Biology of Fcγ Receptors

Selected Functions of Ig Isotypes

<table>
<thead>
<tr>
<th>Antibody isotype</th>
<th>Subtype-specific effector function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>Opsonization of bacteria for phagocytosis by phagocytes</td>
</tr>
<tr>
<td></td>
<td>Activation of the classical pathway of complement</td>
</tr>
<tr>
<td></td>
<td>Antibody-dependent cell-mediated cytotoxicity mediated by natural killer cells and monocytes</td>
</tr>
<tr>
<td></td>
<td>Mast cell degranulation, eosinophil degranulation, platelet aggregation</td>
</tr>
<tr>
<td>IgM</td>
<td>Feedback inhibition of B cell activation</td>
</tr>
<tr>
<td>IgA</td>
<td>Neutralization of bacterial toxins</td>
</tr>
<tr>
<td></td>
<td>Neutralization of viral infections</td>
</tr>
<tr>
<td></td>
<td>Synergistic recruitment of type III innate responses to pathogens</td>
</tr>
<tr>
<td></td>
<td>Activates group I/II/III complement receptors</td>
</tr>
</tbody>
</table>

Functional Sites on the IgG Molecule

Selected Functions of Fc Receptors

FcγRIIA ligand-binding domain

Fcγ Receptor Signaling: ITAM Phosphorylation

Fcγ Receptor Signaling: Syk Activation
**Some Important Fcγ Receptors**

<table>
<thead>
<tr>
<th>Fcγ</th>
<th>Affinity for Immuno globulin</th>
<th>Cell Distributions</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>FcγRI (CD64)</td>
<td>10^-10 M (monocytes, macrophages)</td>
<td>Monocytes, macrophages</td>
<td>Phagocytosis of immune complexes</td>
</tr>
<tr>
<td>FcγRIIA (CD32)</td>
<td>10^-7 M (monocytes, macrophages, granulocytes)</td>
<td>Monocytes, macrophages, granulocytes</td>
<td>Phagocytosis of immune complexes, complement proteins</td>
</tr>
<tr>
<td>FcγRIIB (CD16)</td>
<td>10^-4 M (NK cells)</td>
<td>NK cells, T cells</td>
<td>Phagocytosis, complement activation</td>
</tr>
<tr>
<td>FcγRIIA (CD32)</td>
<td>10^-7 M (monocytes, macrophages)</td>
<td>Monocytes, macrophages</td>
<td>Phagocytosis of immune complexes, complement proteins</td>
</tr>
</tbody>
</table>

*Do not memorize this list but do learn functions of specific Fc receptors. Of these, all are ITAM-associated activating receptors, except FcγRIIB, which is an ITIM-associated inhibitory Fc receptor.

**Phosphoinositide-metabolizing Enzymes Important in Immunity**

**Phosphatidylinositol 3-kinase (PI 3-kinase)**

**SHIP, an Inositol 5' Phosphatase**

**FcγRIIB: an Inhibitory Fcγ Receptor**

**Three Important Phospholipid-modifying Enzymes Worth Knowing: PLC-γ**

Phosphatidylinositol 4,5-bisphosphate (PIP2) → Diacylglycerol, Inositol-3,4,5-trisphosphate (IP3)

**SH2 Domain**

Phosphatidylinositol-3,4-bisphosphate (inactive) → Phosphatidylinositol-3,4,5-trisphosphate (PIP3)
Phagocytosis

Activating Fc, R  Inhibitory Fc, R

Positive and Negative Regulation of the BCR

Ag - Positive and Negative Regulation of the BCR

Therapeutic Uses of Intravenous Immunoglobulin (IVIg)*

Vasculitis
Kawasaki disease
ANCA-positive systemic vasculitis
Antiphospholipid syndrome
Rheumatoid arthritis and Felty’s syndrome
Juvenile Rheumatoid Arthritis
SLE
Thyroid ophthalmopathy
Brilhárd neurochondrolymphopathy
Graft versus host disease
Multiple sclerosis
Insulin-dependent Diabetes mellitus
Steroid-dependent asthma
Steroid-dependent atopic dermatitis
Cohn’s disease

Ag - Positive and Negative Regulation of the BCR

Autoimmune Cytopenias
Idiopathic thrombocytopenic purpura (ITP)*
Acquired immune thrombocytopenias
Autoimmune neutropenia
Autoimmune hemolytic anemia
Autoimmune thrombocytopenia
Parvovirus B19-associated red cell aplasia
Antikörper VIII autoimmune disease
Acquired von Willebrand’s disease
Neurological diseases
Guillain-Barre syndrome
Chronic inflammatory demyelinating polyneuropathy
Myasthenia gravis
Multifocal neuropathy
Polymyositis
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Multifocal neuropathy
Polymyositis
Dermatomyositis

The "Dark Side" of Fc Receptors:
Immune Complex-mediated Injury

Hypersensitivity Diseases

<table>
<thead>
<tr>
<th>Type of hypersensitivity</th>
<th>Pathologic immune mechanisms</th>
<th>Mechanisms of tissue injury and disease</th>
</tr>
</thead>
</table>
| Immediate hypersensitivity
  Type II Fc-dependent,  Type I Fc-dependent | IgE antibody | Mast cells and tissue mast cells release mediators |
| Immune complex-mediated, Type I | IgG and IgM antibodies react with foreign antigens or antibodies in tissues | Complement and IgA and IgG antibodies mediate local tissue damage by activation of complement, chemotaxis and cell-mediated lysis |
| Immune complex-mediated, Type II | Incomplete complex forms antigen-antibody complexes | | | |
| Immune complex-mediated, Type IV | Injury to tissues because of cell-mediated hypersensitivity | | | |

*Other than replacement therapy. Do not memorize this list.
Diseases in blue indicate where therapeutic IVIg plays a major, established role.
The Arthus Reaction: A Model of Type III Hypersensitivity

Requirement of Activating FcRs in Immune Complex-mediated Glomerulonephritis

Absence of the \( \gamma \) subunit of Fc receptors leads to enhanced survival in the F1 generation of NZB/NZW (lupus-prone) mice, a model for autoimmune, immune complex-mediated glomerulonephritis.

Requirement of Activating FcRs in Immune Complex-mediated Glomerulonephritis


Biology of Complement

Glomerulonephritis is blocked in \( \gamma \) chain-deficient NZB/NZW (lupus-prone) mice. Pathological features include mesangial thickening and hypercellularity evolving into end-stage sclerotic and crescentic changes.


Recognized Functions of Complement

1. Host defense
2. Clearance of immune complexes
3. Disposal of apoptotic debris
4. Regulation of the immune response

Complement Activation in Host Defense
Components of Complement

C1q, the Initiator of the Classical Pathway of Complement Activation

Formation of the C3 and C5 Convertases

C3 Contains a Latent, Reactive Thioester Group

The Lectin Pathway and Other Activators of Complement in the Absence of Antibodies

- A lectin is a molecule that binds to carbohydrate structures
- A collectin (like C1q or Mannose Binding Protein) is a lectin with collagen-like features
- First binds to mannose on bacterial cell walls. It then binds serine proteases MASP-1, -2 or -3 (Mannose binding lectin Associated Serine Proteases)
- These can then activate C4 and C2, thus creating a C3 convertase without involving antibodies
- Deficiency in MBL is associated with increased susceptibility to bacterial infections
- It is simplistic to think of each “pathway” as acting in isolation. Thus, once the classical pathway has produced some C3b, these C3b molecules produce more C3b using the alternative pathway
- C-reactive protein (CRP) – An “acute phase” protein produced by the liver, binds to bacterial cell wall lipopolysaccharides. C1q then binds to CRP and thus activates complement without involving antibodies. The test for CRP is frequently ordered in clinical situations where inflammation is suspected

The Mannose-binding Lectin Resembles C1q
The Complement System is Critical for Innate Immunity and is Triggered by Multiple Ligands

C3 Convertase

C5b

C5a Increases Vascular Permeability and is a Potent Chemoattractant

All Roads Lead to Rome

Big MAC Attack

Summary: Three Major Functions of Complement in Host Defense

Complement Regulatory Proteins*

Complement Receptors (Worth Knowing)

*Do not memorize this list but do learn that complement regulatory proteins are either present in soluble form or membrane-bound. Collectively, they interfere with multiple stages of complement activation.
### \( \beta_2 \) (Leukocyte) Integrins

<table>
<thead>
<tr>
<th>Names</th>
<th>CD</th>
<th>Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFA-1</td>
<td>CD11a/CD18</td>
<td>ICAMs</td>
</tr>
<tr>
<td>CR3 (Mac-1)</td>
<td>CD11b/CD18</td>
<td>iC3b, ICAMs, many others</td>
</tr>
<tr>
<td>CR4 (p150, 95)</td>
<td>CD11c/CD18</td>
<td>C3b, iC3b</td>
</tr>
</tbody>
</table>

### Leukocyte Adhesion Deficiency (LAD)

- Absence of CD18
- Decreased to absent surface expression of LFA-1, CR3, CR4
- Phagocytosis impaired
- Diapedesis impaired
- Patients susceptible to bacterial infections

### Recognized Functions of Complement

1. Host defense
2. Clearance of immune complexes
3. Disposal of apoptotic debris
4. Regulation of the immune response

### Clearance of Immune Complexes by Complement Bound to CR1 on Red Blood Cells

- C1q helps removal of apoptotic cell debris (antibody not required)

- Potential immune consequences of C1q deficiency:
  1. Increased deposition of debris in kidney
  2. Possible stimulation of autoantibody production

### Functions of Complement:

- **Disposal of Apoptotic Debris**
- **Immune Regulation**
The “Paradox” of Complement Deficiency and Autoimmunity

Despite a positive role for CR2 in setting the “gain” of B cell responsiveness, it has been suggested that deficiencies in CR2 and C3dg deposition pre-dispose to autoimmunity because the amplification afforded by CR2 occurs inappropriately during tolerance induction.

Disorders of the Complement System

Hereditary Angioneurotic Edema is Due to Deficiency in C1INH*

Models for How Complement Deficiency Predisposes to Autoimmunity

Paroxysmal Nocturnal Hemoglobinuria

1) Defect in enzymes that synthesize GPI-linked proteins (such as DAF and CD59)
2) Red cells and platelets cannot repair damage caused by unregulated complement
3) Patients suffer hemolysis and thrombosis

Hereditary Angioneurotic Edema is Due to Deficiency in C1INH*

*Angioneurotic edema can also be acquired in the course of certain diseases. It is due to a lack of sufficient C1INH, a serine protease inhibitor. C1INH has dual function: it inhibits activation of the classical pathway of complement activation via C1q. C1INH also inhibits pathways leading to bradykinin formation, which is why patients with this disease develop edema.
Complement Deficiencies

<table>
<thead>
<tr>
<th>Component</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1q, C1r, C1s, C2, C4</td>
<td>Markedly increased incidence of autoimmune disease</td>
</tr>
<tr>
<td>H, I, C3</td>
<td>Moderate increased incidence of pyogenic infections</td>
</tr>
<tr>
<td>Properdin, Factor D, C6, C7, C8, C9</td>
<td>Increased incidence of Neisseria infection</td>
</tr>
<tr>
<td>CR3, CR4</td>
<td>Increased incidence of pyogenic infection</td>
</tr>
<tr>
<td>C1INH</td>
<td>Hereditary angioedema</td>
</tr>
<tr>
<td>DAF, CD59</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
</tbody>
</table>

Total Hemolytic Complement Measurement

**Method:** Mix RBC, Anti-RBC, Serial dilutions of serum

**Results:**

<table>
<thead>
<tr>
<th>Serum Dilution</th>
<th>Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/50</td>
<td>100%</td>
</tr>
<tr>
<td>1/100</td>
<td>100%</td>
</tr>
<tr>
<td>1/150</td>
<td>50%</td>
</tr>
<tr>
<td>1/200</td>
<td>20%</td>
</tr>
</tbody>
</table>

The more you are able to dilute the serum to obtain a given degree of hemolysis, the more functional complement is present in the serum. In this case, the CH50 = 150 (Reciprocal of 1/150).

CH50 tends to fall in some autoimmune diseases due to complement consumption.

Summary

1. Ig has multiple isotypes with unique functions.
2. Receptors for the Fc portion of IgG (Fcγ receptors) come in two basic types: ITAM-containing activating receptors (that bind PTKs) and an ITIM-containing inhibitory receptor (that antagonizes the PI 3-kinase pathway). Their relative expression determines the outcome of a given engagement of IgG ligand.
3. Fcγ receptors mediate phagocytosis and, when overactivated by excessive immune complex deposition, tissue injury.
4. Complement is an ancient system of host defense that has well-defined functions in host defense: it opsonizes, stimulates inflammation, and mediates lysis of pathogens by MAC.
5. Additional functions of complement include clearance of immune complexes, clearance of apoptotic debris, and regulation of the immune response. These functions have major implications for the emergence of autoimmunity.
6. Among the known inherited complement deficiencies include Leukocyte Adhesion Deficiency (LAD) and complement component deficiencies; these are associated with frequent infections and, in the latter case, autoimmunity.