The Immune System

A Comprehensive Overview

Cells Genetics Defense Memory

Dr KEHILI H.E

Introduction to the Immune System

What is the Immune System?

The immune system is a sophisticated network of cells, tissues, and organs dedicated to safeguarding the body from infections and diseases. It employs a dual defense mechanism to protect against pathogens.

Innate Immunity

Provides a rapid, non-specific defense as the first line of protection.

Adaptive Immunity

Offers a specific defense with immune memory for targeted and efficient response upon re-exposure.

Key Structures

Primary Lymphoid Organs

Bone Marrow and Thymus

Secondary Lymphoid Organs

Lymph Nodes, Spleen, MALTs

Antigen-Presenting Cells

Dendritic Cells, Macrophages, B Lymphocytes

The immune system works through a complex interplay of these components to provide comprehensive protection against pathogens while maintaining tolerance to self-antigens.

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Dual Defense Mechanisms

The body's defense against pathogens is orchestrated through two primary mechanisms working together:

Innate Immunity

Provides a rapid, non-specific defense as the first line of protection.

- **Rapid Response:**Immediate action without prior exposure
- **Non-specific:**Targets pathogens based on general patterns
- **Inflammation:**Heat, redness, swelling at infection site
- **Barriers:**Skin, mucous membranes, stomach acid

Adaptive Immunity

Offers a specific defense with immune memory for targeted and efficient response upon re-exposure.

- **Specific Recognition:**Targets pathogens based on unique antigens
- **Delayed Response:**Takes time to recognize and respond
- **Immune Memory:**Retains information for faster response to re-exposure
- **Maturation:**Involves development of T and B lymphocytes

Integration: These two defense mechanisms work together, with innate immunity providing immediate protection while adaptive immunity develops a targeted response that provides long-lasting immunity.

Key Structures of the Immune System

The immune system is organized into three main structural components that work together to provide comprehensive protection against pathogens.

Primary Lymphoid Organs

- **Bone Marrow:**Hematopoiesis and B lymphocyte maturation
- **Thymus:**T lymphocyte maturation and selection

Site of immune cell development

Secondary Lymphoid Organs

- **Lymph Nodes:**Filter lymph and initiate immune responses
- **Spleen:**Blood filtration and immune response
- **MALTs:**Located in mucous membranes

Sites where adaptive immune responses are executed

Antigen-Presenting Cells

- **Dendritic Cells:**"Sentinels" that activate T cells
- **Macrophages:**Phagocytosis and antigen presentation
- **B Lymphocytes:**Capture and present antigens

Cells that initiate adaptive immunity

Integration: These three components work together in a coordinated manner, with primary organs producing immune cells, secondary organs housing immune responses, and APCs activating the adaptive immune system.

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Primary Lymphoid Organs: Development and Maturation

Primary lymphoid organs are critical for the genesis and maturation of immune cells, ensuring they acquire the necessary capabilities to recognize and combat pathogens. These organs provide the foundation for the adaptive immune response.

Bone Marrow

- Vital organ for hematopoiesis and B lymphocyte maturation
- Found within long and flat bones (femur, sternum)
- Contains hematopoietic stem cells that differentiate into various immune cell lines

The Thymus

- Crucial organ for the maturation of T lymphocytes
- Bilobed structure in the anterior mediastinum
- Contains distinct microanatomical regions for T cell development

Primary Lymphoid Organs Functions

- Immune cell production
- Cell maturation
- Self-tolerance development

Bone Marrow: Structure and Function

Bone Marrow Overview

Location

Soft tissue found within long and flat bones (e.g., femur, sternum)

Types

- **Red Bone Marrow:**Active in blood cell production, predominant in children and specific adult bones
- **Yellow Bone Marrow:**Primarily adipose tissue, serving as an energy reserve, convertible to red marrow when needed

Key Functions

- **Hematopoiesis:**Main site for production of all blood cells, including immune cells
- **B Lymphocyte Production:**B cells are produced and mature here, crucial for adaptive immunity
- **Hematopoietic Stem Cell Storage:**Contains pluripotent stem cells that differentiate into various immune cell lines

Bone Marrow Structure

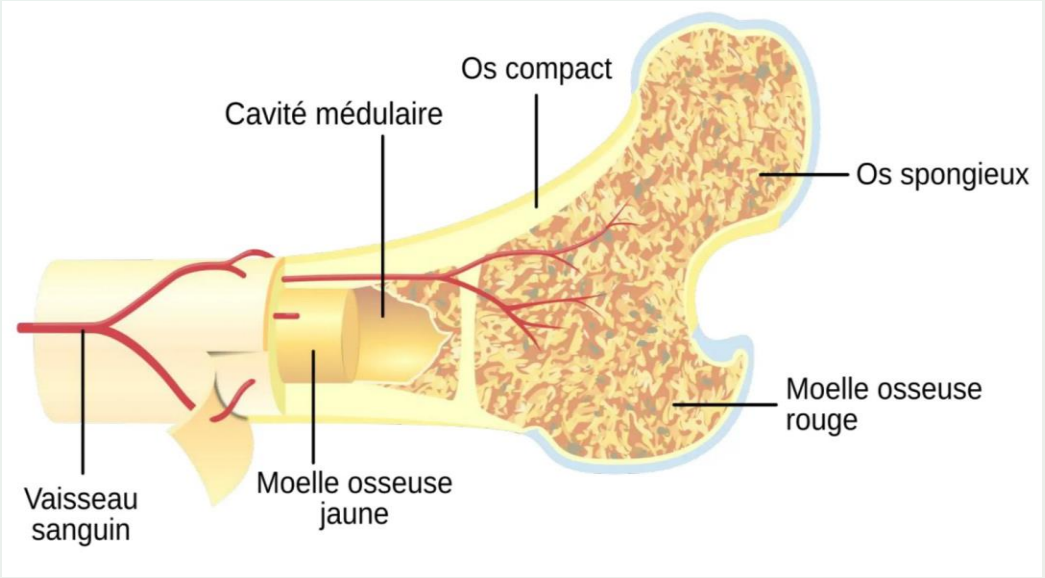

Figure 1. Bone Marrow structure

Long bone cross-section showing bone marrow structure. Red bone marrow (active) and yellow bone marrow (adipose) are labeled.

Clinical Note: Disorders of bone marrow (leukaemia, spinal cord aplasia, multiple myeloma) can severely impact immunity and blood cell production.

The Thymus: Anatomy and Function

Thymus Location & Macroscopic Anatomy

Location
Bilobed organ in the anterior mediastinum, behind the sternum.

Shape & Size
Bilobal structure, large in children (10-15g at birth, up to 30-40g at puberty), atrophies with age.

Color
Pinkish in young children, yellowish in adults due to adipose tissue.

Position
Extends from the thyroid cartilage to the fourth rib, close to vital structures like the heart and large vessels.

Vascularization & Innervation

Primarily by branches of the internal thoracic and lower thyroid arteries

Receives autonomic nerve fibers from the sympathetic system

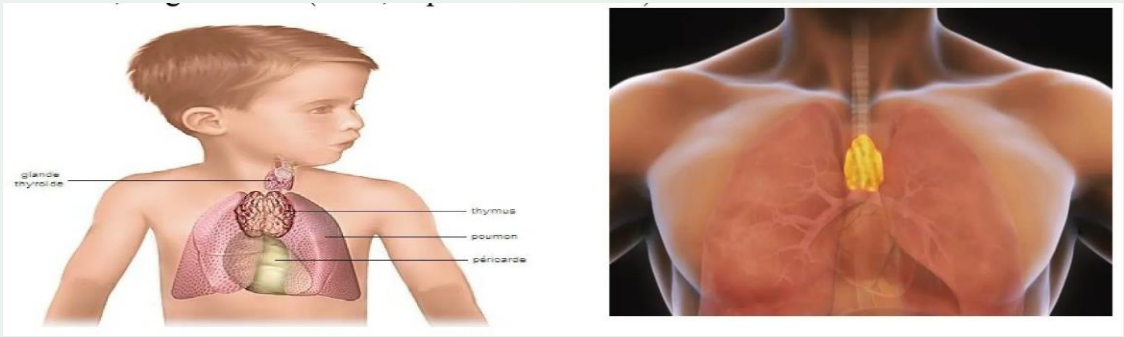

Figure 2. Thymus localization

Functions & Significance

T Cell Maturation
Immature T cells (thymocytes) migrate here for differentiation.

Positive Selection
Selects T cells that recognize the body's own Major Histocompatibility Complex (MHC) molecules.

Negative Selection
Eliminates T cells that overreact to self-molecules, preventing autoimmune reactions.

Age-related Involution
The thymus gradually reduces in size and function with age, with lymphoid tissue replaced by adipose tissue.

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Thymus Microscopic Structure

The thymus is encased by a connective tissue capsule with septa subdividing it into lobules. Each lobule has distinct regions with different functions:

Cortex (External Area)

Rich in immature T lymphocytes (thymocytes) that proliferate and undergo selection. Also contains epithelial cells and macrophages.

Medulla (Internal Area)

Less dense, contains more mature thymocytes and thymic epithelial cells. Features Hassall's corpuscles, potentially involved in eliminating defective T lymphocytes.

Developmental Gradient: Thymocytes mature from immature (cortex) to mature (medulla) during their transit through the thymus.

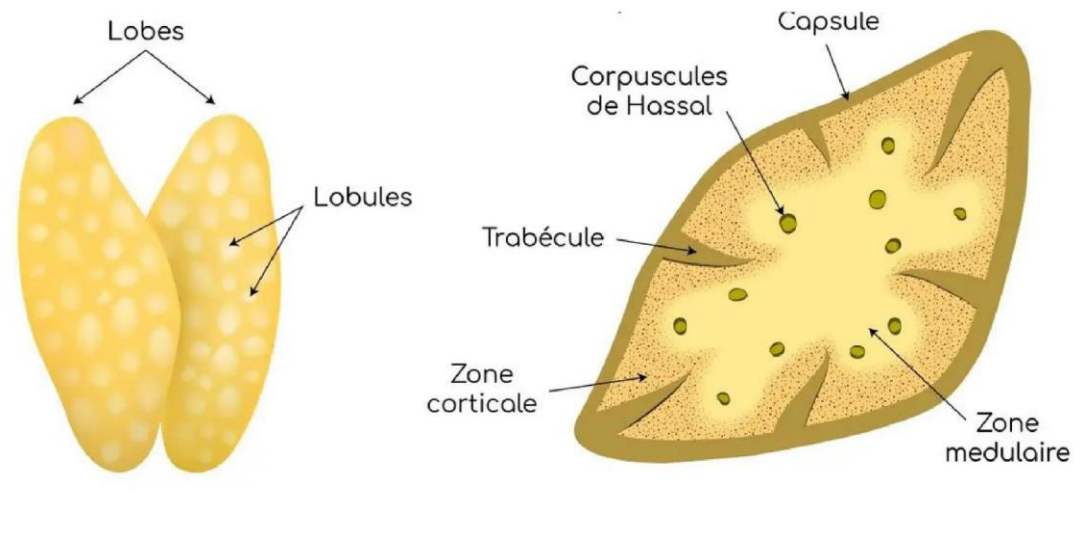

Figure 3. Thymus structure showing lobes, capsules, trabeculae, and Hassall's corpuscles

Clinical Significance: The microscopic structure of the thymus is critical for understanding T cell development and immune function.

T Cell Selection in the Thymus

The thymus ensures only functional and self-tolerant T cells populate lymphoid organs through a two-stage selection process.

Positive Selection

Selects T cells that recognize the body's own MHC molecules.

- Immature T cells (thymocytes) migrate to the thymus
- Undergo proliferation and differentiation

1-3 days

Negative Selection

Eliminates T cells that overreact to self-molecules.

- T cells that recognize self-antigens with high affinity
- Undergo apoptosis, preventing autoimmune reactions

Outcome: Functional and Self-Tolerant T Cells

Functional T Cells

- Activated upon encountering pathogens
- Release cytokines and kill infected cells

Self-Tolerant T Cells

- Do not attack normal self-tissues
- Prevent autoimmune diseases

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Secondary Lymphoid Organs: Immune Response Hubs

What are Secondary Lymphoid Organs?

Secondary lymphoid organs are crucial sites where adaptive immune responses are initiated and executed. They serve as strategic meeting points for immune cells and antigens, functioning as the command centers of the adaptive immune system.

Key Functions

Immune Cell Meeting Points

Serve as strategic locations where B and T lymphocytes interact with antigens and APCs.

Antigen Detection

Monitor for pathogens that have entered the body through breaks in the primary defense.

Immune Response Initiation

Trigger specific adaptive immune responses upon antigen recognition.

Lymph Nodes

Small bean-shaped organs distributed throughout the body, filtering lymph and initiating immune responses.

The Spleen

Vital organ in the upper left abdomen, filtering blood and serving as a secondary lymphoid organ.

Mucosa-Associated Lymphoid Tissue (MALT)

Disseminated lymphoid tissues in mucous membranes, providing immune surveillance at body surfaces.

Lymph Nodes: Structure and Location

Strategic Location

Neck (Cervical Nodes)
Filters lymph from the head and neck regions

Armpits (Axillary Nodes)
Monitors lymph from the upper limbs

Groin (Inguinal Nodes)
Filters lymph from the lower limbs

Abdomen and Thorax
Contains mesenteric and mediastinal nodes

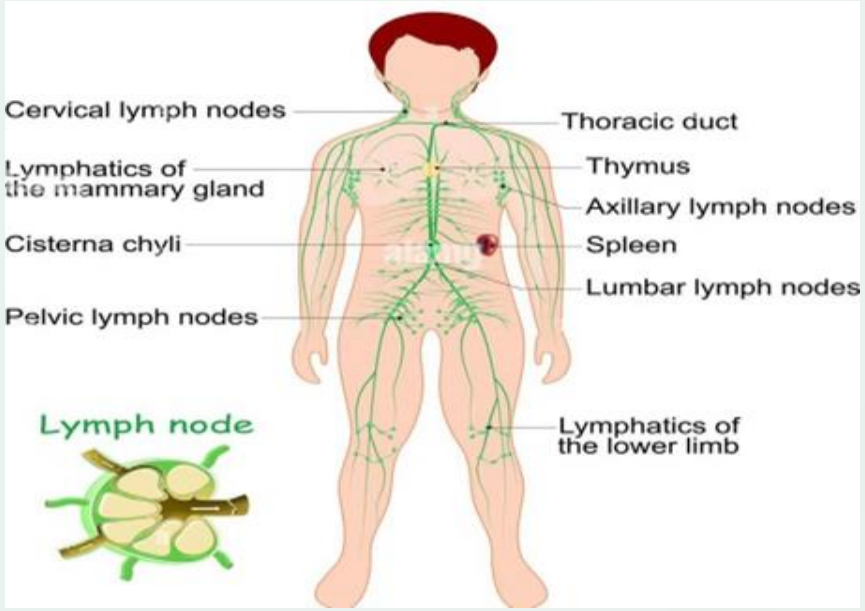

Figure 4. Lymphatic system localization in the human body

Complex Structure

Capsule
External connective tissue envelope, sending trabeculae to subdivide the node

Cortex
Outer layer with lymphoid follicles rich in B lymphocytes, where B cells activate and differentiate

Paracortex
Between cortex and medulla, primarily houses T lymphocytes, where they interact with APCs

Medulla
Central area containing macrophages, plasma cells, and lymphocytes, filtering lymph before exit

Key Measurements
Lymph nodes typically measure 1-25 mm in diameter

Lymph nodes are strategically placed to intercept pathogens at likely entry points, making them crucial hubs for immune response initiation.

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Lymphatic Circulation in Lymph Nodes

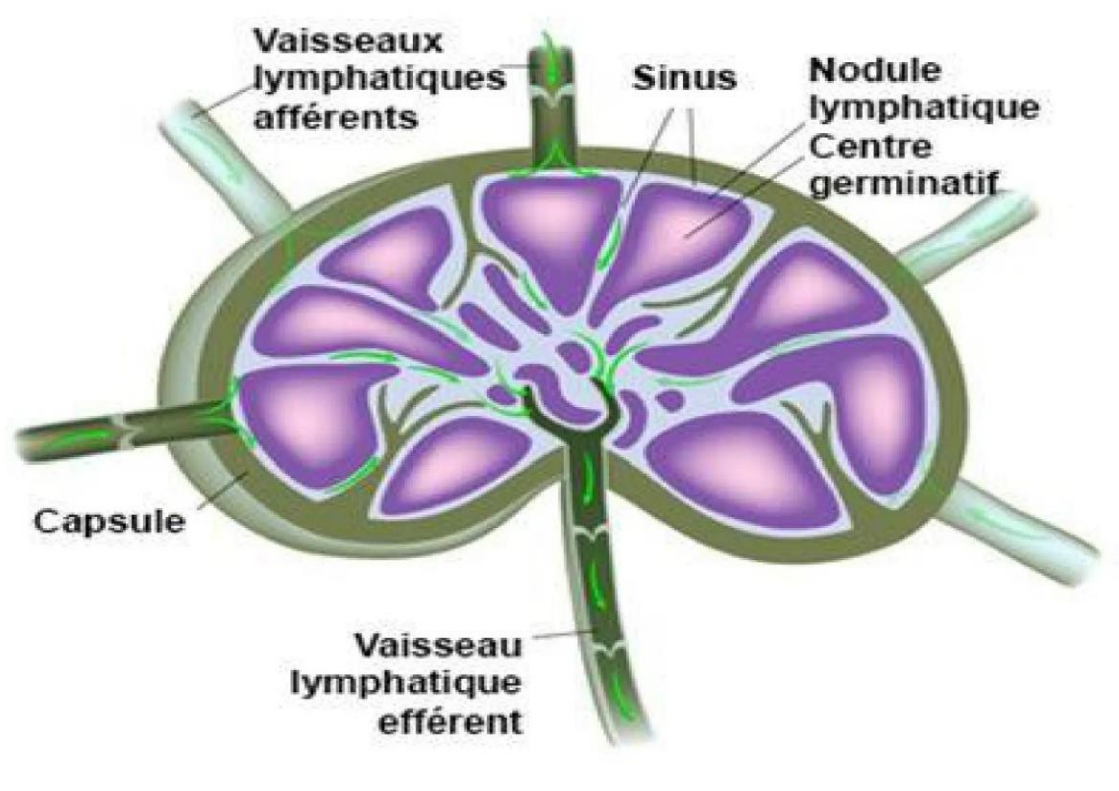

Figure 5. Lymphatic circulation in the lymph node, showing afferent vessels, filtration zones, and efferent vessels.

Lymphatic Flow Process

Lymph Entry

Multiple afferent lymph vessels bring lymph (carrying debris, pathogens, immune cells) into the node.

Filtration and Monitoring

- **Subcapsular Sinus:**First filtration zone, slowing lymph flow for macrophage interaction.
- **Cortical Sinuses:**Lymph flows through B lymphocyte-rich areas, stimulating responses if antigens are detected.
- **Medullary Sinuses:**Deepest channels for final lymph check by macrophages and lymphocytes before exit.

Lymph Outlet

Filtered lymph exits via one or two efferent lymph vessels at the hilum, flowing to other nodes or returning to the bloodstream.

Importance of Lymphatic Circulation

- Intercepts pathogens before deeper penetration
- Activates immune cells upon foreign antigen detection
- Maintains body fluid balance by returning lymph to bloodstream

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The Spleen: Structure and Function

Location

Upper left abdomen, below the diaphragm and to the left of the stomach.

Protected by the rib cage.

Structure

- **Oval-shaped**: About 12 cm long, 150-200g in weight
- **Surrounded by**: Dense fibrous capsule
  - **Red Pulp** : Contains blood-filled sinusoids
  - **White Pulp** : Lymphocytes surrounding arteries

Functions

Blood Filtration

Removes aged/damaged red blood cells and dysfunctional blood cells.

Immune Response

Detects circulating antigens, activates lymphocytes, stimulates antibody production.

Blood Element Storage

Stores platelets (released during injury/hemorrhage) and red blood cells.

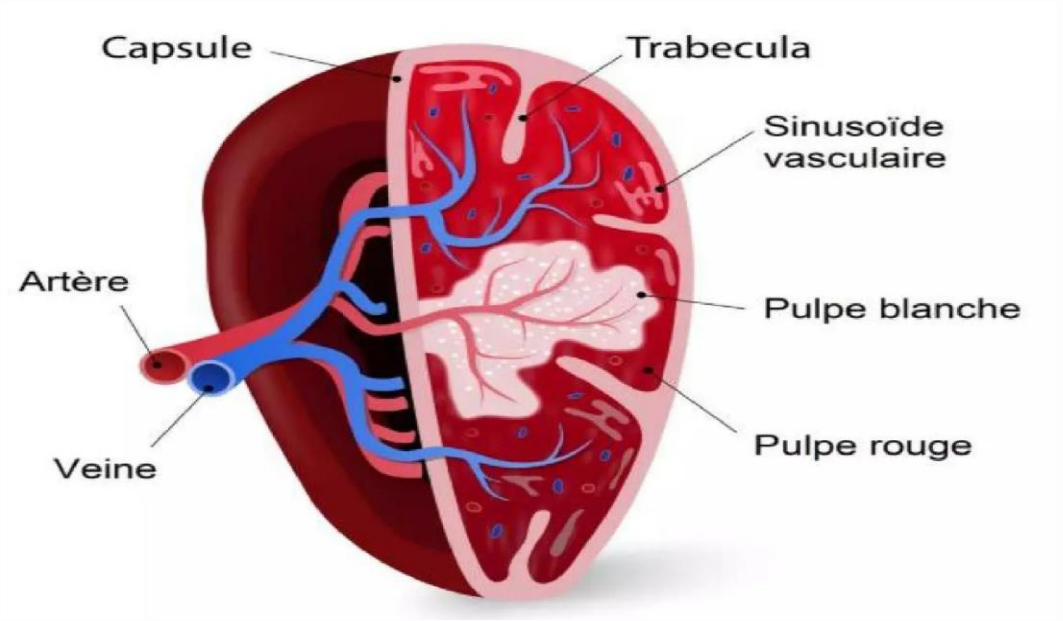

Figure 6. Structure of the spleen, showing the capsule, trabeculae, arteries, veins, vascular sinusoids, white pulp, and red pulp.

Clinical Note: The spleen is often removed (splenectomy) in certain conditions like splenomegaly or asplenia, which can lead to increased susceptibility to certain infections.

Blood Circulation in the Spleen

Unique Circulation System

The spleen has a unique blood circulation that allows close interaction between blood and lymphoid tissue, essential for immune function and blood filtration.

1 Blood Entry

Via splenic artery, branching into central arterioles passing through white pulp.

2 Blood Filtration

Blood enters red pulp from central arterioles, passing through sinusoids where macrophages check blood cells. Damaged red blood cells are phagocytosed.

3 Blood Outflow

Filtered blood exits via splenic veins, joining systemic circulation via the hepatic portal vein.

Open vs. Closed Circulation

Open Circulation: Blood released into red pulp's open spaces for maximum macrophage interaction.

Closed Circulation: Blood flows directly from capillaries to sinusoids, limiting macrophage exposure.

Visual Representation

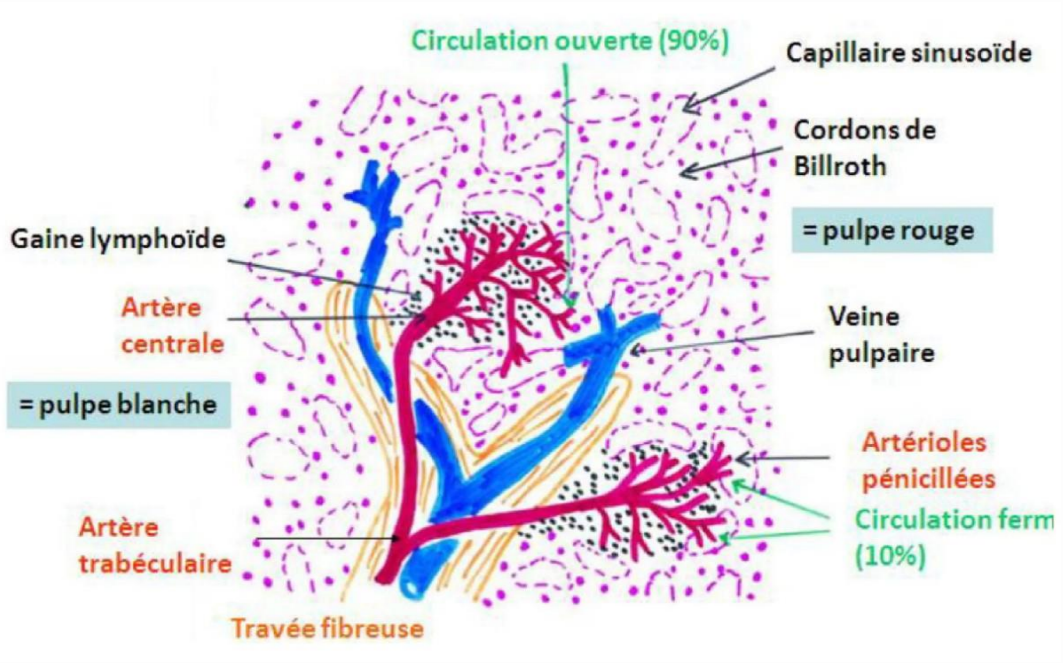

Figure 7. Blood circulation in the spleen, showing the unique pathway and interaction between blood and lymphoid tissue.

Key Insight: This unique circulation system allows for efficient blood filtration while maintaining close contact between blood cells and immune cells, optimizing the spleen's dual functions in blood regulation and immune response.

Mucosa-Associated Lymphoid Tissue (MALT)

Strategic Immune Defense

MALT is a critical component of the immune system, located in mucous membranes to defend against pathogens in these exposed regions. It forms an immune barrier at environmental interfaces.

MALT Variants

GALT (Gut-Associated Lymphoid Tissue)
Digestive tract (Peyer's patches, lymphoid follicles, appendix)

BALT (Bronchus-Associated Lymphoid Tissue)
Respiratory tract (mainly bronchi)

NALT (Nasal-Associated Lymphoid Tissue)
Nasal cavity (tonsils, adenoids)

TALT (Tonsil-Associated Lymphoid Tissue)
Tonsil region (around the throat)

MALT Strategic Locations

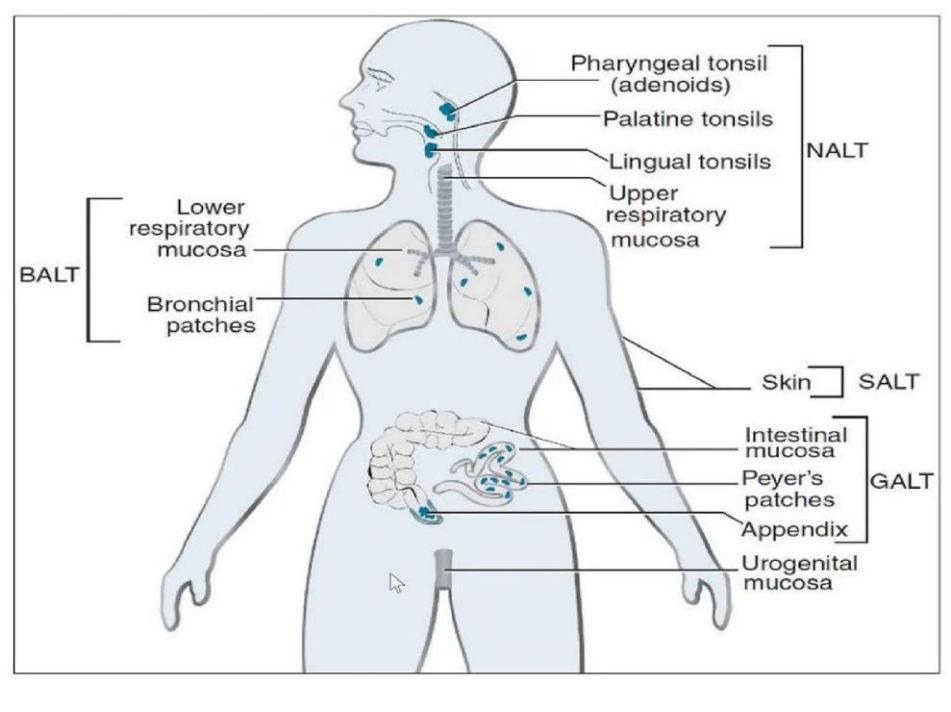

Figure 8. MALT location.

These tissues act as an immune barrier in areas of direct contact with the external environment, providing immediate defense against pathogens.

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MALT Structure and Function

Lymphoid Structure

Lymphoid Follicles

Organized structures where B lymphocytes reside, forming the basis of humoral immunity. Contain germinal centers for B cell proliferation and differentiation.

Immune Cells

- **T-cells:**Orchestrate cellular immune response
- **Macrophages and Dendritic Cells:**Capture and present antigens
- **M Cells:**In Peyer's patches, capture intestinal antigens

T-zones and B-zones

Organized areas for T and B lymphocytes, promoting coordinated responses and antigen-specific immunity.

Key Functions

Immune Surveillance

Detects antigens (bacteria, viruses, toxins) entering via respiratory, digestive, and urogenital tracts. M cells facilitate antigen presentation to underlying immune cells.

Antibody Production

Activated B cells produce antibodies, mainly IgA, secreted into mucous membranes to neutralize pathogens at mucosal surfaces.

Balance with Commensal Flora

In the digestive tract, MALT helps maintain gut microbiota balance, tolerating beneficial bacteria while responding to pathogens.

Clinical Significance: MALT dysfunction is linked to inflammatory bowel disease, malabsorption, and increased susceptibility to mucosal infections.

Antigen-Presenting Cells: Introduction

What are Antigen-Presenting Cells (APCs)?

Antigen-presenting cells (APCs) are specialized immune cells that capture, process, and present pathogen fragments (antigens) on their surface to activate the adaptive immune response. They serve as a bridge between the innate and adaptive immune systems.

Dendritic Cells

Act as "sentinels" in tissues, detecting pathogens and initiating T cell responses. They are highly efficient at capturing and presenting antigens.

Macrophages

Present in tissues, maintaining homeostasis by phagocytosing pathogens and dead cells. They also present antigens to activate adaptive immunity.

B Lymphocytes

Primary APCs for adaptive immunity, presenting antigens to T cells via MHC class II molecules. They are crucial for activating memory B cells.

Key Functions of APCs

Antigen Recognition

Pattern recognition receptors detect pathogen-associated molecular patterns (PAMPs).

Antigen Processing

Internalize pathogens and degrade them into peptide fragments suitable for presentation.

Antigen Presentation

Load peptides onto MHC molecules and present them on the cell surface for T cell recognition.

Immune Activation

Coordinate T cell activation, proliferation, and differentiation to mount a specific immune response.

Dendritic Cells: The Professional Sentinels

Dendritic cells are crucial for activating the adaptive immune response, acting as "sentinels" that detect and capture pathogens to activate T cells.

Types of Dendritic Cells

Myeloid Dendritic Cells
Found in blood, skin (Langerhans cells), and lymphoid organs

Plasmacytoid Dendritic Cells
Produce large amounts of type I interferons in response to viral infections

Monocyte-Derived Dendritic Cells
Differentiate from monocytes during infection or inflammation

Key Characteristics

- Highly specialized for pathogen detection through pattern recognition receptors
- Capture, process, and present pathogen fragments (antigens) on their surface
- Essential for alerting immune cells and coordinating specific responses

Dendritic Cell Structure

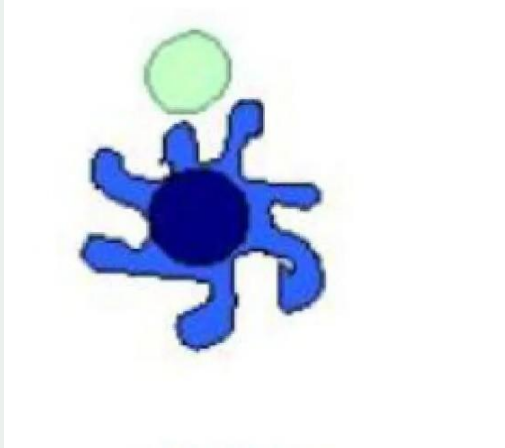

Figure 9. Dendritic cell

Dendritic cells are characterized by their unique appearance with numerous branching protrusions that help them capture and process antigens.

Clinical Significance: Dendritic cells are crucial for linking innate and adaptive immunity, their dysfunction can lead to immune disorders including allergies and autoimmune diseases.

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Dendritic Cell Receptors and Function

Pattern Recognition Receptors

- **TLRs:**Recognize microbial components (LPS, viral RNA)
- **CLRs:**Recognize carbohydrates on pathogens
- **NLRs:**Detect intracellular signals from bacteria

Opsonin Receptors

- **Fc Receptors:**Bind to antibodies on antigens
- **Complement Receptors:**Recognize complement protein fragments coating pathogens

Additional Receptors

- **Chemokine Receptors:**CCR7 for lymph node migration
- **Co-stimulation Molecules:**CD80, CD86 for T cell activation
- **Antigen Uptake Receptors:**Transferrin and scavenger receptors

Antigen Recognition, Uptake and Presentation Process

Antigen Recognition

TLRs and CLRs detect pathogens

NLRs sense danger signals

Antigen Uptake

Pseudopods engulf target

Form phagosome with lysosome

Antigen Presentation

MHC Class I: Intracellular antigens

MHC Class II: Extracellular antigens

Key Insight: Dendritic cell receptors work in an integrated pathway to capture, process, and present antigens to T cells, bridging innate and adaptive immunity.

Dendritic Cell Maturation and Migration

The Journey of Dendritic Cells

Antigen Uptake

Immature DCs capture antigens in peripheral tissues through various receptors.

Dendritic Cell Maturation

After antigen capture, DCs mature, modifying surface molecule expression, especially MHC molecules.

Migration to Lymph Nodes

Mature DCs migrate to lymph nodes via afferent lymphatic vessels.

Antigen Presentation

In lymph nodes, DCs present antigen fragments to T cells using MHC molecules.

Visual Representation

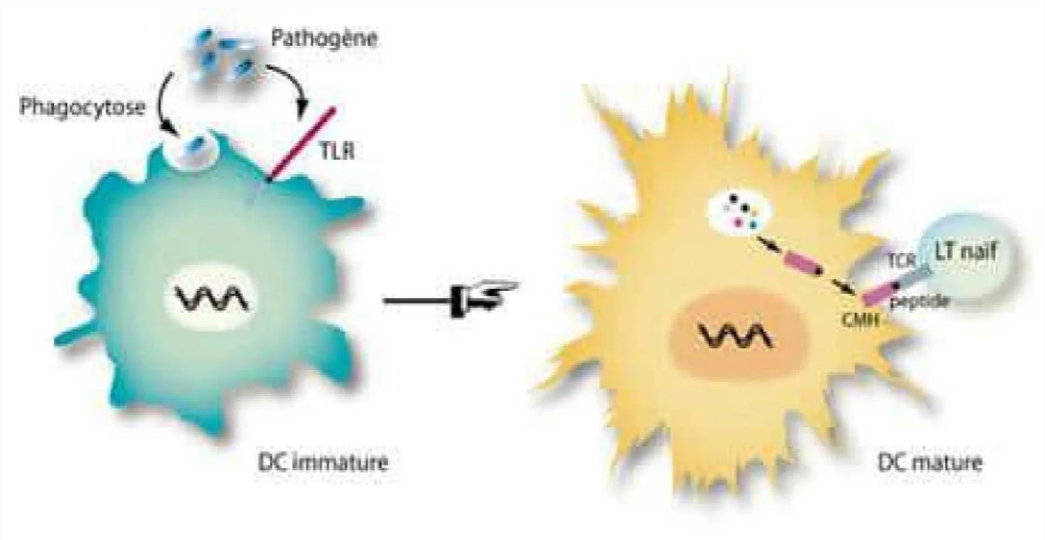

Figure 10. Dendritic cell maturation

Key Insight: The maturation of dendritic cells is a critical link between the innate and adaptive immune responses, bridging early detection of pathogens with the development of specific immune memory.

Macrophages: Origin and Function

Origin and Development

From Monocytes to Macrophages

- Origin: Monocyte precursor cells produced in bone marrow
- Development: Monocytes migrate to tissues and differentiate into macrophages
- Lifespan: Can live for months or years in tissues

Tissue-Specific Forms

Kupffer Cells
Liver

Microglial Cells
Brain

Macrophages are part of the innate immune system, present in tissues to detect, phagocytose, and destroy pathogens or dead cells, maintaining tissue balance.

Key Roles of Macrophages

Phagocytosis

Ingest and digest pathogens and dead cells, eliminating immediate threats

Antigen Presentation

Expose pathogen fragments on surface to stimulate T cells, activating adaptive immunity

Cytokine Secretion

Produce cytokines to regulate and activate other immune cells, coordinating responses

Tissue Repair

Contribute to healing and regeneration by producing growth factors

Macrophage Types

M1 (Pro-inflammatory)
Activated during infections

M2 (Anti-inflammatory)
Involved in inflammation resolution

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Macrophage Receptors and Phagocytosis

Macrophage Receptors

Pattern Recognition Receptors (PRRs)

Detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)

- **Toll-Like Receptors (TLRs):**Recognize microbial components
- **Nod-Like Receptors (NLRs):**Detect intracellular signals from bacteria

Receptors for Opsonins

Facilitate recognition and ingestion of protein-coated pathogens

- **Fc Receptors (FcR):**Bind to antibodies attached to antigens
- **Complement Receptors (CRs):**Recognize complement protein fragments

Chemokine Receptors

Important for migration from peripheral tissues to lymph nodes

- **CCR7:**Essential for DC migration to lymph nodes after antigen capture

Phagocytosis Process

1. **Pathogen Recognition and Attachment**
   Macrophage receptors recognize targets through PAMPs or opsonins
2. **Internalization (Phagosome)**
   Macrophage emits pseudopods to engulf the particle, forming an intracellular phagosome
3. **Phagolysosome Formation**
   Phagosome fuses with lysosomes to form a phagolysosome, rich in digestive enzymes
4. **Degradation of Phagocytic Material**
   Lysosomal enzymes degrade pathogen components, and toxic molecules (ROS, NO) are produced
5. **Presentation of Antigens**
   Pathogen fragments loaded onto MHC Class II molecules and presented on the macrophage surface

Role in Immune Regulation: Phagocytosis maintains tissue homeostasis, resolves inflammation, and activates adaptive immune responses by presenting antigens to T cells.

B Lymphocytes as Antigen-Presenters

Unique Role in Antigen Presentation

High Specificity

B cells selectively present antigens recognized by their BCR, unlike dendritic cells which present a wide range.

Effective Humoral Response

Facilitates B cell activation, immunoglobulin class switching, and memory B cell formation.

Memory B Cells

Serve as APCs during re-infection, reacting more quickly and efficiently due to immunological memory.

> *B cells are crucial for the adaptive immune response, providing a link between innate and adaptive immunity.*

Antigen Presentation Process

Antigen Uptake

BCR recognizes and internalizes specific antigens via endocytosis.

Antigen Processing

Antigen degraded into peptides in phagosomes/endosomes.

Presentation on MHC-II

Peptides loaded onto MHC-II molecules and transported to B lymphocyte surface.

T-Cell Activation

Activated T cells (CD4+) interact with MHC-II complexes, triggering cytokine release and B cell differentiation.

B Lymphocyte Surface Receptors

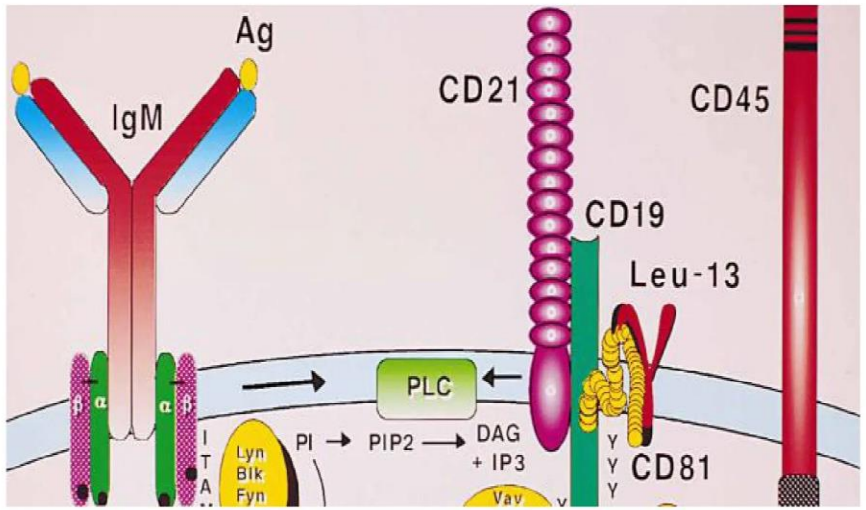

Figure 11. B-cell receptors.

Function Overview

- Recognize and internalize antigens
- Activate B cells through signaling pathways
- Promote interaction with T cells
- Support immune complex formation

Key Receptor Types

B-Cell Receptor (BCR)

Membrane-bound antibody (IgM/IgD) that recognizes foreign antigens.

Structure: Two heavy and two light chains.

Co-receptor Molecules

Amplify or modulate B cell response.

- Igα/CD79a and Igβ/CD79b
- CD19-CD21-CD81 Complex
- CD40 Receptor

MHC Class II Receptors

Present captured antigens to helper T cells.

Load peptides onto MHC-II molecules for T cell recognition.

Toll-Like Receptors (TLRs)

Innate immunity receptors recognizing pathogen patterns.

Enhance B cell activation in early immune responses.

Other Surface Receptors

Inhibitory Receptors
CD32, CD22

Cytokine Receptors
IL-4R, IL-10R

Complement Receptors
CR1, CR2

Key Insight: B cell receptors work together in a coordinated manner to facilitate antigen recognition, B cell activation, and subsequent interaction with T cells to initiate adaptive immune responses.

Immune System Integration: Conclusion

The immune system functions through a coordinated network of specialized components, each playing a critical role in maintaining homeostasis and defending against pathogens.

Primary Lymphoid Organs

Bone marrow and thymus are crucial for immune cell production and maturation, ensuring cells acquire capabilities to recognize pathogens.

Secondary Lymphoid Organs

Lymph nodes, spleen, and MALTs serve as hubs for immune response initiation, filtering pathogens and activating immune cells.

Antigen-Presenting Cells

Dendritic cells, macrophages, and B lymphocytes coordinate adaptive responses by activating T cells and presenting antigens.

Key Takeaways

- Specialized roles ensure efficient pathogen detection and response
- Coordinated interaction creates a layered defense system
- Memory mechanisms allow for faster response to re-infections
- Balance between innate and adaptive immunity provides comprehensive protection