Humoral Immunity and Complement

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MCB150

Humoral Immunity

- Transfer of non-cell components of blood--antibodies, complement

Humoral immunity = antibody mediated

B cell Antigens

<table>
<thead>
<tr>
<th>T cell dependent B cell antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majority of antigens.</td>
</tr>
<tr>
<td>Most protein antigens.</td>
</tr>
<tr>
<td>T cell help required for B cell</td>
</tr>
<tr>
<td>activation and antibody production.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T cell independent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not require thymus.</td>
</tr>
<tr>
<td>No memory.</td>
</tr>
</tbody>
</table>

**B Cell Activation of T-dependent antigens**

- B cell binds virus through viral coat protein
- Peptides from internal proteins of the virus are presented to the T cell, which activates the B cell
- Virus particle is internalized and degraded
- Activated B cell produces antibody against viral coat protein

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B Cell Activation T-dependent antigens

- Linked Recognition
  Need T cell epitope along with B cell epitope to get antibody response.

B cells get help from T cells, help = CD40Ligand and IL-4.

Location of B Cell Activation

Antigen activated B cells remain in T cell zones of LN.
Maximize contact of B cells with T cells.

Clonal proliferation
In Follicles

Affinity maturation

Isotype Switching

Proliferating B cells (centrocytes)
- IFN-Γ
- TGF-β

Activated B cell (centroblast)
- IL-2, IL-4, IL-5

Plasma cells
- IgG2a or IgG3
- IgA or IgG2b
- IgE or IgG1
- IgM

Proliferation cytokines:
- IL-2, IL-4, IL-5

Differentiation cytokines:
- IL-2, IL-4, IL-5, IFN-γ, TGF-β
**T cell Independent Antigens**  
**B-1 cells**  
Activated by repeating CHO epitopes that provide crosslinking to induce antigen uptake and activation.

Antigen specific immune response  
Lower affinity, lower numbers, no memory. Primarily IgM.

**B cell mitogens** (e.g. LPS)  
At low levels normal immune response to LPS  
At high levels LPS can cause non-antigen specific activation of B cells. **Mitogen effect**

**Antibody Effector Functions**  
**Neutralization**
Neutralizing abs block active site for adherence, entry into host cell, or active site of toxin

Neutralizing antibodies are usually high affinity and primarily IgG.
Antibody-dependent cell-mediated cytotoxicity (ADCC)

Antibody binds to pathogen or infected target cell. Fc portion of antibody binds to Fc receptors of a cytotoxic cell.

Complement Activation

Antibody binds to antigen…….complement binds.  Kill, kill, kill…….

Which we will talk about in great detail----very shortly.

Location of Antibody Isotype Influences Function

- IgA  Mucosal
- IgG  Tissues/blood  crosses placenta
- IgE  Parasitic, mast cells
- IgM  Peritoneum, tissues,

Control of Antibody Effector Functions

Fcγ Receptors
- opsonization and ADCC

FcRα1 for IgA
- opsonization and ADCC

FcεR1  on Mast cells
- can prolong life of IgE (role in hypersensitivity)
Complement Pathways

**Classical Pathway**

C1q binds to 1 IgM molecule

OR

2 IgG molecules

**Alternative Pathway**

C1q binds to antigen antibody complex

**Classical Pathway**

Q: Why don't Complement proteins bind to antibodies in serum or lymph fluid?

Answer: Antibodies only expose Fc domain for Complement binding when bound to antigen.
Once C1q binds to antibodies it provides site for serine proteases C1s and C1r to bind.

Full C1 molecule is made of 1 C1q with 2 C1r and 2 C1s molecules.

C1 cleaves C4 and C2. C4b and C2b stay bound to cell surface to form C3 convertase (cleaving C3).

Once C5b is bound then C6, C7, C8 all bind to attract multiple C9s. C9 is pore-forming protein.
Alternate Pathway

- C3 spontaneously cleaves. C3b is bound.
- Factor B binds C3b-B is cleaved by D forms C3bBb.
- C3bBb is a C3 convertase stabilized by Properdin.
- Amplification making more C3b.
- C3bBb3b is C5 convertase.

Biological Functions of C' Lysis of pathogen of infected cell

Complement Receptors initiate other functions of C'

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Major ligands</th>
<th>Activity</th>
<th>Cellular distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 (CD55)</td>
<td>C3b, C4b</td>
<td>Blocks formation of C3 convertase; binds immune complexes to cells</td>
<td>Erthrocytes, neutrophils, monocytes, macrophages, eosinophils, follicular dendritic cells, B cells, some T cells</td>
</tr>
<tr>
<td>CR2 (CD21)</td>
<td>C3b, C4b, C1q</td>
<td>Part of B-cell receptor; binds Epstein-Barr virus</td>
<td>B cells, follicular dendritic cells, some T cells</td>
</tr>
<tr>
<td>CR3 (CD11b/18)</td>
<td>C3b</td>
<td>Bind cell adhesion molecules on neutrophils, facilitating their extravasation; bind immune complexes, enhancing their phagocytosis</td>
<td>Monocytes, macrophages, neutrophils, natural killer cells, some T cells</td>
</tr>
<tr>
<td>CR4 (CD11c/18)</td>
<td>C1q, C3b, C4b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3a/C4a receptor</td>
<td>C3a, C4a</td>
<td>Induces degranulation of mast cells and basophils</td>
<td>Mast cells, basophils, granulocytes</td>
</tr>
<tr>
<td>C5a receptor</td>
<td>C5a</td>
<td>Induces degranulation of mast cells and basophils</td>
<td>Mast cells, basophils, granulocytes, monocytes, macrophages, platelets, endothelial cells</td>
</tr>
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</table>

CRs vs FcRs
Biological Functions of C'

Clearance of Immune complexes

- **LYSIS**
- **OPSONIZATION**
- **ACTIVATION OF INFLAMMATORY RESPONSE**
- **CLEARANCE OF IMMUNE COMPLEXES**

Proteins that Regulate and Inhibit Complement

**TABLE 13-2**: Proteins that regulate the complement system

<table>
<thead>
<tr>
<th>Protein</th>
<th>Type of protein</th>
<th>Pathway affected</th>
<th>Immunologic function</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 inhibitor (C1inh)</td>
<td>Soluble</td>
<td>Classical</td>
<td>Serine protease inhibitor causes C1q to dissociate from C1tq</td>
</tr>
<tr>
<td>C4b-binding protein (C4bBP)</td>
<td>Soluble</td>
<td>Classical and lectin</td>
<td>Blocks formation of C3 convertase by binding C4b; cofactor for cleavage of C4b by factor I</td>
</tr>
<tr>
<td>Factor H*</td>
<td>Soluble</td>
<td>Alternative</td>
<td>Blocks formation of C3 convertase by binding C3b; cofactor for cleavage of C3b by factor I</td>
</tr>
<tr>
<td>Complement receptor type 1 (CRI) (*)</td>
<td>Membrane bound</td>
<td>Classical, alternative, and lectin</td>
<td>Blocks formation of C3 convertase by binding C4b or C3b; cofactor for factor I-stabilized cleavage of C4b or C3b</td>
</tr>
<tr>
<td>Membrane cofactor protein (MCP) (*)</td>
<td>Membrane bound</td>
<td>Classical, alternative, and lectin</td>
<td>N/A</td>
</tr>
<tr>
<td>Decay-accelerating factor (DAF or CD55) (*)</td>
<td>Membrane bound</td>
<td>Classical, alternative, and lectin</td>
<td>Accelerates dissociation of C4b2a and C3b3b (classical and alternative C3 convertases)</td>
</tr>
</tbody>
</table>

*An RCA (regulator of complement activation) protein. In humans, all RCA proteins are encoded on chromosome 1 and contain short consensus repeats.

Biological Functions of C'

Inflammation

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<td>Factor I</td>
<td>Soluble</td>
<td>Classical, alternative, and lectin</td>
<td>Serine protease cleaves C4b or C3b using C4bBP, CRI, factor H, DAF, or MCP as cofactor</td>
</tr>
<tr>
<td>5 protein</td>
<td>Soluble</td>
<td>Terminal</td>
<td>Briefly soluble C5b67 and prevents its insertion into cell membrane</td>
</tr>
<tr>
<td>Homologous restriction factor (HRF)</td>
<td>Membrane bound</td>
<td>Terminal</td>
<td>Binds to C5b67 on autologous cells, blocking binding of C9</td>
</tr>
<tr>
<td>Membrane inhibitor of neurexins (MIRL or CD59)</td>
<td>Membrane bound</td>
<td>Terminal</td>
<td>N/A</td>
</tr>
<tr>
<td>Anaphylatoxin inactivator</td>
<td>Soluble</td>
<td>Effector</td>
<td>Inactivates anaphylatoxin activity of C3b, C4b and C5b by converting protein N-terminal Arg</td>
</tr>
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