Medical Immunology for M.D. Students

IMMUNODEFICIENCY DISORDERS (1)

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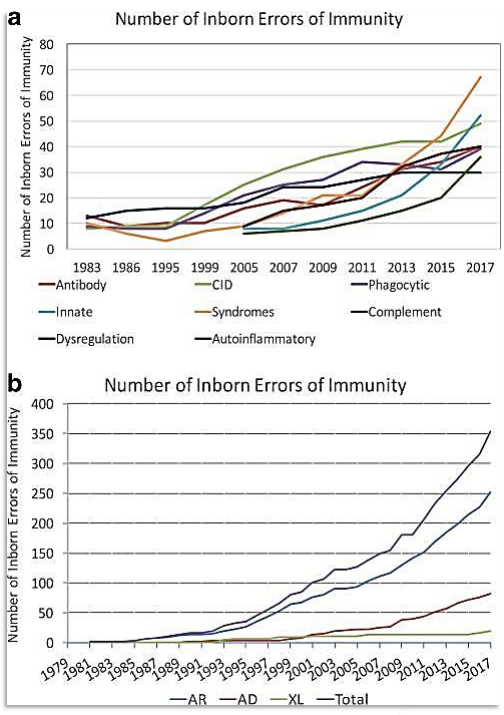
Introduction

- Immunodeficiencies (IDs) are a group of diseases caused by quantitative and/or functional changes in the different mechanisms involved in both the innate and the adaptive immune response.
- Immunodeficiency resulting from an inherited genetic or developmental defect in the immune system is called a **primary immunodeficiency**.
- **Secondary immunodeficiency**, also known as acquired immunodeficiency, is the loss of immune function that results from exposure to an external agent.

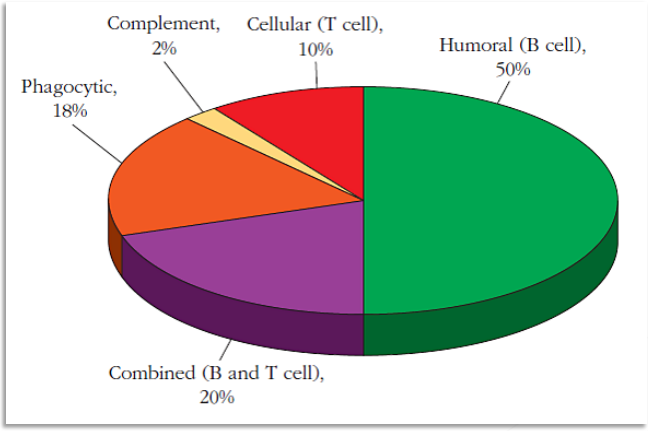
Primary Immunodeficiency

- To date, over 300 different types of primary, or inherited, immunodeficiency have been identified.
- Most of these disorders are **monogenic** (caused by defects in a single gene), and are **extremely rare**.
- Primary immunodeficiency diseases vary in severity from mild to nearly fatal.
- Due to the complex interconnections of the immune response, defects in one pathway can also manifest in other arms of the immune response, and different gene defects can produce the same phenotype, making strict categorization complicated.


a
Number of Inborn Errors of Immunity
Number of Inborn Errors of Immunity
80
70
60
50
40
30
20
10
0
1983 1986 1995 1999 2005 2007 2009 2011 2013 2015 2017
Antibody
CID
Phagocytic
Innate
Syndromes
Complement
Dysregulation
Autoinflammatory
b
Number of Inborn Errors of Immunity
Number of Inborn Errors of Immunity
400
350
300
250
200
150
100
50
0
1979 1981 1983 1985 1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017
AR
AD
XL
Total

Classification of Primary Immunodeficiency

PIDs can be loosely categorized as affecting either innate immunity or adaptive responses, and are often grouped by the specific components of the immune system most affected.



When should we investigate a possible immunodeficiency disorder?

Clinical Signs That Suggest a Primary Immunodeficiency Disease

Positive family history
Infections in multiple anatomic locations
Increasing frequency and severity of infections with age
Recurrent serious infections with common pathogens
Serious infections with unusual pathogens

How to diagnose PIDs?

- Hx & PE.
- CBC & differential.
- Quantitative Igs.
- Review of previous culture results.
- Titers for administered vaccines.
- Lymph enumeration using FCM.
- Skin testing.
- CH50, C3 & C4.
- Phagocyte studies, NBT.
- Enzyme studies.

Patterns of illness associated with PIDs

Disorder	Disease	
	OPPORTUNISTIC INFECTIONS	OTHER SYMPTOMS
Antibody	Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	Autoimmune disease (autoantibodies, inflammatory bowel disease)
Cell-mediated immunity	Pneumonia (pyogenic bacteria, *Pneumocystis carinii*, viruses) Gastrointestinal (viruses), mycoses of skin and mucous membranes (fungi)	
Complement	Sepsis and other blood-borne infections (streptococci, pneumococci, neisseria)	Autoimmune disease (systemic lupus erythematosus, glomerulonephritis)
Phagocytosis	Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)	
Regulatory T cells	N/A	Autoimmune disease

Primary Immunodeficiency Disorders (Selected Examples)

Defects of the B-Cell System

X-Linked Bruton's Agammaglobulinemia

Selective IgA Deficiency

Common Variable Immunodeficiencies

Defects of the T-Cell System

DiGeorge Anomaly

Severe Combined Immunodeficiency (SCID)???

Hyper IgM Syndrome

Defects of Neutrophil Function

Chronic Granulomatous Disease

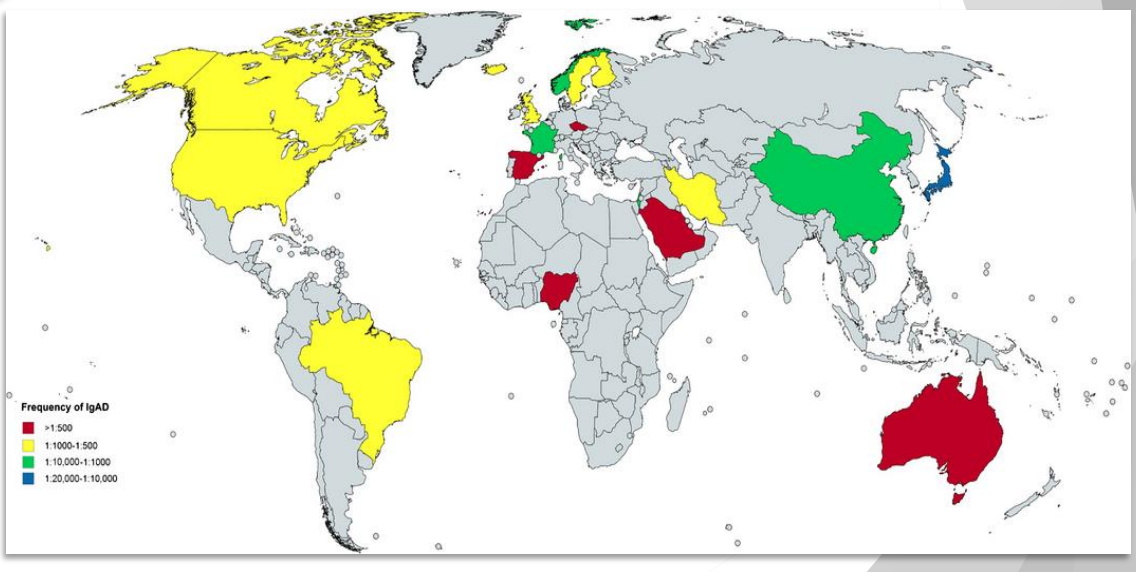
Leukocyte Adhesion Deficiency

Complement Deficiencies

Defects of the B-Cell System
Selective IgA Deficiency

- **Selective IgA deficiency is the most common congenital immunodeficiency**, occurring in about 1 in 500 persons of American-European descent.
- Individuals with selective IgA deficiency typically exhibit normal levels of other antibody isotypes and may enjoy a full life span, troubled only by a greater-than-normal susceptibility to infections of the respiratory and genitourinary tracts, the primary sites of IgA secretion.
- Although the genetic defect has not been established, it is hypothesized that lack of IgA is caused by impaired differentiation of lymphocytes to become IgA-producing plasma cells.

Defects of the B-Cell System
Selective IgA Deficiency

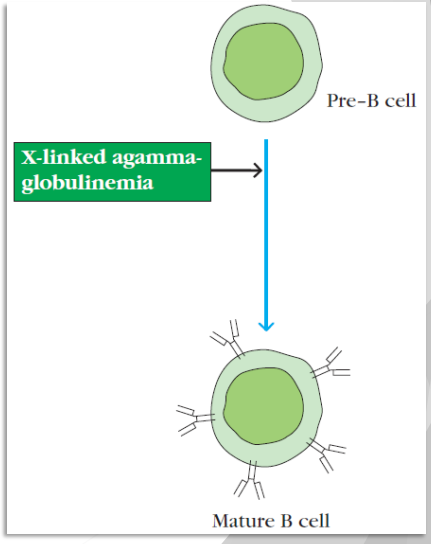


Defects of the B-Cell System
X-Linked Bruton's Agammaglobulinemia

- Bruton's agammaglobulinemia, first described in 1952, is an X chromosome-linked, so this syndrome affects males almost exclusively.
- Patients with X-linked agammaglobulinemia lack circulating mature CD19 positive B cells and exhibit a deficiency or lack of immunoglobulins of all classes.
- Furthermore, they have no plasma cells in their lymphoid tissues, but they do have pre-B cells in their bone marrow.
- Because of the lack of B cells, the tonsils and adenoids are small or entirely absent, and lymph nodes lack normal germinal centers. T cells are normal in number and function.

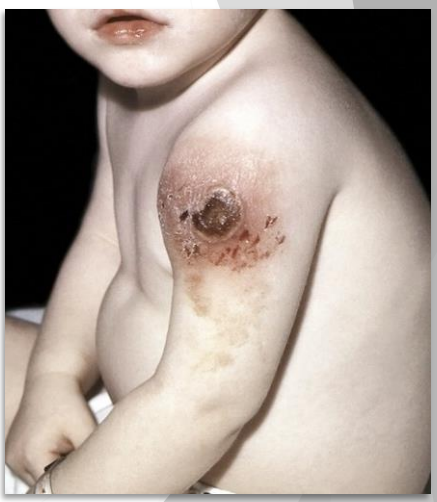
Defects of the B-Cell System
X-Linked Bruton's Agammaglobulinemia

- X-linked agammaglobulinemia results from arrested differentiation at the pre-B cell stage, leading to a complete absence of B cells and plasma cells.
- The underlying genetic mechanism is a deficiency of an enzyme called the Bruton tyrosine kinase (*Btk*) in B-cell progenitor cells.
- Lack of the enzyme apparently causes a failure of V_H gene rearrangement.



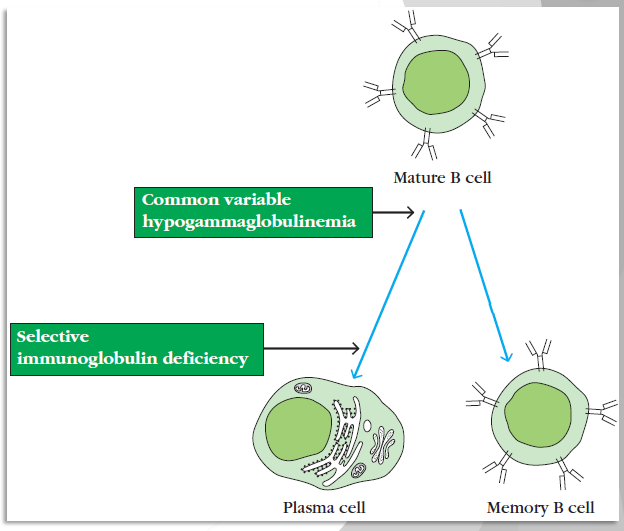
Defects of the B-Cell System
X-Linked Bruton's Agammaglobulinemia

- Patients most commonly develop sino-pulmonary infections caused by encapsulated organisms such as streptococci, meningococci, and *Haemophilus influenzae*.
- Other infections seen include bacterial otitis media, bronchitis, pneumonia, meningitis, and dermatitis.
- Present-day use of antibiotics and replacement therapy in the form of passively administered antibodies can make this disease quite manageable.



Defects of the B-Cell System
Common Variable Immunodeficiencies (CVID)

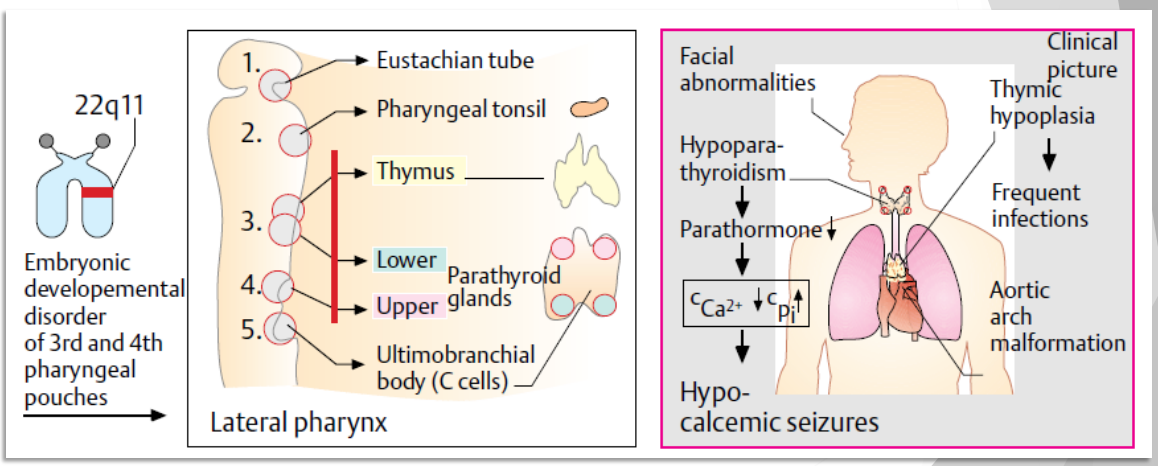
- CVID encompasses the largest group of symptomatic primary immunodeficiencies, with an estimated incidence between 1:10,000 and 1:50,000.
- Patients usually begin to have symptoms in their 20s and 30s, but age at onset ranges from 7 to 71 years of age. Respiratory tract infection by common bacterial strains is the most common symptom.



Defects of the T-Cell System
DiGeorge Anomaly

- **Developmental abnormality of the third and fourth pharyngeal pouches that affects thymic development**. Specifically, most patients show a deletion in chromosome 22, region q11.
- The severity and extent of the developmental defect can be quite variable. Many patients with a partial DiGeorge anomaly have only a minimal thymic defect and are thus near normal immune function.
- However, 20% of children with a defect of the third and fourth pharyngeal pouches have a severe decrease in T-cell numbers. These children tend to have severe, recurrent viral and fungal infections. Severely affected children usually present in the neonatal period with tetany (caused by hypocalcemia resulting from hypoparathyroidism) or manifestations of cardiac defects.

Defects of the T-Cell System
DiGeorge Anomaly



Severe Combined Immunodeficiency (SCID)

- The most serious of PIDs is SCID. It is a group of related diseases that all affect T- and B-cell function but with differing causes. **X-linked SCID is the most common form of the disease**.
- The abnormal gene involved codes for a protein chain called the **common gamma chain**, which is common to receptors for interleukins- 2, 4, 7, 9, 15, and 21. The gene is referred to as the *IL2RG* gene and is located on the X chromosome.
- Normal signaling cannot occur in cells with defective receptors, preventing natural maturation. Although this chain was first identified as a part of the IL-2 receptor, **impaired IL-7 signaling is likely the source of both T-and B-cell developmental defects**, while lack of **IL-15** signaling is believed to account for the block to **NK cells**.

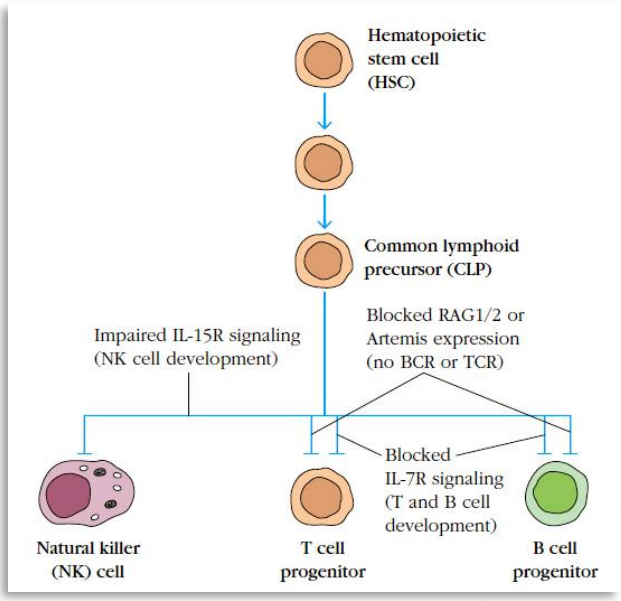
Severe Combined Immunodeficiency (SCID)

- A JAK3 deficiency may be found without the common gamma chain deletion.
- This results in an autosomal recessive form of SCID, affecting both males and females.
- Defects in the pathways involved in the recombination events that produce immunoglobulin and T-cell receptors highlight the importance of early signaling through these receptors for lymphocyte survival.
- Mutations in the recombinase activating genes (RAG1 and RAG2) and genes encoding proteins involved in the DNA excision-repair pathways employed during gene rearrangement (e.g., Artemis) can also lead to SCID.

Severe Combined Immunodeficiency (SCID)

- Another relatively common defect resulting in SCID is adenosine deaminase (ADA) deficiency.
- Adenosine deaminase catalyzes conversion of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively.
- Its deficiency results in the intracellular accumulation of toxic adenosine metabolites, which interferes with purine metabolism and DNA synthesis.
- This housekeeping enzyme is found in all cells, so these toxic compounds also produce neurologic and metabolic symptoms, including deafness, behavioral problems, and liver damage.

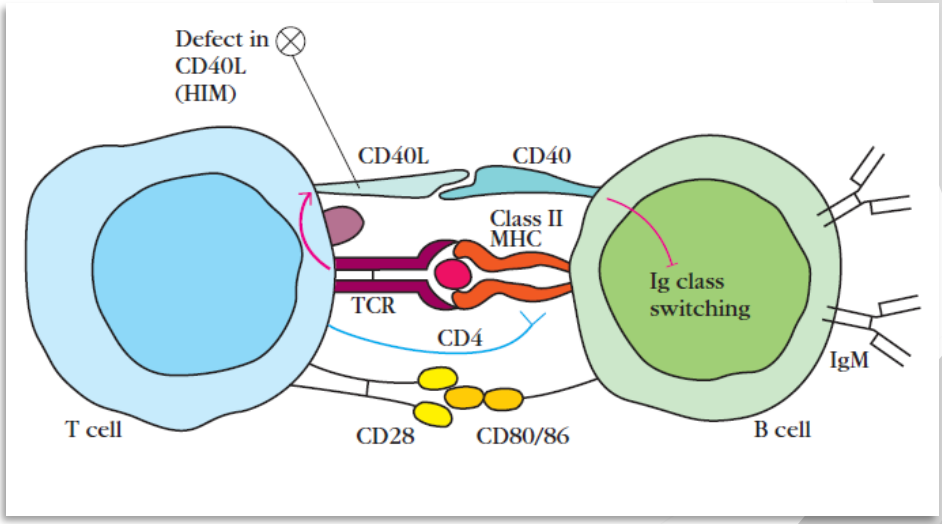
Severe Combined Immunodeficiency (SCID)



Defects of the T-Cell System
Hyper IgM Syndrome

- An inherited deficiency in CD40 ligand (CD40L or CD154) leads to impaired communication between T cells and antigen-presenting cells (APCs), highlighting the role of this surface molecule in this co-stimulatory process.
- In this X-linked disorder, TH cells fail to express functional CD40L on their plasma membrane, which typically interacts with the CD40 molecule present on B cells and dendritic cells (DCs).
- The B-cell response to T-independent antigens, however, is unaffected, accounting for the presence of IgM antibodies in these patients, which range from normal to high levels and give the disorder its common name, hyper IgM syndrome.

Defects of the T-Cell System
Hyper IgM Syndrome



Defects of Neutrophil Function
Chronic Granulomatous Disease

- CGD is caused by an inherited defect in the **(NADPH) oxidase** enzyme complex present in a variety of cells including phagocytes.
- The NADPH oxidase enzyme complex consists of two membrane-spanning subunits, **gp91phox** and **p22phox**, as well as three cytosolic components p47phox, p67phox, and p40phox.
- Approximately, 66% of all CGD cases result from mutations within the X-linked gp91phox gene, followed by the autosomal recessive forms of CGD, with defects in the gene coding for p47phox, accounting for 30% of all CGD cases.

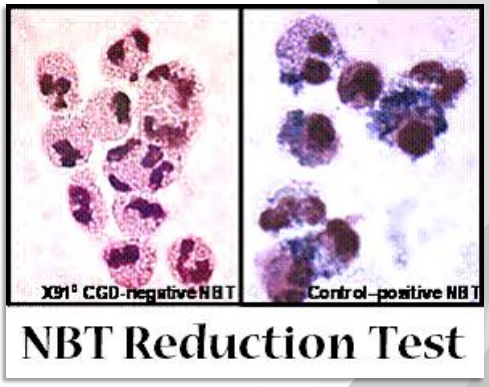
Defects of Neutrophil Function
Chronic Granulomatous Disease

- **NADPH oxidase** is required for the 'respiratory burst' and has a critical role in microbial killing.
- It reduces molecular oxygen to superoxide, which subsequently forms reactive oxygen species (ROS) such as hydrogen peroxide, hypochlorous acid, and hydroxyl radicals.
- Patients are particularly susceptible to fungal infection, typically from *Aspergillus* species, but also catalase-positive bacteria including *Staphylococcus aureus*, *Serratia marcescens* and *Burkholderia cepacia*.
- Most patients present with infections, typically lymph node abscesses, but also recurrent respiratory infection, deep-seated abscesses and septicaemia.

Defects of Neutrophil Function
Chronic Granulomatous Disease

- Making the diagnosis of CGD is not technically difficult, and historically is based on the use of the "gold standard" nitro-blue tetrazolium assay.

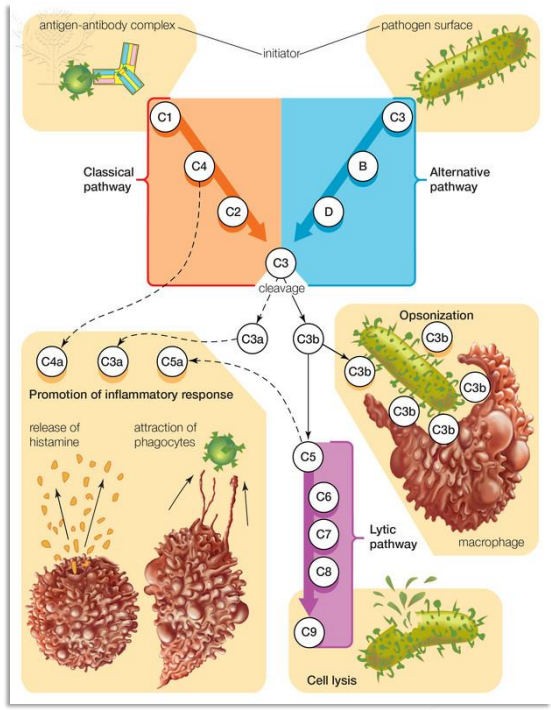
- Recent assay is FCM based on the reduction of **dihydrorhodamine (DHR)** by stimulated phagocytic cells and is particularly useful as it can demonstrate two populations of cells in carriers.



NBT Reduction Test

Complement Deficiencies

- Deficiencies in the early complement components, C1q, 4, and 2, are usually associated with a **lupus-like syndrome**.
- C3 deficiency may also have a **lupus-like clinical presentation** but is more likely to involve **recurrent encapsulated organism infection**.
- Deficiencies of the **later components of complement** (C5 through C9) are often associated with recurrent *Neisseria* infections.
- A deficiency of **C1 esterase inhibitor** has been found in patients with **hereditary angioedema**. Most complement deficiencies appear to be inherited in an autosomal recessive manner.


antigen-antibody complex
initiator
pathogen surface
C1
C4
C2
Classical pathway
C3
B
D
Alternative pathway
C3
cleavage
C3a
C3b
C4a
C3a
C5a
Promotion of inflammatory response
release of histamine
attraction of phagocytes
Opsonization
C3b
C3b
C3b
C3b
C3b
macrophage
C5
C6
C7
C8
Lytic pathway
C9
Cell lysis

Any Questions?

Thanks for Listening