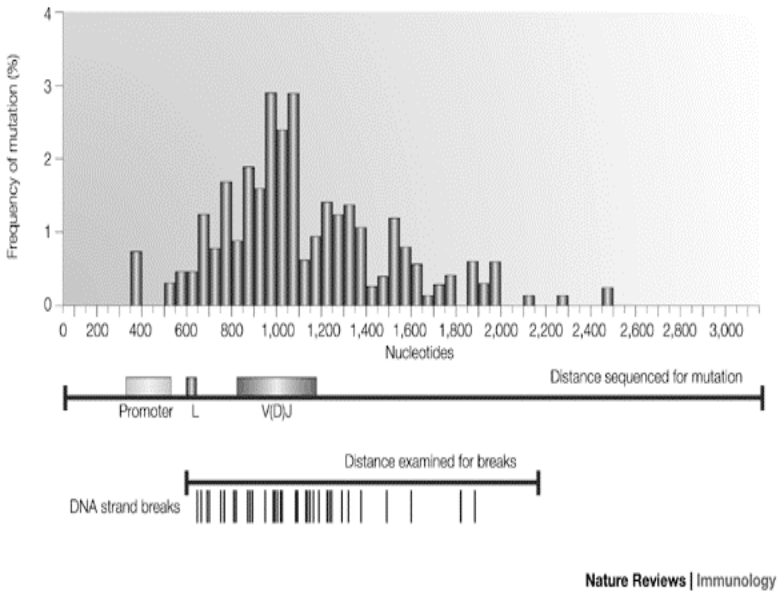
G.O.D and Antibodies

Mechanisms for diversity.

- Multiplicity of germ-line V,D,J genes
  - H : DJ, VDJ, VDJC
  - L : VJ, VJC
- VJ and VDJ recombinations
- Junctional diversity (N-region)
- Heavy and light chain assembly
- Somatic hypermutation
  - Replacement mutation– change in codon results in a different amino acid
  - Silent mutation – no change in the amino acid
  - R/S ratio is always higher in the CDRs than in the framework
- Class switch recombination

Variable Regions

- Complementarity determining regions (CDR) make contact with the antigen, and are the most variable regions, site of most somatic mutations
- Framework regions provide structure
- In man the V-genes of 95 genes, only ~50 of which are used to form antibodies
- V-genes grouped into seven families based on similarity of structure



Antigen may select for variability.

- **Antibodies to *Pseudomonas aeruginosa* LPS O-polysaccharide, or hydrophobic core**
  - 6 different VH3 gene families
  - All JH gene elements used
  - Somatic mutations in all HC, and in some LC

  ➡***Diverse response***
- **Human response to *Haemophilus influenza* polysaccharide**
  - 6 of 7 used the same VH3 gene
  - 4 of 7 used the same lambda LC
  - Mutations varied

  ➡ ***Restricted*** response

Effector functions

- Determined by the Fc portion
- Bind complement
  - IgM – C1q (classical pathway)
  - IgG – C1q or C3 (classical pathway)
  - IgA – C3b (alternate pathway)
- Bind Fc receptors
- Bind polyimmunoglobulin receptor (secretory component), IgM and IgA only

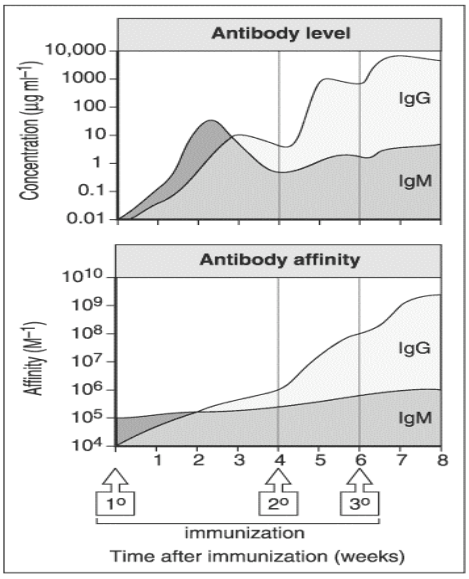
What determines the Ab subclass in anti-bacterial responses?

- *Primary* response
  - IgM
- *Secondary* response
  - IgA if infection is mucosal
  - IgG if infection is systemic
- IgG heavy chain class switch is influenced by *cytokines* secreted by T cells, and thus reflects the role of Th1 or Th2
- *Type of antigen* (I.e. T-cell independent)

Neonatal “adaptive” immunity

- Neonatal immune system not fully developed, thus immunocompromised.
- Relies solely on maternal antibodies:
  - Placental transfer- IgG
  - Breast milk- IgA
- Immunizations of mothers during pregnancy

Kinetics, isotype, affinity and amplitude of Ab response.



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