PRIMARY IMMUNODEFICIENCY (PI) – ANATOMY AND PHYSIOLOGY OF THE IMMUNE SYSTEM

RARE DISEASE HUB

C-ANPROM/UK/IG/0022 February 2022

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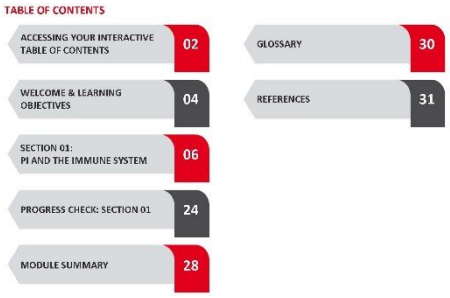

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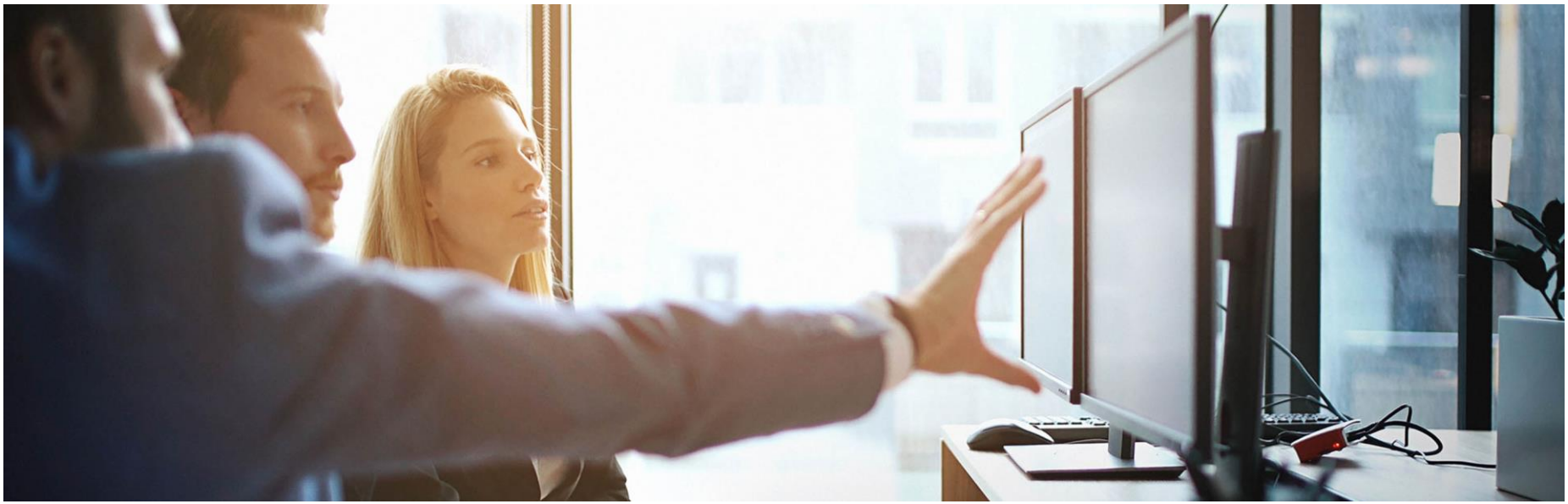
TABLE OF CONTENTS



WELCOME & LEARNING OBJECTIVES

Upon completion of this module, you will be expected to demonstrate that you can…

- Recall the key components of the immune system involved in primary immunodeficiency (PI)
- Define the basics of PI disease (PID)

Welcome to Primary Immunodeficiency (PI) – Anatomy and Physiology of the Immune System module!

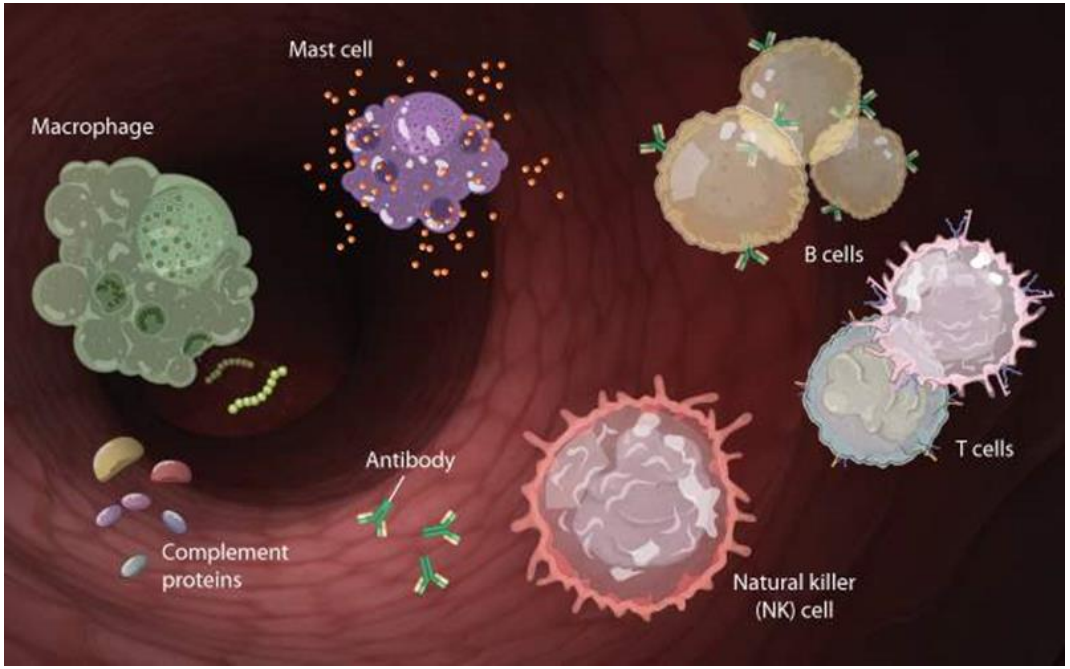
We all fall ill now and then and recover with minimal or no treatment—thanks to our immune system. Most individuals' immune systems are capable of recognising and fighting a vast array of foreign invaders. However, for a small percentage of individuals, the immune response does not work properly. Often these individuals suffer from recurrent and severe infections and are diagnosed with PI.

So, what are the components of the immune system and which of them are involved in PI? Answering these questions will be the focus of this module.

SECTION 01:
PI AND THE IMMUNE SYSTEM

Primary Immunodeficiency (PI)

PI is an inborn (congenital) defect in which immune system components are missing or not working properly



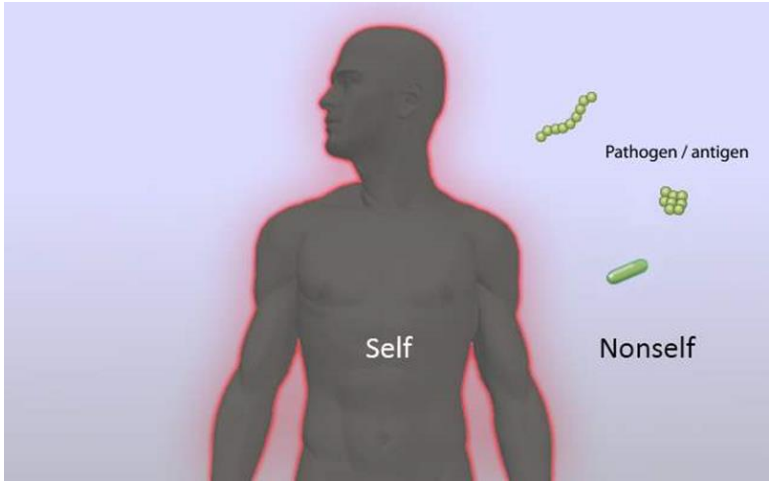
- Characterised by increased susceptibility to recurrent infections and sometimes also malignancy and **autoimmunity**
- Encompasses >350 diverse diseases that involve one or more abnormalities of the immune system

Autoimmunity
Condition in which the body's ability to tolerate the antigens on its own cells is disrupted.

Immune System Overview

The immune system response:

- Defends the body against infection from **pathogens**, i.e., disease-causing agents such as bacteria, viruses, fungi, and parasites
- Distinguishes between self and non-self (foreign)
  - **Antigens**: molecules that are capable of provoking an immune response



- Consists of:
  - Physical barriers (e.g., skin and mucous membranes)
  - Cellular components (e.g., phagocytes and lymphocytes)
  - Soluble mediators (e.g., **complement** proteins, **antibodies**, and **cytokines**)

- Has two main mechanisms:
  - Innate **immunity**
  - Adaptive immunity (includes cell-mediated and humoral)

Pathogen
Any microorganism capable of producing disease.

Antigen
Any substance that is capable of activating an immune response or binding with an antibody.

Complement
A group of proteins in the blood that play a vital role in the body's immune defences through a cascade of interactions.

Antibody
Immunoglobulin molecule produced by B lymphocytes (also known as B cells) that combines specifically with an antigen to destroy or control it.

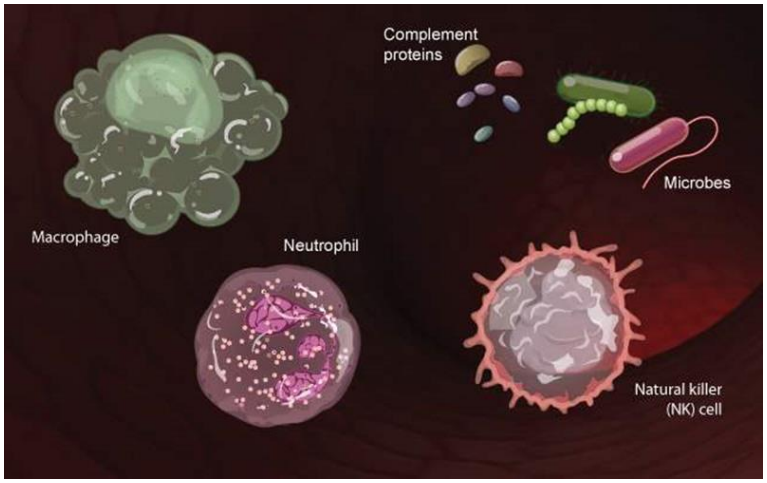
Cytokine
Any of more than 100 small proteins produced and released by cells that regulate immunological aspects of cell growth and function during both inflammation and immune responses.

Immunity
Protection from diseases, especially from infectious diseases.

Innate Immunity

Innate immunity provides immediate, nonspecific protection

- Present at birth and always on
- First line of defence: external barriers (skin and mucous membranes)
- Second line of defence: internal defenders (**natural killer [NK] cells**, phagocytes, complement system, and **inflammation**)

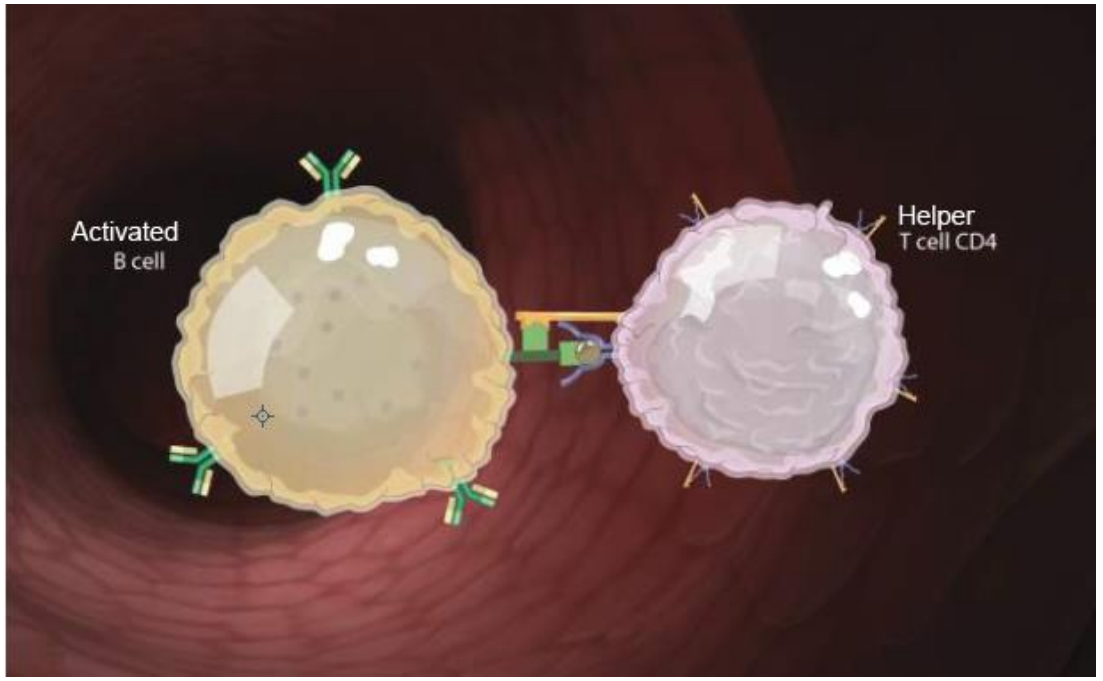


Natural killer (NK) cell
A large granular lymphocyte that can react against and destroy cancer cells and virus-infected cells without prior sensitisation to it.

Inflammation
An immunological defence against injury, infection, or allergy, marked by increases in regional blood flow, immigration of white blood cells, and release of chemical toxins. Inflammation is one way the body uses to protect itself from invasion by foreign organisms and to repair wounds to tissue. Clinical hallmarks of inflammation are redness, heat, swelling, pain, and loss of function of a body part.

Adaptive Immunity

Adaptive immunity relies on immunological “memory” to recognise and react to specific reinvading foreign antigens



Adaptive immunity is carried out by lymphocytes, a class of leukocytes (white blood cells):

- Each lymphocyte responds with specific antigen recognition based on the shape of protein receptors on the surface of the cells

Adaptive Immunity (Cont.)

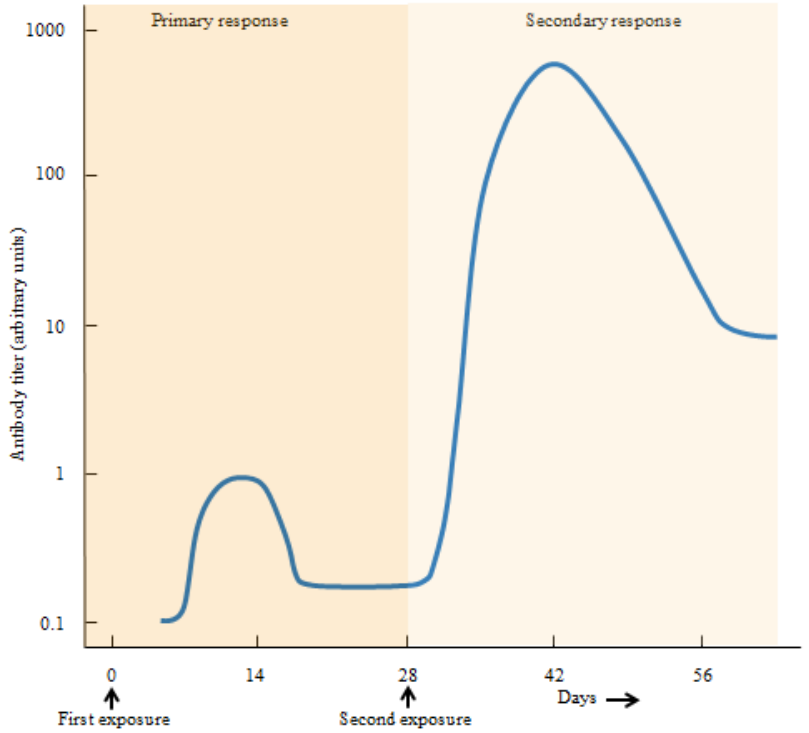
Primary response:

- First time lymphocytes encounter and react to a foreign antigen
- Relatively weak antibody response with a 5- to 7-day lag time

Secondary response:

- Triggered by subsequent lymphocyte encounters with the same antigen
- Much stronger antibody response with little or no lag time

Production of immunoglobulin G (IgG) antibodies in the primary (after first exposure) and secondary (after second exposure) responses to a given antigen



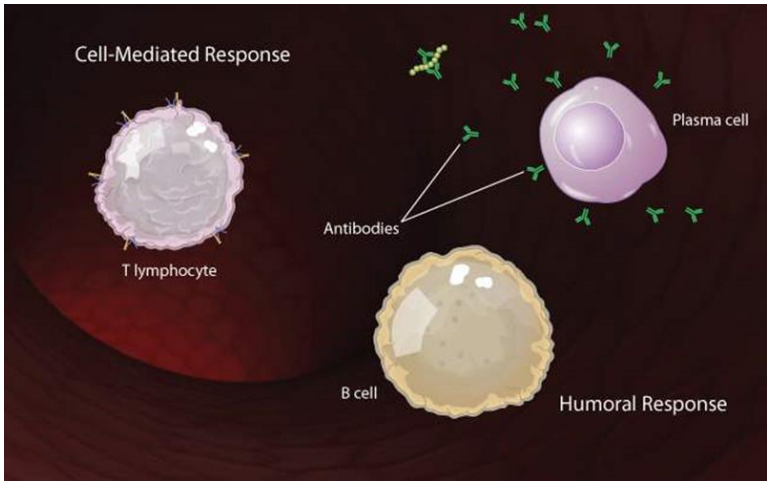
Adapted from Tortora *et al.*, 2012

Types of Adaptive Immunity

There are two types of adaptive immunities.

Cell-mediated immunity

- Particularly effective against intracellular pathogens such as bacteria, viruses, and fungi
- Involves **T cells**
  - Cytotoxic T cells bind to antigens and destroy foreign cells



Humoral immunity

- Works mainly against antigens present in body fluids and extracellular pathogens such as bacteria, viruses, and fungi
- Activated **B cells** differentiate into plasma cells or memory B cells
- Plasma cells produce immunoglobulins (antibodies) which bind to and disable antigens

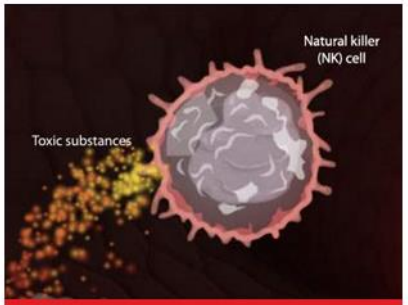
Helper T cells recognise and respond to foreign antigens to initiate an immune response and are involved in both cell-mediated and humoral immunity. An antigen can provoke both types of adaptive immune responses, as many copies of specific antigens may spread throughout the body's tissues and fluids.

T cell
Type of lymphocyte that responds to specific antigens with the assistance of antigen-presenting cells via cell-mediated immunity. May be further categorised by function as T helper cell or cytotoxic T cell.

B cell
Type of lymphocyte that identifies antigens and differentiates into antibody-producing plasma cells or memory cells.

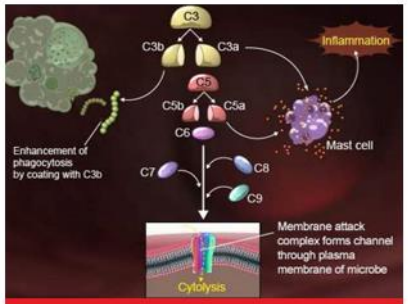
Key Elements of Immune System

Many of the immune system elements play critical roles in both innate and adaptive immunity. In the following pages, we will learn more about each of these elements that comprise the immune response mechanisms.

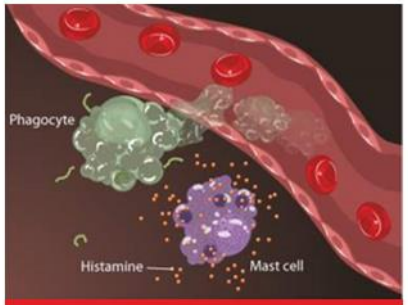


Natural killer cells

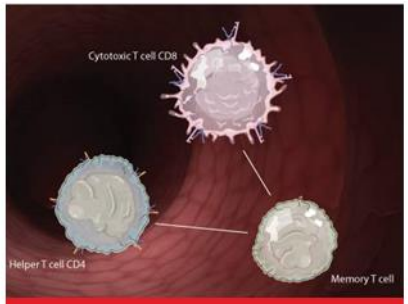
Phagocytes



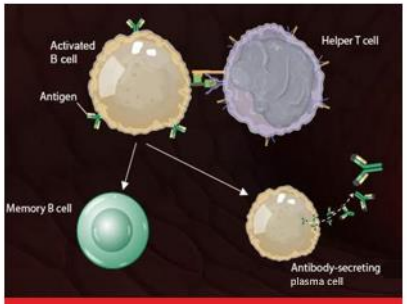
Complement system



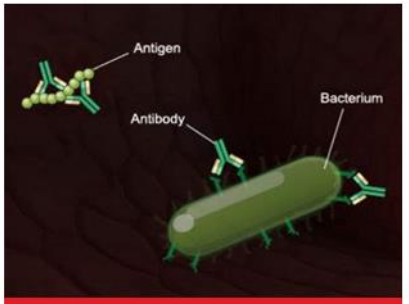
Inflammation



T cells



B cells

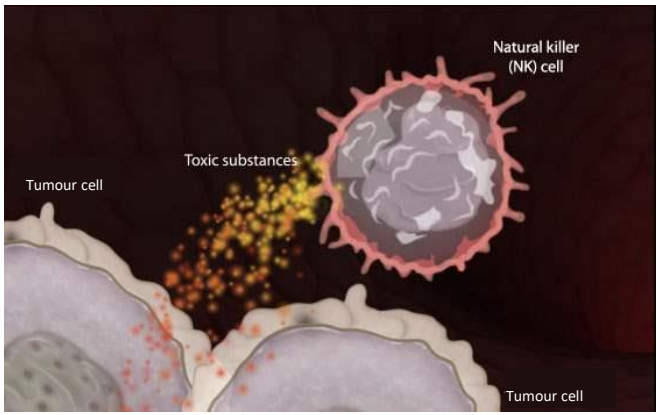


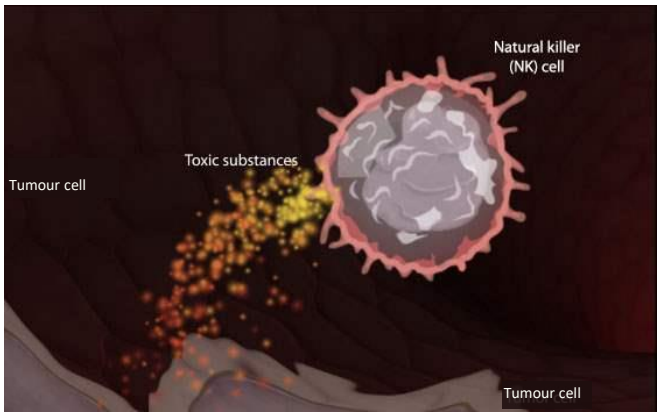
Antibodies (immunoglobulins)

Natural Killer Cells

Natural killer cells kill a wide variety of infected body cells and certain cancer cells

- A major component of innate immunity
- Bind to the target cell and release toxic substances that perforate the target cell's membrane causing it to burst open, in a process called **cytolysis**





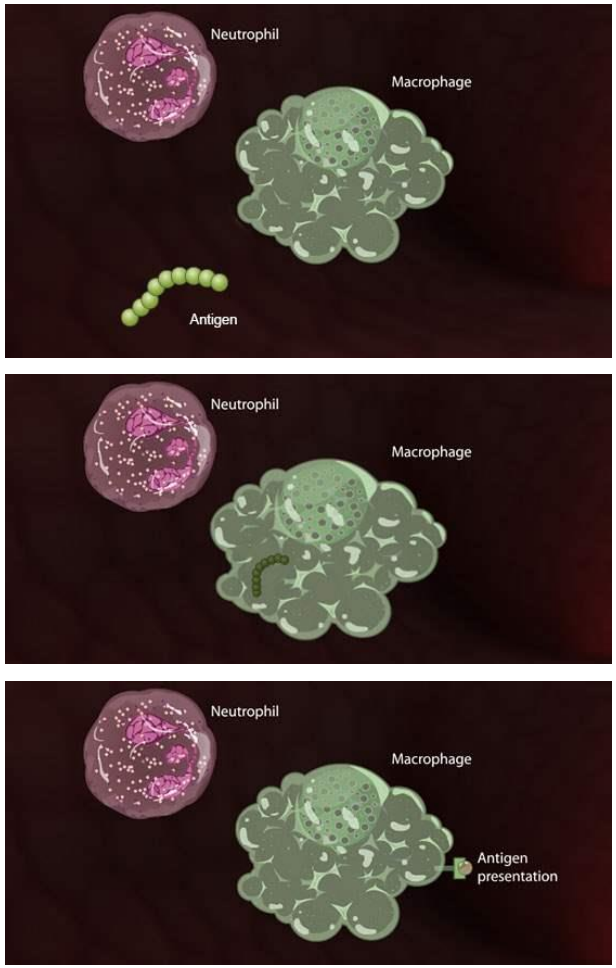
Cytolysis
Dissolution or destruction of living cells.

Phagocytes

Phagocytes engulf and digest pathogens and cellular debris

Include **neutrophils** and **macrophages**:

- Neutrophils arrive at the site of inflammation early, and recognise pathogens with broad specificity
- Macrophages in innate immunity:
  - Non-discriminately engulf invading agents and destroy them, in a process called **phagocytosis**
  - Can function as antigen-presenting cells by processing and presenting a portion of the antigens derived from the pathogens they ingest
  - Helper T cells recognise the antigen on the macrophage's surface as foreign, which is the first step in the adaptive immune response
- Macrophages in adaptive immunity:
  - Phagocytosis occurs again – this time in conjunction with antibodies and the complement system – to destroy specific antigens



Neutrophil
Most common white blood cell responsible for much of the body's protection against infection. Has a primary role in inflammation functioning as a phagocyte. Releases microbe-destroying enzymes when killed during inflammation.

Macrophage
Phagocytic cell that plays a key role in the body's defence against a broad range of pathogens and can serve as an antigen-presenting cell.

Phagocytosis
Process of ingestion and digestion by phagocytes of solid substances (e.g., microorganisms, foreign antigens, cell debris).

Complement System

Complement system enhances or "complements" immune response mechanisms

- Comprised of >30 proteins, synthesised in the liver, which are found in blood and body tissues
- Main proteins are numbered C1–C9, each with their own specific role in complement activation, such as: enhancing phagocytosis, binding to **mast cells** to trigger **histamine** release, recruiting phagocytes to sites of inflammation, and causing cytolysis
- Activated by three ways:
  - Antibodies binding to antigens (classical pathway; part of adaptive immunity)
  - Interactions with the surface of a microbe (alternative pathway; part of innate immunity)
  - Macrophages that digest microbes release chemicals that lead to the production of proteins from the liver called lectins; lectins bind to the surface of microbes, ultimately causing the activation of C3 (lectin pathway)
- Proceeds in a cascading fashion with sequential activation of the various proteins

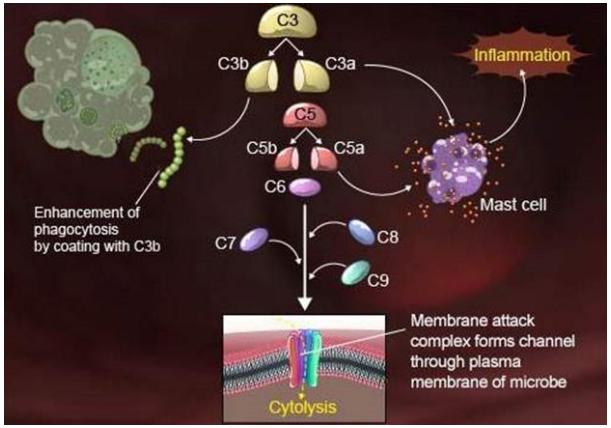


Image adapted from Tortora et al. 2012

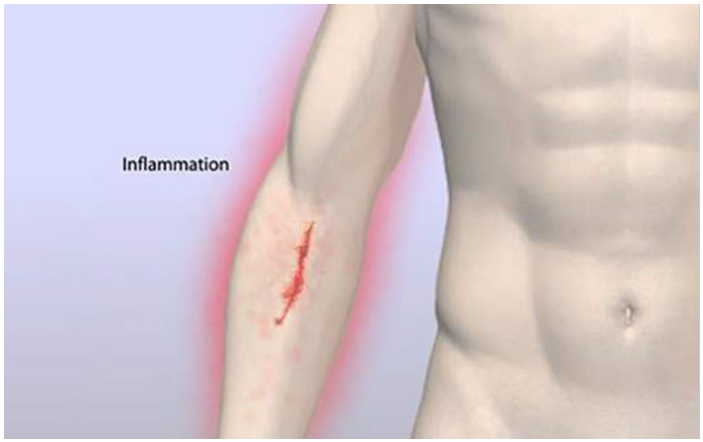
Mast cell
A large, non-circulating tissue cell covered in IgE that binds foreign antigens and stimulates degranulation. Releases mediators such as histamine from densely packed granules within the cytoplasm to produce type I hypersensitivity reactions.

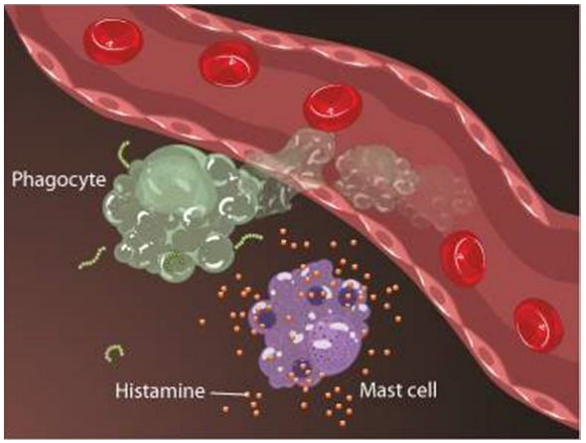
Histamine
A substance that causes dilation of blood vessels, increased gastric acid secretion, smooth muscle constriction (as in the bronchi), and mucus production, tissue swelling, and itching (during allergic reactions). Histamine is stored within mast cell granules.

Inflammation

Inflammation is the body's defensive response to tissue damage

- Characterised by redness, pain, heat, and swelling
- In response to injury, mast cells release histamine and **leukotrienes** that increase permeability of blood vessels
- Phagocytes are recruited to the site of injury and activated to kill invaders





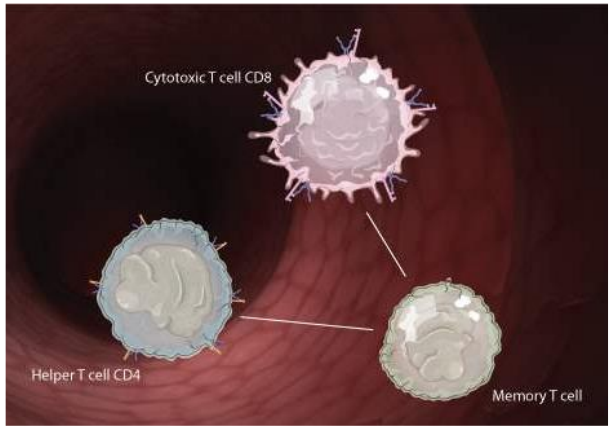
Leukotriene
Any of a group of chemical mediators of allergic reactions and inflammation all of which are synthesised by cells in response to inflammation or tissue injury.

T Cells

T cells are a type of lymphocyte that drive adaptive immunity (specifically, cell-mediated immunity)

Activation occurs through two signals:

- Binding to a specific antigen presented on the surface of an antigen-presenting cell (APC; e.g., macrophage)
- Co-stimulation with a cytokine and/or with pairs of plasma membrane molecules – one on the APC and one on the T cell, enabling the cells to adhere to one another



Once activated, T cells form a clone of cells that can later recognise the same antigen as the original T cells; T cells proliferate and differentiate into three types (helper T cells, cytotoxic T cells, and memory T cells):

- Helper T cells activate NK cells, B cells, and other T cells by producing cytokines that promote the growth and differentiation of these cells
  - e.g., helper T cells are involved in activating B cells to produce antibodies
- Cytotoxic T cells directly bind to and destroy antigen-bearing cells (especially virus-infected cells) by releasing chemicals that either disrupt the infected cell's membrane or trigger **apoptosis**
- Memory T cells remain after an immune response to a specific antigen and initiate a secondary response, differentiating into cytotoxic T cells, if the body is invaded again by a pathogen with the same antigen usually before there are any signs or symptoms of the disease

Apoptosis
Programmed cell death.

B Cells

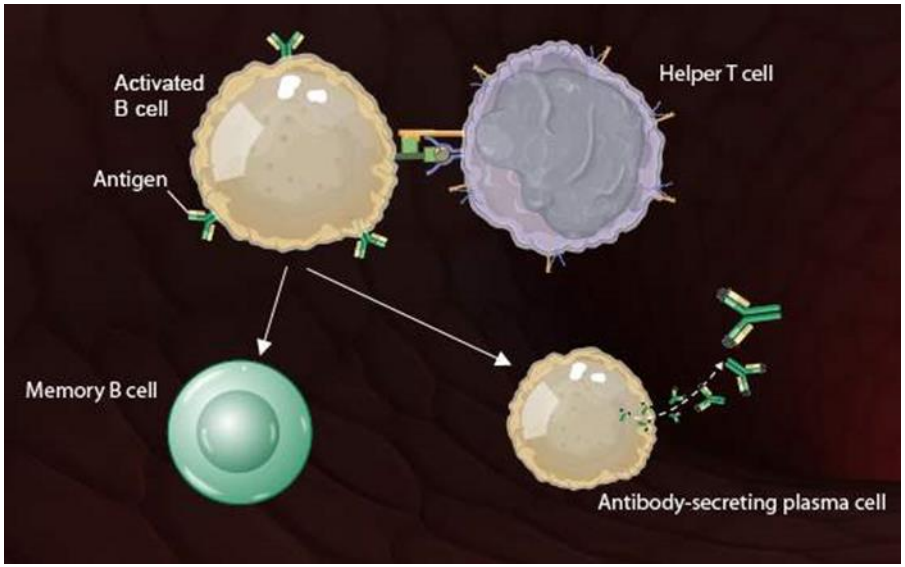
B cells are a type of lymphocyte that drives adaptive immunity (specifically, humoral immunity)

Activated by two ways:

- Helper T-cell-dependent (response more intense):
  - B cell takes in an antigen, processes it, and presents the processed antigen on its surface
  - Helper T cells recognise the processed antigen and release cytokines that complete the B cell's activation
- Helper T-cell-independent:
  - Certain unprocessed antigens recognise and bind to surface receptors of the B cell, triggering its activation
  - Cytokines are still required, but the B cells may receive these from sources such as macrophages

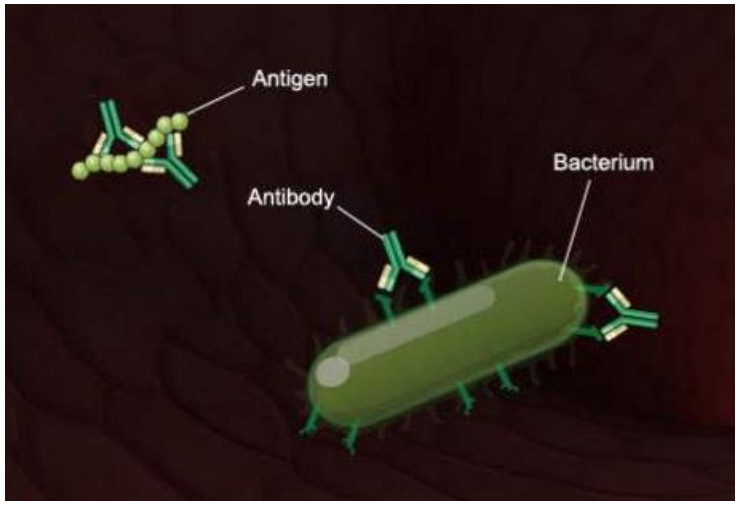
Once activated, B cells multiply and differentiate into:

- Plasma cells that produce antibodies (immunoglobulins)
  - B cell's specificity for a particular antigen is owed to the use of antibody molecules on its surface as receptors; the shape of the antigen binding site of its surface receptor dictates to which antigen the B cell will react
- Memory B cells
  - Remain inactive until they encounter the specific antigen for which they were created, triggering a rapid and strong secondary response



Antibodies (Immunoglobulins)

Antibodies are Y-shaped protein molecules found in three kinds of fluids: blood, lymph, and tissue fluids



- Bind to specific antigens on an invading cell or particle
  - Neutralise antigens
  - Target antigens for elimination by other immune responders, including complement proteins and phagocytes

KEY POINT

Antibodies are critical to the highly specific immune responses mounted by adaptive immunity. The fit between an antibody and antigen is very specific, like a lock and key.

Antibody Structure: IgG

Each class of antibody includes one or more Y-shaped components as part of their basic structure. Let's examine the structure of an IgG antibody, the class of antibody that predominates in the bloodstream.

Four chains:

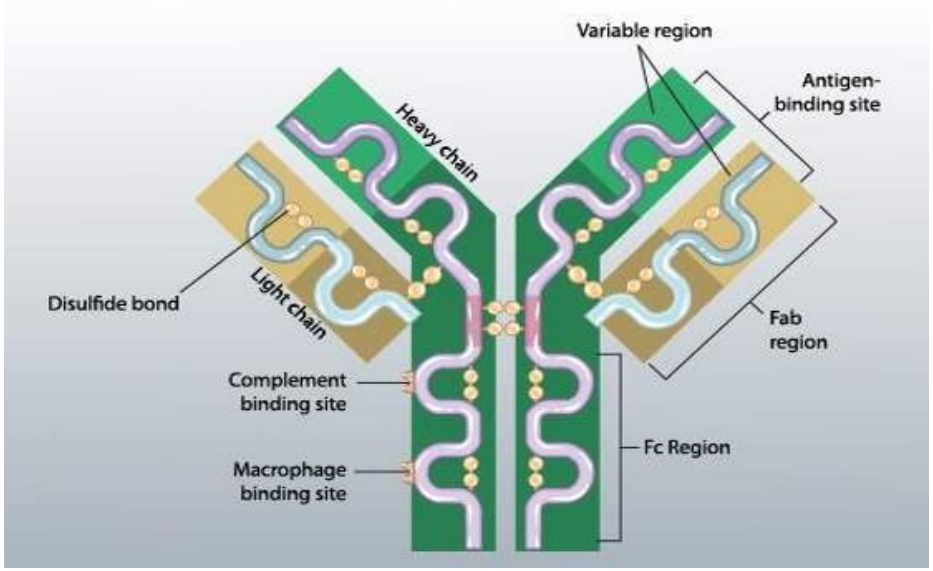
- Two identical heavy chains that are linked to two identical light chains
- Each chain has a variable region and a constant region

Antigen-binding fragment (Fab) region (two arms of the Y):

- Tip of each arm has an antigen-binding site, formed by the variable region
- Variable region is distinct for each kind of antibody and fits the shape of a specific antigen, like a key fits a lock

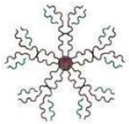
Fragment crystallisable (Fc) region (base of the Y):

- Includes constant regions of the heavy chains
- Constant region is similar within each antibody class and binds to various components of the immune system, depending on the class
- For IgG, the Fc region binds to Fc receptors on phagocytes and complement after the Fab region has bound its antigen



Classes of Antibodies

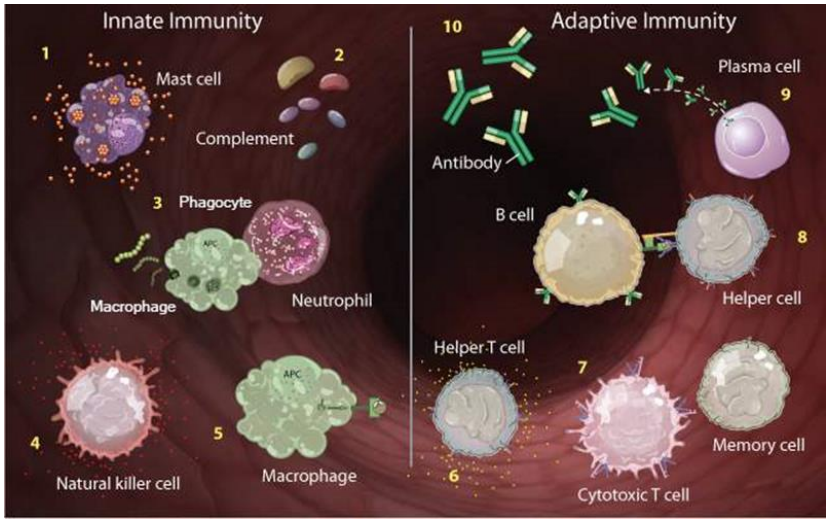
Let's now take a closer look at the other antibody classes. There are five main classes of antibodies, four of which are relevant to PI.

 **IgG**	• Most abundant type of antibody, accounts for 80% of antibodies in blood and is also found in lymph and the intestines • Four subclasses; deficiency in a subclass can be a factor when diagnosing PI • Passes from mother to foetus via the placenta, allowing immune protection in new-borns • Activates complement and binds to phagocytes
 **IgM**	• Accounts for 5–10% of antibodies in blood and is also found in lymph • Produced by B cells activated via the T-cell independent pathway • First type of antibody to be secreted by plasma cells after initial exposure to antigen • Activates complement
 **IgA**	• Accounts for 10–15% of antibodies in blood • Found mainly in sweat, tears, saliva, mucus, breast milk, and gastrointestinal secretions • Protects against infections of the respiratory tract and intestines
 **IgE**	• Accounts for 0.1% of antibodies in blood • Found on mast cells and **basophils** • Involved in allergic and hypersensitivity reactions • Protects against parasitic worms
 IgD	• Accounts for 0.2% of all antibodies in blood • Mainly found on surfaces of B cells as antigen receptors, and is involved in B cell activation

Basophil
White blood cell with granules which contain enzymes that promote inflammation.

Immune Response Summary

Innate immunity and adaptive immunity act both independently and cooperatively to protect against pathogens. We will now review the key elements of the immune system and their interactions.



1. Innate immune mechanisms provide an initial response to tissue damage. Once activated, the complement system causes mast cells to release histamines and other substances that contribute to the inflammatory response.
2. Complement activation leads to direct cell lysis, enhanced phagocytosis, and inflammation.
3. Phagocytes (neutrophils and macrophages) engulf and destroy pathogens.
4. NK cells release toxic substances causing cells to lyse.
5. Macrophages also present antigens to T cells (part of the adaptive immune response), leading to T-cell activation, followed by proliferation and differentiation.
6. Some activated T cells become helper T cells that produce cytokines which subsequently activate NK cells, B cells, and other T cells.
7. Other activated, T cells become cytotoxic T cells that destroy antigen-bearing infected cells. Others become memory T cells.
8. B cells bind antigens and present antigens to helper T cells. They develop into mature plasma cells or memory B cells.
9. Plasma cells secrete antibodies.
10. Antibodies bind to specific antigens on an invading cell or particle, neutralising them or targeting them for elimination by other immune responders – of both the innate and adaptive systems.

HERE IS THE CONNECTION

Antigen-antibody binding activates complement, leading to direct cell lysis, enhanced phagocytosis, and inflammation. In addition, after an antibody binds to an antigen, phagocytes bind to the Fc region of antibodies, facilitating destruction of the bound antigen.

PROGRESS CHECK

QUESTION ONE

Think about how you would complete the following question, then select the Check Your Answer button.

Define primary immunodeficiency.

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION ONE

Define primary immunodeficiency.

Primary immunodeficiency (PI) is an inborn (congenital) defect in which immune system components are missing or not working properly.

PROGRESS CHECK (CONT.)

QUESTION TWO

Think about how you would complete the following question, then select the Check Your Answer button.

Match each immune system term to the most appropriate description.

Provides immediate, nonspecific protection	
Recognises and reacts to specific reinvading antigens via immunological “memory”	
Lymphocytes encounter and react to a new antigen, mounting a relatively weak antibody response with a 5- to 7-day lag time	
Rapid, strong antibody response occurring upon re-exposure to a recognised antigen	
Activated after binding to a specific antigen presented on an APC; memory cells are involved in the secondary response	
Engulf, process, and present antigens	
Become plasma cells that secrete antibodies after being activated	

B cells
Adaptive immunity
Innate immunity
Macrophages
Primary response
T cells
Secondary response

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION TWO

Match each immune system term to the most appropriate description.

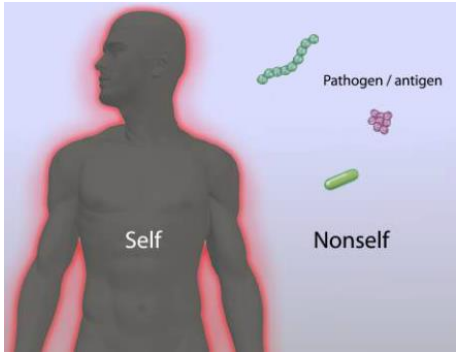
Provides immediate, nonspecific protection	**Innate immunity**
Recognises and reacts to specific reinvading antigens via immunological “memory”	**Adaptive immunity**
Lymphocytes encounter and react to a new antigen, mounting a relatively weak antibody response with a 5- to 7-day lag time	**Primary response**
Rapid, strong antibody response occurring upon re-exposure to a recognised antigen	**Secondary response**
Activated after binding to a specific antigen presented on an APC; memory cells are involved in the secondary response	**T cells**
Engulf, process, and present antigens	**Macrophages**
Become plasma cells that secrete antibodies after being activated	**B cells**

Module Summary

The Immune System

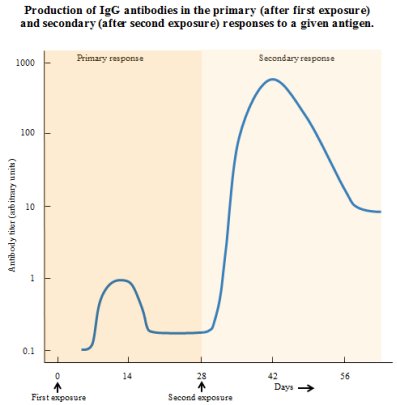
Overview

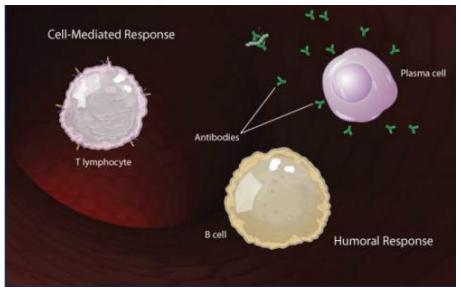
- Provides defence against pathogens by distinguishing “self” from “non-self”
- Consists of two main mechanisms:
  - Innate immunity: provides immediate, nonspecific protection; includes natural killer cells, phagocytes, complement proteins, and inflammation
  - Adaptive immunity: relies on immunological “memory” to recognise and react to specific reinvading antigens; includes T cells, B cells, and antibodies



Adaptive immunity

- Primary response:
  - First time lymphocytes encounter and react to a foreign antigen
  - Relatively weak antibody response with a 5- to 7-day lag time
- Secondary response:
  - Subsequent lymphocyte encounters with the same antigen
  - Much stronger antibody response with little or no lag time
- Cell-mediated immunity:
  - Particularly effective against intracellular pathogens such as bacteria, viruses, and fungi
  - Involves helper T cells that activate B cells and cytotoxic T cells that directly destroy pathogen-infected cells, and produces memory T cells
- Humoral immunity:
  - Works mainly against antigens in body fluids and extracellular pathogens such as bacteria, viruses, and fungi
  - Involves plasma cells that produce antibodies which bind to and disable pathogens, and produces memory B cells

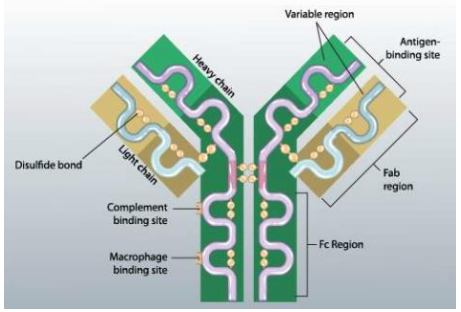




Module Summary (Cont.)

Antibodies

- Y-shaped protein molecules in blood, lymph, and tissue fluids
- Bind to specific antigens on invading pathogens, neutralising them or targeting them for elimination by other immune responders including complement proteins and phagocytic cells (neutrophils and macrophages)
- Fab region includes antigen-binding site; Fc region binds to various components of the immune system
- Antibody-antigen binding triggers subsequent phagocyte and complement activity to ultimately protect against infection and damage to body tissues



Primary Immunodeficiency

- Congenital defect in which immune system components are missing or not working properly
- Characterised by increased susceptibility to infections and sometimes malignancy or autoimmunity
- Encompasses >350 diverse diseases

GLOSSARY

Antibody
Immunoglobulin molecule produced by B lymphocytes (also known as B cells) that combines specifically with an antigen to destroy or control it.

Antigen
Any substance that is capable of activating an immune response or binding with an antibody.

Apoptosis
Programmed cell death.

Autoimmunity
Condition in which the body's ability to tolerate the antigens on its own cells is disrupted.

B cell
Type of lymphocyte that identifies antigens and differentiates into antibody-producing plasma cells or memory cells.

Basophil
White blood cell with granules which contain enzymes that promote inflammation.

Complement
A group of proteins in the blood that play a vital role in the body's immune defences through a cascade of interactions.

Cytokine
Any of more than 100 small proteins produced and released by cells that regulate immunological aspects of cell growth and function during both inflammation and immune responses.

Cytolysis
Dissolution or destruction of living cells.

Histamine
A substance that causes dilation of blood vessels, increased gastric acid secretion, smooth muscle constriction (as in the bronchi), and mucus production, tissue swelling, and itching (during allergic reactions). Histamine is stored within mast cell granules.

Immunity
Protection from diseases, especially from infectious diseases.

Inflammation
An immunological defence against injury, infection, or allergy, marked by increases in regional blood flow, immigration of white blood cells, and release of chemical toxins. Inflammation is one way the body uses to protect itself from invasion by foreign organisms and to repair wounds to tissue. Clinical hallmarks of inflammation are redness, heat, swelling, pain, and loss of function of a body part.

Leukotriene
Any of a group of chemical mediators of allergic reactions and inflammation all of which are synthesised by cells in response to inflammation or tissue injury.

Macrophage
Phagocytic cell that plays a key role in the body's defence against a broad range of pathogens and can serve as an antigen-presenting cell.

Mast cell
A large, non-circulating tissue cell covered in IgE that binds foreign antigens and stimulates degranulation. Releases mediators such as histamine from densely packed granules within the cytoplasm to produce type I hypersensitivity reactions.

Natural killer (NK) cell
A large granular lymphocyte that can react against and destroy cancer cells and virus-infected cells without prior sensitisation to it.

Neutrophil
Most common white blood cell responsible for much of the body's protection against infection. Has a primary role in inflammation functioning as a phagocyte. Releases microbe-destroying enzymes when killed during inflammation.

Pathogen
Any microorganism capable of producing disease.

Phagocytosis
Process of ingestion and digestion by phagocytes of solid substances (e.g., microorganisms, foreign antigens, cell debris).

T cell
Type of lymphocyte that responds to specific antigens with the assistance of antigen-presenting cells via cell-mediated immunity. May be further categorised by function as T helper cell or cytotoxic T cell.

REFERENCES

American Academy of Allergy, Asthma & Immunology. Primary Immunodeficiency Disease. https://www.aaaai.org/conditions-and-treatments/primary-immunodeficiency-disease. Accessed February 2022.

Birdsall H. Antibodies. In: Mandell G, Bennett J, Dolin RI, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 7th ed. Elsevier; 2009:59–75.

Bonilla FA, Bernstein IL, Khan DA, *et al.* Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol.* 2005;94(suppl 1):S1–S63.

Cooper MA, Pommering TL, Koranyi K. Primary Immunodeficiencies. *Am Fam Physician.* 2003;68:10:2001–8.

Hirayama D, Iida T, Nakase H. The phagocytic function of macrophage-enforcing innate immunity and tissue homeostasis. *Int J Mol Sci.* 2018;19(1):92. doi: 10.3390/ijms19010092.

Kumar V, Abbas AK, Fausto N, Aster JC. Diseases of the Immune System. Robbins and Cotran Pathological Basis of Disease, Professional Edition. 8th ed. Philadelphia, PA: Saunders, An Imprint of Elsevier; 2009.

Paul S, Lal G. The molecular mechanism of natural killer cells function and its importance in cancer immunotherapy. *Front Immunol.* 2017;8:1124. doi: 10.3389/fimmu.2017.01124.

Picard C, Gaspar HB, Al-Herz W, *et al.* International Union of Immunological Societies: 2017 primary disease committee report on inborn errors of immunity. *J Clin Immunol.* 2018; 38:96–128.

Quinley ED. Immunohematology Principles and Practice. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1998.

Taber's Medical Dictionary. https://www.tabers.com/tabersonline. Accessed February 2022.

ThermoFisher Scientific. Antibody Fragmentation. https://www.thermofisher.com/ca/en/home/life-science/antibodies/antibodies-learning-center/antibodies-resource-library/antibody-methods/antibody-fragmentation.html#ab-igg. Accessed February 2022.

Tortora GJ, Derrickson B. Principles of Anatomy and Physiology. 13th ed. Hoboken, NJ: John Wiley & Sons Inc.; Biological Science Textbooks, Inc., and Bryan Derrickson; 2012.