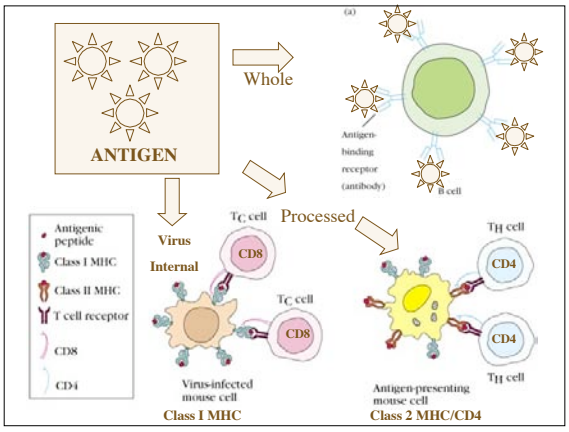
Antigenicity / Immunogenicity

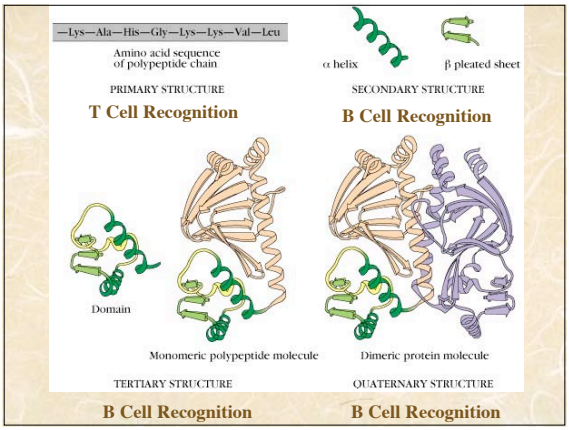
- What is the distinction between **antigenicity** and **immunogenicity?**
- What factors affect the ability of an antigen to induce a strong immune response?
  - Immunogen versus Host Factors

Some Definitions…refined

- **Antigen** - any substance that binds to an antibody or T cell Receptor
- **Immunogen -** any substance which induces a humoral and / or cellular immune response (goal of vaccines).

All immunogens are antigens, but not all antigens are immunogens!





Humoral Immunogenicity

- By 3-Dimensional antigen-peptide, sugar, DNA, monomeric protein, dimeric protein, complex chemical.

B cells + Antigen (3-D) —Ab⇒ Effector B + memory B cells (plasma cells)

Cellular Immunogenicity

- Processed antigen (peptide), which must bind as a small stretch of amino acids to Class I (internal pathway) or Class II (external uptake) MHC on APC.

T cells + Antigen (peptide) —TcR + MHC⇒ Effector T + memory T cells (CTL, T_H)

When is an antigen NOT an immunogen?

- **Haptens** are small molecules, usually organic, which may bind to antibody or TcR, but will not by themselves induce an immune response
  - To generate antibody against haptens, they must be conjugated to a complex protein carrier (e.g. Bovine Serum Albumin).

What Influences Immunogenicity?

- Humoral Immunity - Proteins, polysaccharides are good immunogens
  - Lipids, nucleic acids generally poor immunogens (with some exceptions)
- Cell-mediated Immunity - Proteins, SOME lipids and glycolipids(non-traditional using CD1).

Immunogenicity cont'd…

- Type of **Immunogen**
  - "Foreignness"
  - Size
  - Chemical Composition
  - Susceptibility to Ag processing
- **Host** Factors
  - Genotype (MHC linkages)
  - Dosage/Route of Administration
  - Adjuvants

Foreignness of the Antigen

- Immunogens must be NON-SELF
  - i.e. must NOT have been seen during "education" in the bone marrow or thymus
- This could be due to:
  - Phylogenetic distance - mice, rabbits, and goats are routinely used for antibody production
    - *Exceptions: highly conserved proteins, such as collagen, cytochrome c.*
  - Antigen sequestration - e.g. eye proteins, sperm.
- Problems arise if foreign organisms use **molecular mimicry** to escape the immune system - failure to clear, or autoimmune disorders.

Molecular Size

- Protein size is measured as a **molecular weight**, generally given in daltons (Da) or kilodaltons (Kda)
- Generally, proteins of less than 10KDa make poor immunogens.
- Optimum size is around 50-100KDa.

Chemical Composition

- **Heterogeneity** increases immunogenicity. Polymers (sugar or amino-acid) tend to be less immunogenic then more diverse molecules.
- Charged amino acids tend to increase immunogenicity.
- Addition of **aromatic** amino acids further increases immunogenicity

Ag Processing/Presentation

- If the molecule cannot be internalized or degraded, it will not provoke a strong T cell response
  - Internalization - INSOLUBLE molecules tend to be easier to phagocytose, and will provoke a better response.
    - *Can be increased by chemical crosslinking, heat-induced aggregation, attachment to insoluble matrices/compounds, beads.*
  - Degradation - If the APC cannot process (degrade) the antigen for adequate presentation, it will be a poor antigen
    - *E.g. stereoisomeric D-amino acids cannot be degraded as opposed to naturally occuring L-amino acids.*

General Characteristics of a Good Immunogen

1) It must have a strong B-cell (3-D) binding region (**B cell epitope**)
2) It must have at least one site that binds both MHC and the TcR (a good peptide, **T-cell epitope**)
3) It must be **degradable**.

If these factors are all present, and no response takes place, it may be a HOST factor which is lacking.

Host Factors

- Nature of the host (MHC Genotype)
- Dose, route of administration of antigen
- Adjuvants

Haplotype/Genotype

- The Major Histocompatibility Complex genes regulate the diversity of Class I and Class II proteins on antigen presenting cells
  - Some peptides do not bind efficiently to certain MHC proteins.
  - This produces a "hole" in the repertoire

Genotype/Haplotype

- MHC genes may also regulate the TYPE of response (i.e. humoral or cellular, T_H1 or T_H2).
  - This is especially evident in certain mouse strains, which are highly inbred.
  - In the human population, this may partially explain susceptibility to allergy.

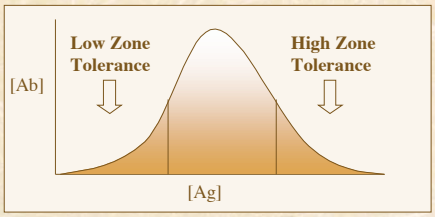
Note that the MHC is a genetic locus, and (as we will cover later in the course) includes many cytokine and complement genes in addition to the traditional Class I and Class II antigen presentation genes.

Immunogen Dosage, Route

- Can affect the ***failure to respond*** to antigen, or induce ***tolerance.***
- ***Low*** antigen doses may fail to stimulate sufficent immune cells (not recognized as dangerous?)
- Normally, a single antigen dose will not stimulate an immunogenic response.

Tolerance

- Dose and route of administration may induce antigen non-responsiveness or ***tolerance***



Route of Administration

- Tolerance - ORAL adminstration of antigen tends to induce tolerance
- Other routes which induce Immune Response include:
  - Intravenous (IV)
  - Intradermal (ID)
  - Subcutaneous (SC)
  - Intramuscular (IM)
  - Intraperitoneal (IP)

Adjuvants

- **Adjuvants** are substances mixed with antigen prior to immunization which enhance the immunogenicity of that antigen

Adjuvants cont'd

- Their precise mechanism of action remains unknown, but is thought to involve
  - Prolonging antigen experience - **Ag Depot**
  - Enhancing co-stimulatory signals (cytokines)
  - Inducing granuloma formation (organized lymphoid tissue)
  - Non-specifically stimulating lymphocyte proliferation.

TABLE 3-3 Postulated mode of action of some commonly used adjuvants

	POSTULATED MODE OF ACTION			
Adjuvant	Prolongs antigen persistence	Enhances co-stimulatory signal	Induces granuloma formation	Stimulates lymphocytes nonspecifically
Freund's incomplete adjuvant	+	+	+	–
Freund's complete adjuvant	+	++	++	–
Aluminum potassium sulfate (alum)	+	?	+	–
Mycobacterium tuberculosis	–	?	+	–
Bordetella pertussis	–	?	–	+
Bacterial lipopolysaccharide (LPS)	–	+	–	+
Synthetic polynucleotides (poly IC/poly AU)	–	?	–	+

CpG Dinucleotides - are bacterial nucleotides (differentially methylated) which appear to non-specifically stimulate cell activation

- these hold promise as natural adjuvants for use in vaccine development.

Summary

- The ability to stimulate an immune response is dependant on both the **antigen** and the **host environment**.
- Strong immunogens should stimulate both a **B and T cell response**, and be available for **antigen processing/presentation**.
- A good host response is dependant on the **genotype** of the individual, and may be boosted by altering the **site** and **timing** of immunization, and by using **adjuvants**.

For next lecture…

- Differences in antigen recognition by B and T cells/Haptens
- Read Chapter 3!