Immunology 2011
Lecture 9
Immunoglobulin Biosynthesis
3 October
Antigen-specific triggering

Proliferation

Differentiation

ANTIGEN

Ag/Ab complexes

Antigen "presentation"

Antigen processing (dendritic cells, MΦ et al.)

APC

T-cell "help"

T-cell killing: virus-infected cells, transplants

Treg Tolerance, suppression

TH1 Delayed type hypersensitivity, (DTH); e.g. tuberculin reaction

MLR Mixed Lymphocyte Reaction

Inflammation

Killing of bacteria

Inactivation of viruses

Allergy

Complement

T-CELL FUNCTIONS

AUTOIMMUNITY

THREE "LIMBS" OF THE IMMUNE RESPONSE
OUTLINE: *Ig BIOSYNTHESIS*

Synthesis/Assembly
Secretion (x2)
Memory
Key Features

1 cell - 1 Ab
*Allelic Exclusion*
*Isotype Switching*
*Membrane vs. secreted Ig*

*Problem Set #2 Answer Key on web site*
Immunoglobulin Expression in the B-cell Lineage

- **Stem cell**
- **Pre-B cell** *(H-chain only, cytoplasm)*
- **B-cells** *(IgM & IgD, membrane)*
- **Plasma cell** *(secreted IgM)*

**Markers**
- Gene rearrangements
- Membrane molecules
Components of Immunoglobulin

- Light Chains
- Heavy Chains
- CHO (only on CH)
- J-Chain (IgM, [IgA]_{2,3})
- Secretory Piece (sIgA)
IMMUNOGLOBULIN BIOSYNTHESIS

- conventional mRNA
- translation
- translocation/cleavage
- spontaneous assembly of H & L-chains
- transport to Golgi, PG vesicles
- addition of J-chain
- release from cell (plasma cell)
- membrane-bound Ig (B-cell)
Carbohydrate on Immunoglobulins

- Oligosaccharides on Ig are heterogeneous and vary over time.
- Percent of “G0” forms (no galactoses) correlates with disease progression in RA; exposed NAcGlu reacts with MBLectin.
- Terminal sialic acids decrease affinity of IgG for some Fc receptors; induce expression of an inhibitory FcR on МΦ – responsible for protective (anti-inflammatory) effects of IVIg?

See commentary by Burton & Dwek, Science 313:627, 2006
Components of Immunoglobulin

- Light Chains
- Heavy Chains
- CHO (only on CH)
- J-Chain (IgM, [IgA]n)
- Secretory Piece (sIgA)
Secretory IgA

TRANSPORT OF EXOCRINE IgA

- Selective transport of polymeric IgA (participation of J-chain)
- Addition of S-piece to secreted molecule
Key Features of Immunoglobulin Biosynthesis

1) An AFC produces only one kind of Ab
   - only one heavy chain isotype
   - only one light chain isotype
   - only one kind of VH and one VL

The two halves of IgG are identical

Stretching the rules...
- Virgin B-cell may produce both IgM & IgD
- B-cells bearing mIg will shift to secreting Ig, transiently expressing both (likewise for cells during the process of isotype switching).
If an AFC were to produce two different L-chains...

Two different antigen-binding sites:
\[ V_L^1 + V_H = S_1 \]
\[ V_L^2 + V_H = S_2 \]

Three different IgG molecules, 50% asymmetric:

For \( 2V_L + 2V_H \) - even more combinations...
Key Features of Immunoglobulin Biosynthesis

2) **Allelic exclusion for H-chains & L-chains**
   Only one of two chromosomes is expressed
   (although both may be rearranged).
   Ensures symmetry of Ig - 2 identical combining sites
   Single-cell level only; overall expression is co-dominant

3) **Heavy chain class switching**
   Change CH only, retain VH & entire L-Chain
   Unidirectional
   Functional diversity; cheaper molecules (compared with IgM)

4) **Secreted vs. membrane Ig**
   Alternate RNA splicing selects anchoring exon
   All Ig isotypes
   Membrane receptor = Ab which will be secreted
Allelic exclusion is critically important for antibodies...but it is not unique to Ig.

“Monoallelic” expression once thought to be rare may represent ~5% of all genes in human somatic cells.

**B-cell Triggering: Proliferation and Differentiation**

**IMMUNOGLOBULIN EXPRESSION BY B-CELLS AND THEIR PROGENY**

*Figure 9-3*
Implications of Tumor Monoclonality

1) Can distinguish between different forms of lymphoproliferative disease (e.g. stain for \( \kappa \) vs. \( \lambda \), or use Southern blots to analyze gene rearrangements). Treatment & prognoses are different for monoclonal vs. polyclonal gammopathies.

2) Anti-idiotypic therapy may be possible for some B-cell and T-cell tumors, since they are monoclonal (but there are practical limitations).

- Antibody responses, B-cells and T-cells, are polyclonal.
- Tumors (myelomas, lymphomas, leukemias) are monoclonal
TUESDAY
ABO & Rh Blood Groups, Chapter 10

THURSDAY
Inbreeding, Appendix 10
MHC & Transplantation, Chapter 11
**Problem Set 2: Complement fixation assay**

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<th>Sample</th>
<th>Dilution</th>
<th>Lysis with added antibody</th>
<th>Lysis with no added antibody</th>
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This serum sample is "anti-complementary"; complement is consumed even without the addition of specific Ab. One can only conclude that the true endpoint must be less than 1:400 (but could be zero!).
Problem Set 2: One Shot Serum Sickness

1. Primary
   - "biological clearance"
   - "immune clearance"
   - immune complexes
   - free Ab

2. $2^\circ$, no remaining Ab

3. $2^\circ$, remaining Ab
Gm Genetics Problems

- All heavy chain loci are closely linked (we ignore the possibility of crossing-over)

- All allelic forms are known, assumption of homzygosity is good.
**Gm Genetics Problem**

3. Fred and Wilma Flintstone and their daughter Pebbles have been typed for allotypes of IgG1 and IgG3 with the following results:

   Fred:      G1m (1+); G3m (5+ 11+)
   Wilma:     G1m (1+ 2+); G3m (6+ 7+)
   Pebbles:   G1m (1+2+); G3m (6+11+)

Which of the following would be the LEAST likely phenotype for their second child?

A.   G1m (1+); G3m (7+11+)
B.   G1m (1+ 2+); G3m (5+ 6+)
C.   G1m (1+ 2+); G3m (6+ 11+)
D.   G1m (1+ 2+); G3m (7+ 11+)
E.   G1m (1+); G3m (5+ 7+)
Fred

Wilma

G1m  G3m

G1m  G3m

Fred

Wilma

G1m  G3m

G1m  G3m

Pebbles

G1m  G3m

G1m  G3m

Four possible phenotypes:

G1m(1+);G3m(5+7+)
G1m(1+2+);G3m(5+6+)
G1m(1+);G3m(7+11+)
G1m(1+2+);G3m(6+11+)

Very unlikely:  G1m (1+ 2+); G3m (7+ 11+)
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