"Discovery consists of seeing what everybody has seen, and thinking what nobody has thought."

--Albert Szent-György
Nobel prize in Physiology or Medicine, 1937

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**The Biology of Fc Receptors and Complement**

<table>
<thead>
<tr>
<th>Antibody Isotypes</th>
<th>Isotype-Specific Receptor Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td></td>
</tr>
<tr>
<td>IgD</td>
<td></td>
</tr>
<tr>
<td>IgE</td>
<td></td>
</tr>
</tbody>
</table>

Selected Functions of Ig Isotypes

- **IgG**: Cytotoxicity, cell adhesion, transglutaminase function, complement binding, and Fc receptor binding.
- **IgM**: Antibody-dependent cell-mediated cytotoxicity, activation of the classical complement pathway.
- **IgA**: Primarily secreted in saliva, breast milk, and intestinal mucus.
- **IgD**: Low abundance, associated with normal B cells.
- **IgE**: Major role in allergic responses, interaction with mast cells.

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**Serum Protein Electrophoresis (SPEP): the γ-Globulin Peak Contains Multiple Ig Isotypes**

- **α1**: α1-antitrypsin
- **α2**: haptoglobin
- **β**: lipoproteins, transferrin, clotting factors, complement
- **γ**: IgG, IgA, IgM, IgD, IgE

Normal serum total protein: 5.5-8 g/dL
Normal albumin: 3.5-5.5 g/dL

Note that the ‘γ’ in “gammaglobulin” does not refer to the isotype of the antibody (e.g., IgG), but the migration pattern of proteins on SPEP.

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**A Monoclonal "Spike" in the SPEP is Seen in Multiple Myeloma, a Plasma Cell Dyscrasia**

Bone marrow biopsy from a patient with multiple myeloma
Selected Functions of Fc Receptors

Some Important Receptors for IgG (Fcγ Receptors)*

<table>
<thead>
<tr>
<th>FcγR</th>
<th>Affinity (nM)</th>
<th>Cell Distribution</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>FcγRI (CD64)</td>
<td>&gt;10000</td>
<td>Monocytes, macrophages, neutrophils, eosinophils</td>
<td>Phagocytosis</td>
</tr>
<tr>
<td>FcγRIIA (CD32a)</td>
<td>1-10</td>
<td>Macrophages, neutrophils, eosinophils</td>
<td>Phagocytosis, ADCC in NK cells</td>
</tr>
</tbody>
</table>
| FcγRIIB (CD32b) | 10-100 | Leukocytes | \( \gamma \) 

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

How do Fcγ Receptors Perform Effector Functions?

Fc Receptor Signaling: Phosphorylation of Immunoreceptor Tyrosine-based Activation Motifs (ITAMs)

Phosphorylated ITAMs Recruit Another Tyrosine Kinase, Syk, which Phosphorylates Other Substrates

Two Enzymes Worth Knowing
Phosphatidylinositol 3-kinase (PI 3-kinase)

Lipid products of PI 3-kinase (i.e., PIP₃) bind and activate other proteins (e.g., Bruton’s tyrosine kinase).

SHIP, an Inositol 5’ Phosphatase

SHIP counteracts positive signals generated by PI 3-kinase (by catalyzing the hydrolysis of its lipid product, PIP₃).

Fc,RIIB: an Inhibitory Fc, Receptor

Hypothesis: The balance of activating* and inhibitory Fc, receptors determines the outcome of IgG-initiated events in health and disease.

*Activating: Fc,RI, Fc,RIIA, Fc,RIII
Inhibitory: Fc,RIIB

Therapeutic Uses of Intravenous Immunoglobulin (IVIg)*

Autoimmune Cytopenias
- Idiopathic thrombocytopenic purpura (ITP)
- Acquired immune thrombocytopenias
- Autoimmune neutropenia
- Autoimmune hemolytic anemia
- Autoimmune erythroid aplasia
- Parvovirus B19-associated red cell aplasia
- Anti-factor VIII autoimmune disease
- Acquired von Willebrand’s disease

Neurological diseases
- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Myasthenia gravis
- Multifocal neuropathy
- Polymyositis
- Dermatomyositis

Vasculitis
- Kawasaki disease
- ANCA-positive systemic vasculitis
- Antiphospholipid syndrome
- Recurrent spontaneous abortions
- Rheumatoid arthritis and Felty’s syndrome
- Juvenile Rheumatoid Arthritis
- SLE
- Thyroid orbitopathy
- Behçet retinoceroidopathy
- Graft versus host disease
- Multiple sclerosis
- Insulin-dependent Diabetes mellitus
- Steroid-dependent asthma
- Steroid-dependent atopic dermatitis
- Crohn’s disease

*Other than replacement therapy for hypogammaglobulinemia. Do not memorize this list.
Blue denotes diseases in which IVIg plays a major, established therapeutic role.
The "Dark Side" of Fc Receptors: Immune Complex-mediated Injury

The Arthus Reaction: A Model of Type III Hypersensitivity

Requirement of Activating Fc Rs in Immune Complex-mediated Glomerulonephritis

Summary: Fcγ receptors

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 a variety of immune functions: phagocytosis, secretion of pro-inflammatory mediators, and ADCC.
4. Unregulated activation of Fcγ receptors can lead to immune complex disease.

Biology of Complement

Absence of the γ 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.

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

C3 Contains a Latent, Reactive Thioester Group
The Classical Pathway of Complement Activation


The Mannose-binding Lectin Resembles C1q

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 Lectin) is a lectin with collagen-like features
- MBL first binds to mannose on bacterial cell walls. It then binds serine proteases MASP-1, -2 or -3 (Mannose Binding Lectin Associated Serine Proteases)
- MASP 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.

C5a Increases Vascular Permeability and is a Potent Chemoattractant

All Roads Lead to Rome

The Complement System is Critical for Innate Immunity and is Triggered by Multiple Ligands

Big MAC Attack
**Summary: Three Major Functions of Complement in Host Defense**

- Opsonization and phagocytosis
- Elimination of invaders by recruiting phagocytes
- Formation of an inflammatory response

**Complement Regulatory Proteins***

*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.

**Complement Receptors Worth Knowing**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Specificity</th>
<th>Functions</th>
<th>Cell types</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5b-9</td>
<td></td>
<td>Stimulates phagocytes</td>
<td>Monocytes, macrophages, endothelia</td>
</tr>
<tr>
<td>C5a</td>
<td></td>
<td>Binding of C5a activates C5 protein</td>
<td>Endothelial cells, mast cells, phagocytes</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

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**Names**

<table>
<thead>
<tr>
<th></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>
Clearance of Immune Complexes by Complement Bound to CR1 on Red Blood Cells

Functions of Complement: Disposal of Apoptotic Debris

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

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 a 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.

Disorders of the Complement System

Paroxysmal Nocturnal Hemoglobinuria

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

Inherited Complement Deficiencies

C1q, C1r, C1s, C2, C4  Markedly increased incidence of autoimmune disease
Moderate increased incidence of pyogenic infections

H, I, C3  Increased incidence of pyogenic infections. Moderately increased incidence of autoimmune disease

Properdin, Factor D, C6, C7, C8, C9  Increased incidence of Neisseria infection

CR3, CR4  Increased incidence of pyogenic infection

C1INH  Hereditary angioedema

DAF, CD59  Paroxysmal nocturnal hemoglobinuria
How is Complement Activity Measured?

Method: Incubate antibody-coated erythrocytes with serial dilutions of serum

Results:

<table>
<thead>
<tr>
<th>Serum Dilutions</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: Complement

1. Complement is an ancient system of host defense that has well-defined functions in host defense: it opsonizes microbes (C3b, C3bi), stimulates inflammation (C3a, C4a, C5a), and mediates lysis of pathogens by the membrane attack complex (C5-9).

2. Additional functions of complement include clearance of immune complexes and apoptotic debris. These functions have major implications for the emergence of autoimmunity.

3. 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.