“Discovery consists of seeing what everybody has seen, and thinking what nobody has thought”

--Albert Szent-Györgyi, Nobel prize in Physiology or Medicine, 1937
How do Fc\(_\gamma\) Receptors Perform Effector Functions?

Fc\(_\gamma\)R ligand-binding domain

ITAM-bearing \(\gamma\) subunit

Src family tyrosine kinase

Opsonized Bacterium

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

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

Opsonized Bacterium

Phagocytosis
Secretion
ADCC
Ag presentation

Two Enzymes Worth Knowing

Phosphatidylinositol 3-kinase (PI 3-kinase)

Lipid products of PI 3-kinase (i.e., PIP\(_3\)) 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, PIP\(_3\))
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: FcRI, FcRIIA, FcRIII
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
Antibody-associated autoimmune disease
Acquired von Willebrand’s disease

Neurological diseases
Guillain-Barré syndrome
Chronic inflammatory demyelinating polyneuropathy
Myasthenia gravis
Malignant hypertension
Polymyositis
Dermatomyositis

Vasculitis
Kawasaki disease
ANA-positive systemic vasculitis
Anti-cardiolipin antibody
Renal glomerulonephritis
Rheumatoid arthritis
Felt’s disease
SLE
Thrombotic thrombocytopenic purpura
Bacterial endocarditis
Graft versus host disease
Multiple sclerosis
Type 1 diabetes mellitus
Steroid-dependent asthma
Steroid-dependent atopic dermatitis
Celiac 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 Arthus Reaction: A Model of Type III Hypersensitivity

Locally injected collagen in immune complex with antibody
Local immune complex formation
Activation of FcR by immune complex
Increased blood and protein leakage
Blood vessel necrosis
1-2 hr
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.

Requirement of Activating FcγRs 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

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 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 Protease)
- 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.
The Complement System is Critical for Innate Immunity and is Triggered by Multiple Ligands

All Roads Lead to Rome

C5a Increases Vascular Permeability and is a Potent Chemoattractant

Summary: Three Major Functions of Complement in Host Defense

Big MAC Attack

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.
**β₂ (Leukocyte) Integrins**

<table>
<thead>
<tr>
<th>Names</th>
<th>CD</th>
<th>Ligands</th>
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<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>
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**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**

**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

**Disorders of the Complement System**
Hereditary Angioneurotic Edema is Due to Deficiency in CIINH*

*Angioneurotic edema can also be acquired in the course of certain diseases. It is due to a lack of sufficient CIINH, a serine protease inhibitor. CIINH has a dual function: it inhibits activation of the classical pathway of complement activation (via C1r-C1s). CIINH also inhibits pathways leading to bradykinin formation, which is why patients with this disease develop edema.

Complement Deficiencies

<table>
<thead>
<tr>
<th>Protein</th>
<th>Deficiency</th>
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<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>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>CI1NH, DAF, CD59</td>
<td>Hereditary angioedema, Paroxysmal nocturnal hemoglobinuria</td>
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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

How is Complement Activity Measured?

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

Results:

<table>
<thead>
<tr>
<th>Serum Dilution</th>
<th>Hemolysis (%)</th>
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<tbody>
<tr>
<td>1/50</td>
<td>100%</td>
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<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>
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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.