ORGANS OF IMMUNITY

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The Lymphoid System

Functions

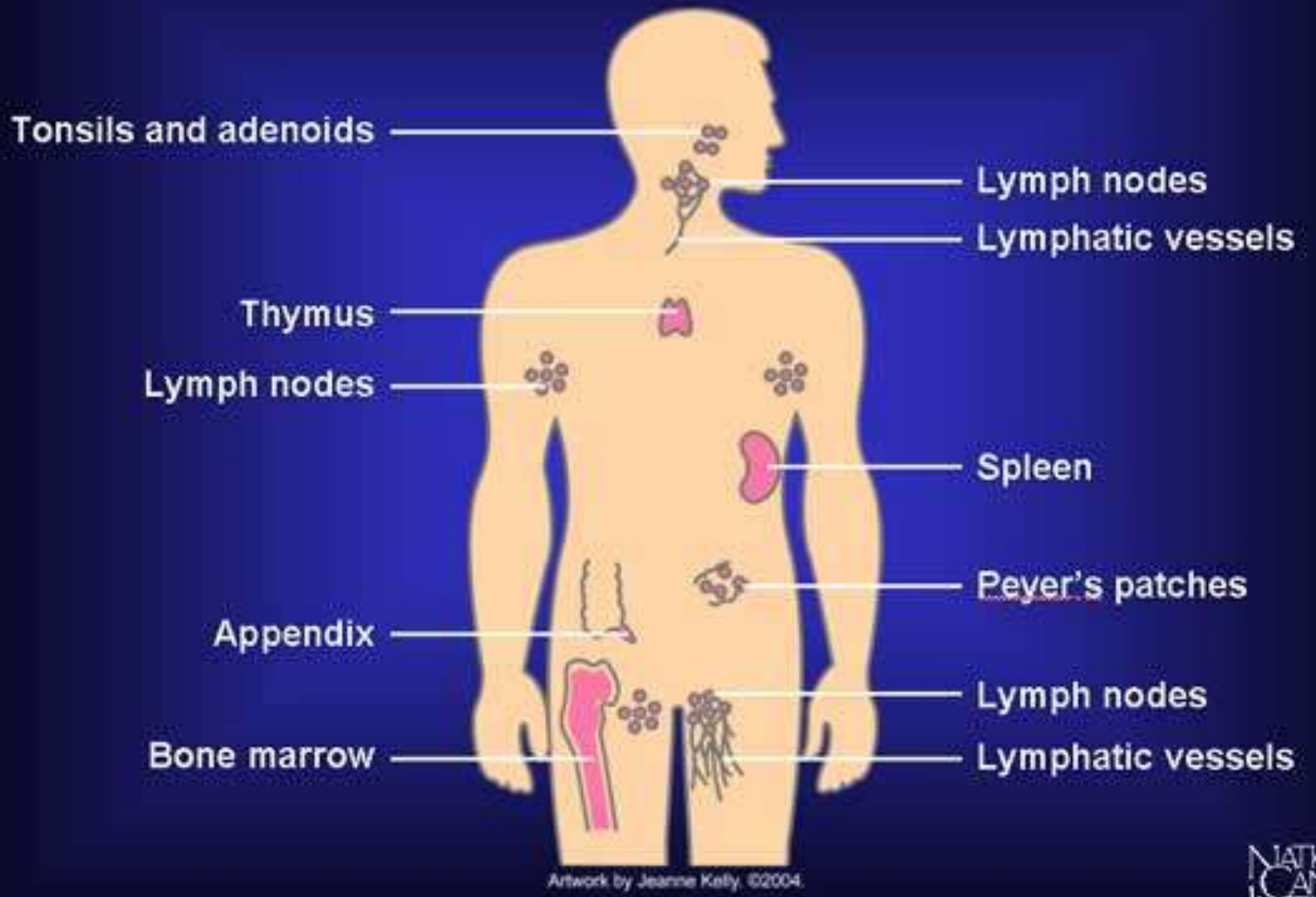
- To mature and educate naïve lymphocytes
- To provide a seat for mature lymphocytes
- To provide site for interaction of antigen with components of adaptive immunity

Includes

- Source of lymphocytes
- Site for maturation of lymphocytes (primary or central lymphoid organs)
- Site for residence of mature lymphocytes and their interaction with antigen (secondary or peripheral lymphoid organs)

- **Source of lymphocytes: foetal yolk sac and liver, bone marrow**
- **Primary (central) lymphoid organs: thymus, bursa of Fabricus, bone marrow, Peyer's patches**
- **Secondary (peripheral) lymphoid organs**
  - ✓ **organised (capsulated): spleen, lymph nodes, bone marrow**
  - ✓ **unorganised (non-capsulated): SALT, MALT, BALT, Peyers' patches**

Organs of the Immune System

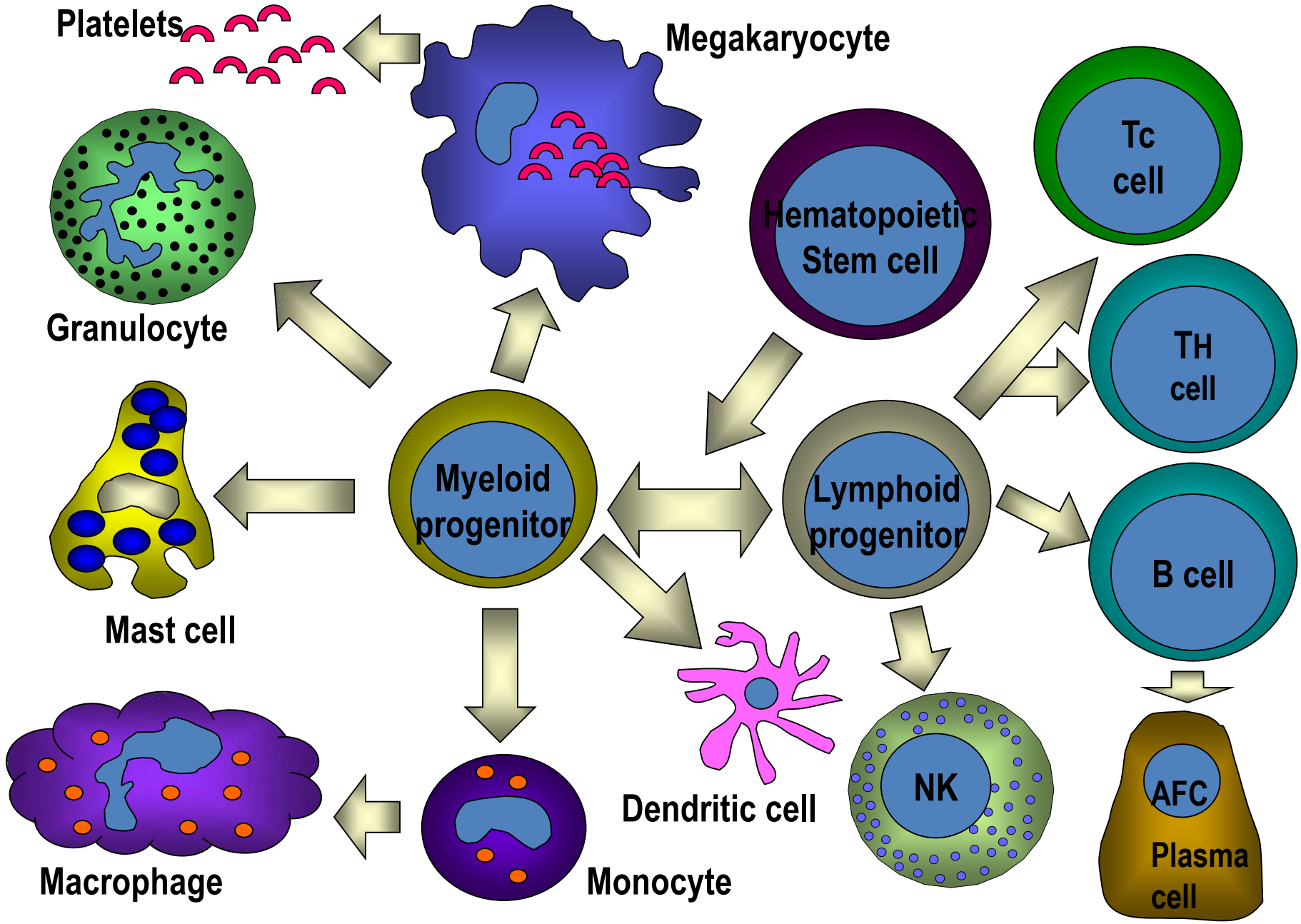


Source of Lymphocytes

Bone Marrow

- The bone marrow is responsible for generating the HSCs which give rise to all cells of immune system, besides erythrocytes and platelets.
- Both B-lymphocytes and T-lymphocytes are produced from stem cells in the bone marrow (source).
- In adult mammals, B-lymphocytes also mature in the bone marrow (primary lymphoid organ).
- Bone marrow also traps antigen from blood (dendritic cells and macrophages) and present to mature B-cells (secondary lymphoid organ).

Hematopoiesis



Primary versus Secondary Lymphoid Organs

Primary Lymphoid Organ	Secondary Lymphoid Organ
Ectodermal or Ecto-endodermal junction in origin	Mesodermal in origin
Develops early in embryonic life	Develops late in fetal life
Removal in early age results in loss of functional lymphocytes and immune response	Minimal or no effects
Examples – Thymus, Bone marrow, Bursa of Fabricus, Illeal Peyer's Patches (only in Group-I mammals)	Examples – Spleen, Lymph nodes, Bone marrow, SALT, MALT

PRIMARY LYMPHOID ORGANS VERSUS SECONDARY LYMPHOID ORGANS

PRIMARY LYMPHOID ORGANS	SECONDARY LYMPHOID ORGANS
Organs of the immune system where lymphocytes are formed and mature	Organs of the immune system which maintain mature naive lymphocytes and initiate an adaptive immune response
Allow lymphoid stem cells to proliferate, differentiate, and mature	Allow lymphoid cells to become functional
Contain either T cells or B cells	Contain both T cells and B cells
Have no contact with antigens	Have contact with antigens
Undergo atrophy with age	Increase size with age

Primary (Central) Lymphoid Organs

- Organs where lymphocytes undergo maturation after being produced in bone marrow.
- Maturation:
    a) learn to discriminate self from non-self ; cells that would react against self antigens are eliminated, and
    b) acquire appropriate repertoire of receptors

- Bone marrow - *B lymphocytes* mature here in mammals
- Thymus - *T lymphocytes* mature here in mammals and avians
- Bursa of Fabricus (avian) - *B lymphocytes* mature here in avians
- Intestinal lymphoid tissue - *B lymphocytes* mature here only in group-I mammals

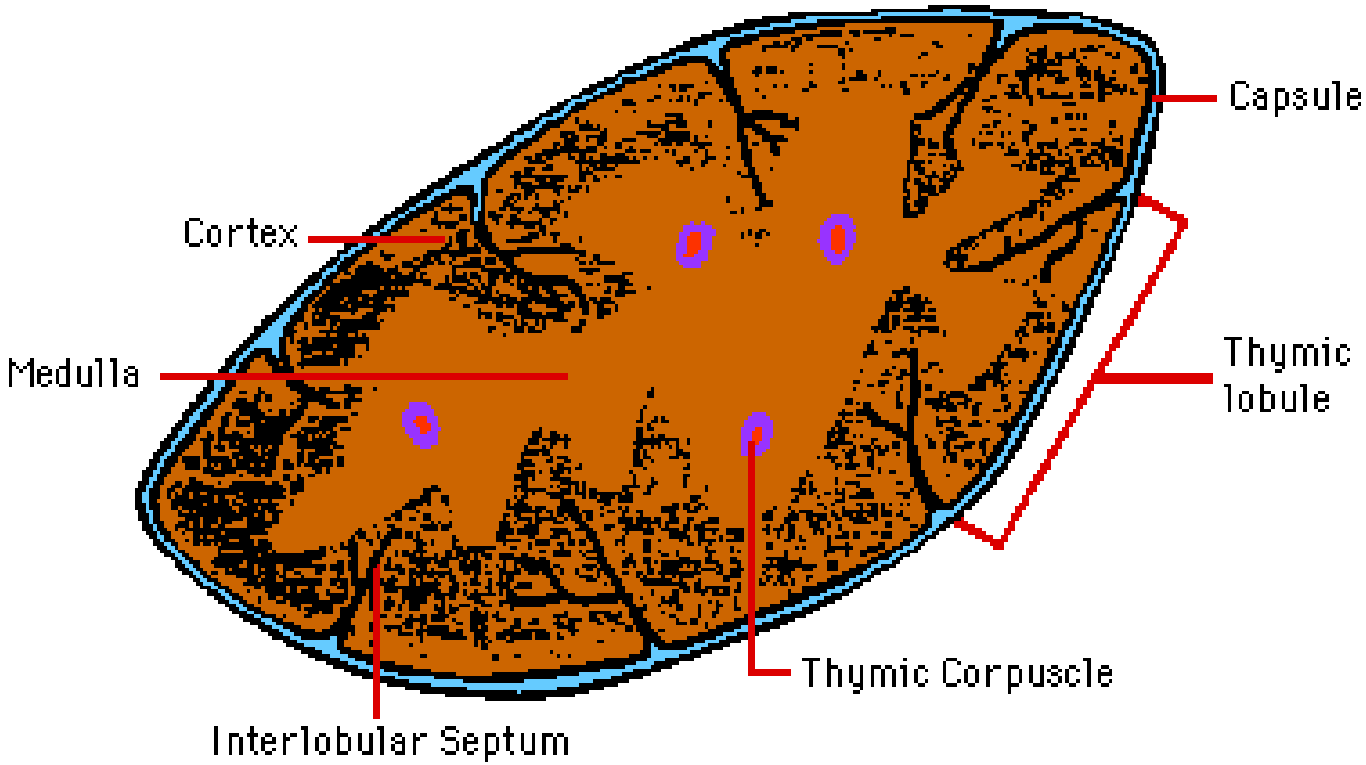
Thymus

- **found in the thorax in the anterior mediastinum**
- **gradually enlarges during young age**
- **after puberty undergoes a process of involution resulting in a reduction in the functioning mass of the gland, but do not atrophy**
- **continues to function throughout life**

Thymus

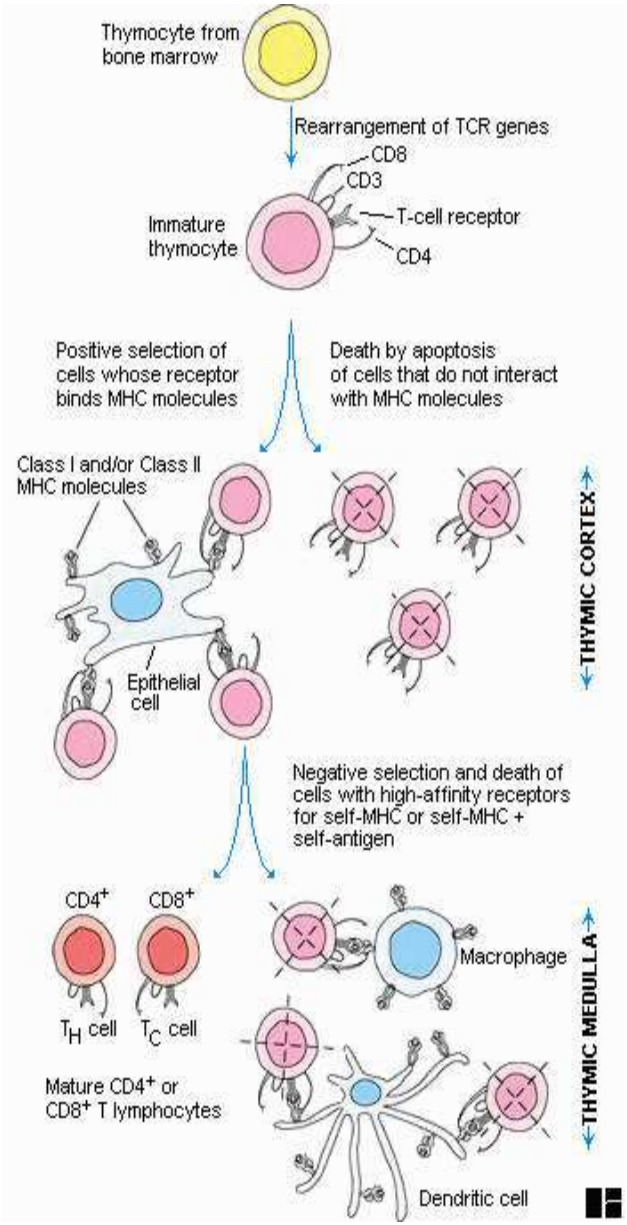
- arranged into an outer, more cellular cortex, and an inner, less cellular medulla.
- cell types present in thymus - lymphoid cells, epithelial cells, macrophages, and other supporting cells
- cortex is densely packed with lymphocytes & macrophages
- immature lymphoid cells enter from blood into the cortex to mature (4-5 days), and pass to medulla from where mature T lymphocytes enter in blood for distribution to secondary lymphoid organs.
- no lymphatic vessel leave from thymus
- a thick epithelial layer prevent antigen from entering into the cortex
- thymic macrophages remove dead / apoptotic cells

Thymus


Capsule
Cortex
Medulla
Thymic lobule
Thymic Corpuscle
Interlobular Septum

Maturation of T-cells

- **Thymocytes mature by positive and negative selection**
  - **positive selection – cells whose receptor binds to MHC molecules (in cortex)**
  - **negative selection – (in medulla)**
    a) cells whose receptor does not bind to MHC molecules;
    b) cells whose receptors bind with high affinity to MHC and/or self antigens
- **Thymic hormones, such as thymosin and thymopoeitn, appear to play role in maturation**


Thymocyte from bone marrow
Rearrangement of TCR genes
CD8
CD3
T-cell receptor
CD4
Immature thymocyte
Positive selection of cells whose receptor binds MHC molecules
Death by apoptosis of cells that do not interact with MHC molecules
Class I and/or Class II MHC molecules
Epithelial cell
THYMIC CORTEX
Negative selection and death of cells with high-affinity receptors for self-MHC or self-MHC + self-antigen
CD4+
CD8+
Macrophage
TH cell
TC cell
Mature CD4+ or CD8+ T lymphocytes
Dendritic cell
THYMIC MEDULLA

Bursa of Fabricus

- only in avians
- round sac, above cloaca
- present at birth, increase in size maximum within 1-2 weeks, involutes
- divided into bursal follicles which open into a common duct
- each follicles has a cortex and a medulla
- cortex contains lymphocytes, plasma cells and macrophages
- medulla contains epithelial cells, lymphoblasts
- B cells mature by negative selection of self reactive cells
- Some degree of secondary function too.

Peyers' Patches

- **in small intestines**

- **<u>Group-I mammals</u>(ruminants, pigs, horses, dogs and humans)**

Ileal PP – 80-90%, a single continuous structure at ileo-caecal junction, only B cells, disappear on maturity, primary lymphoid organ

Jejunal PP - 10-20%, in jejunum, pear shaped discrete follicles, both B (upto 70%) and T cells, persists throughout life, secondary lymphoid organ

Peyers' Patches (contd.)

- **Group-II mammals(primates, rabbits and rodents)**
  - **randomly distributed throughout intestines in ileum and jejunum**
  - **develop 2-4 weeks after birth**
  - **Persists throughout life**
  - **Secondary lymphoid organ only**

Secondary (Peripheral) Lymphoid Organs

Secondary (Peripheral) Lymphoid Organs

- **mesodermal in origin**
- **arise late and persist throughout the life**
- **residence of mature lymphocytes**
- **site of interaction between antigen and lymphocytes**
- **contain macrophages and dendritic cells which trap antigen and present to lymphocytes**

Include

- **Lymph nodes and spleen (capsulated)**
- **Mucosa associated lymphoid tissue (MALT) (uncapsulated)**
  - **gut - GALT (tonsils, Peyer's patches, isolated lymphoid follicles, appendix)**
  - **eustachian tube - EALT**
  - **nasal – NALT**
  - **bronchus – BALT**
- **Skin associated lymphoid tissue (SALT).**

Lymph Nodes

- small, round or bean shaped, capsulated, subcapsular sinus
- fibrous capsule of connective tissue at periphery extend into parenchyma forming trabeculae
- Parenchyma is divided into
  - cortex – peripheral, a B cell area
  - medulla – central, sinuses
  - paracortex – between cortex and medulla, a T cell area
- lymph enter via afferent lymphatics at circumference and leave via efferent lymphatic at hilus
- Site of inducing an immune response to antigen drained by afferent lymphatics from regional area after being trapped by dendritic cells, and processed and presented to naïve and/or memory lymphocytes

Lymph Nodes

- cells
  - reticular cells
  - lymphocytes (naïve and memory)
  - accessory cells
    - sinus macrophages (highly phagocytic),
    - tingible body macrophages (removal of cell debris),
    - marginal zone macrophages (subcapsular sinus),
    - follicular dendritic cells (FDC) (cortex),
    - inter digitating cells (IDC) (paracortex)

(antigen is trapped, processed and presented by macrophages, FDCs and IDCs)

Lymph Nodes - cortex

- predominantly B cells, few T cells
- B cells arranged as nodules – primary follicle (follicle central cells)
- interaction of B cells with its antigen ⟶ activation ⟶ 2° follicle
- secondary follicle
  - central area – pale, rapidly dividing B cells (germinal centre)
  - peripheral area – resting naïve B cells and few T cells (mantle zone)
- germinal centre
  - dark zone – proliferating B cells, somatic mutation (affinity maturation)
  - light zone – memory B cells (Ig class switching)

Lymph Nodes - paracortex

- predominantly T cells
- site of interaction between antigen presented by APC (IDC) and T cells

Lymph Nodes – medulla

- comprises blood vessels, medullary cords and medullary sinuses
- medullary cords – plasma cells
- also contain macrophages
- antibodies secreted by plasma cells

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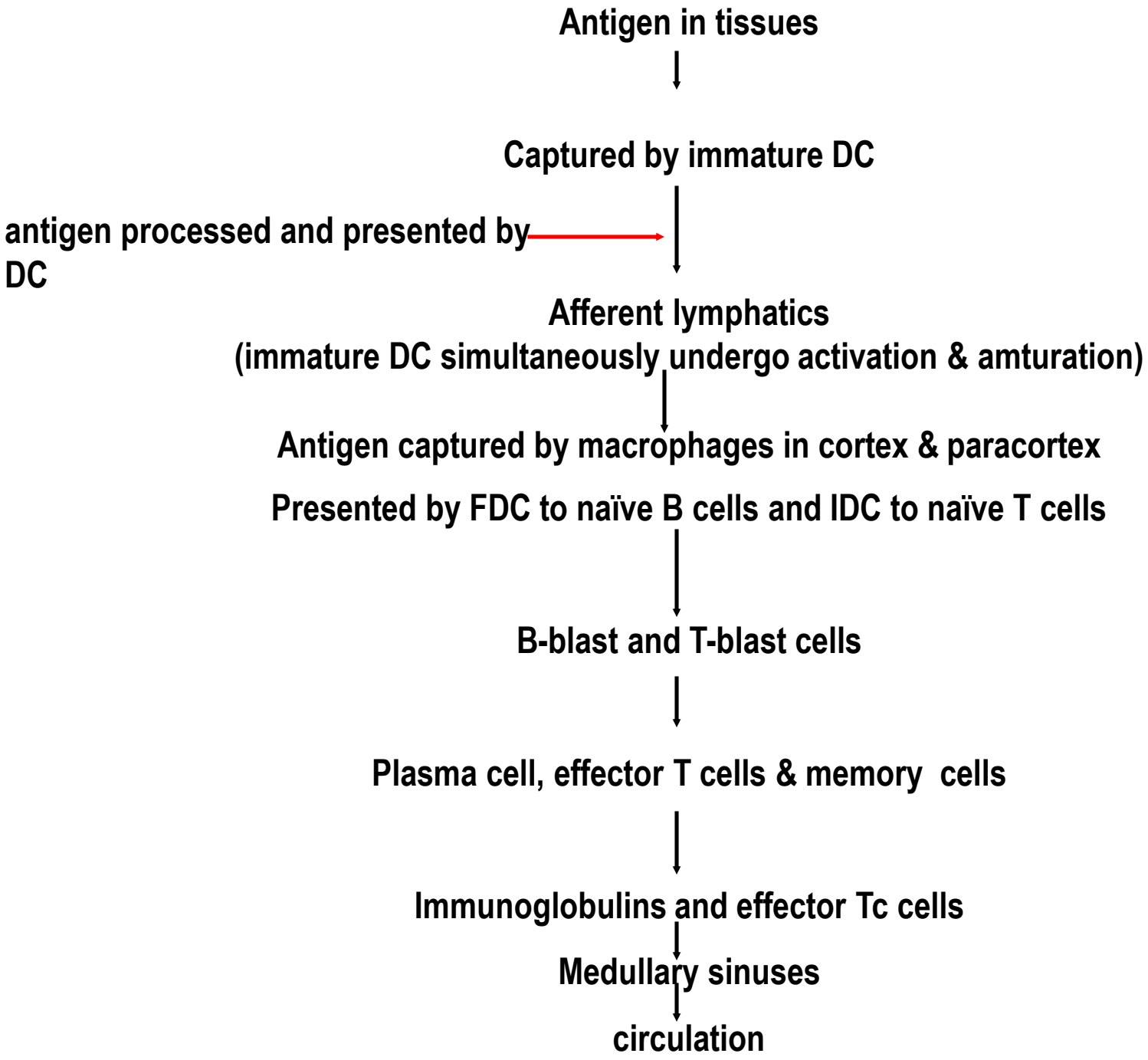
efferent lymphatics and bood

- **When an antigen enter a lymph node, there occur a temporary halt in the circulation of lymphocytes through it.**
- **The node undergoes swelling (lymphadenitis)**
- **Lymphocytes are directed towards antigen for interaction**
- **Followed by interaction of BCR/TCR of lymphocytes with their specific antigen, stimulation and co-stimulation of an appropriate lymphocyte occurs, followed by its activation and differentiation.**
- **Lymphocyte traffic reopens after approximately 24 hours**
- **Chemokines play major role in distribution of T and B cells to different compartments of nodes, e.g. CCL19/21 for T cells, CXCL3 for B cells**


Antigen in tissues
Captured by immature DC
antigen processed and presented by DC
Afferent lymphatics
(immature DC simultaneously undergo activation & amturation)
Antigen captured by macrophages in cortex & paracortex
Presented by FDC to naïve B cells and IDC to naïve T cells
B-blast and T-blast cells
Plasma cell, effector T cells & memory cells
Immunoglobulins and effector Tc cells
Medullary sinuses
circulation

Spleen

- Located in left quarter of abdominal cavity
- Secondary lymphoid organ - Traps and filter antigen from blood
- Store house for erythrocytes and platelets
- fibrous capsule of connective tissue at periphery extend into parenchyma forming trabeculae
- Parenchyma
  - Red pulp – storage of rbc, filtration of antigen from blood, consists of blood vessels, sinuses lined by HEVs and sinusoids
  - White pulp – storage of lymphocytes, interaction of antigen with cells of immunity
  - Two are separated by a marginal sinus, a reticulum sheath and a marginal zone of cells; marginal zone is rich in DC and B-blast cells

Spleen – white pulp

- consists of lymphocytes and accessory cells
- present as PALS surrounding arterioles
- PALS is mainly a T-cell area
- scattered in PALS are B-cell area (primary follicle), surrounded by T cell
- on interaction of B cells with its antigen → activation → 2° follicle with germinal centre
- DC in marginal zone traps the antigen as blood passes from

splenic artery → arterioles → marginal sinuses → marginal zone

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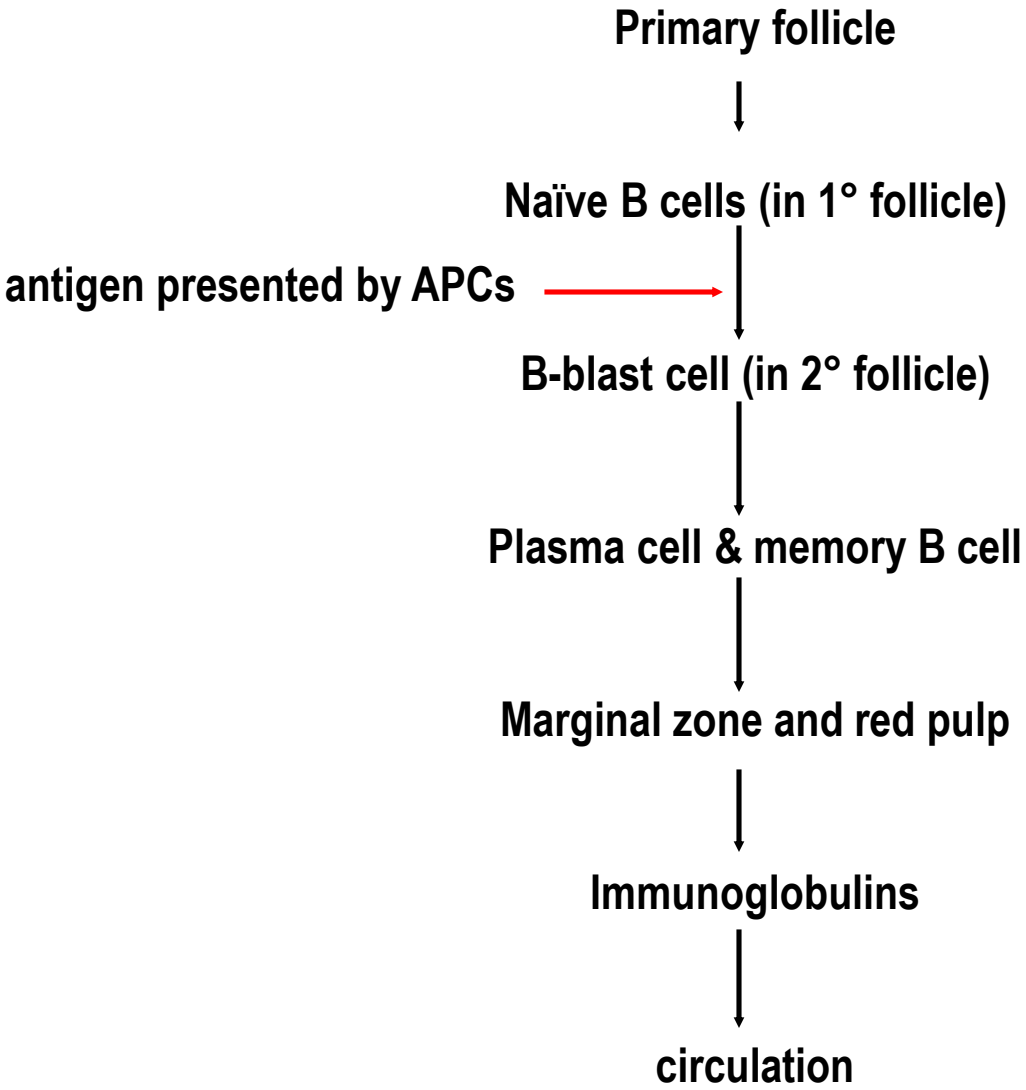
splenic vein ← venules ← venous sinuses


Primary follicle
Naïve B cells (in 1° follicle)
antigen presented by APCs
B-blast cell (in 2° follicle)
Plasma cell & memory B cell
Marginal zone and red pulp
Immunoglobulins
circulation

Tertiary lymphoid organs/tissues -

- Ectopic or tertiary lymphoid tissues develop at sites of inflammation or infection in peripheral, non-lymphoid organs.
- These tissues are architecturally similar to conventional secondary lymphoid organs, with separated B and T cell areas, specialized populations of dendritic cells, well-differentiated stromal cells and high endothelial venules.
- Most important of these sites are those tissues with direct contact with the "external" environment, primarily the skin and mucosal lining of the gastrointestinal, pulmonary, and genitourinary tracts.

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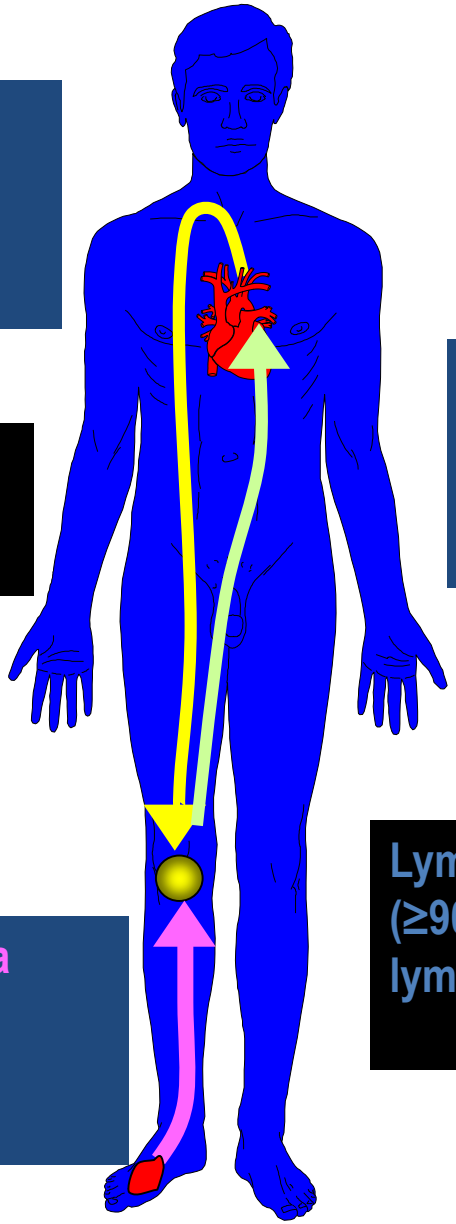
Ann Rheum Dis 2010;69(Suppl 2):A1–A76

Lymphocyte recirculation

Naïve lymphocytes
enter lymph nodes
from the blood circulation

Majority of circulating
lymphocytes are T cells



Lymphocytes return
to blood
via the thoracic duct

Lymphocytes enter L.N mainly
(≥90%) via blood; very less via
lymph

Antigens from infected area
go to lymph nodes
via the lymphatic system

Lymphocyte Recirculation

- **Mature naïve lymphocytes reach secondary lymphoid organs via blood**
- **90% of lymphocytes are derived from cells entering through HEVs; only 10% enter through afferent lymphatics**
- **Secondary lymphoid tissues (lymph nodes, spleen) are main sites where mature naïve virgin lymphocytes encounter antigen**
- **Frequency of lymphocytes having a receptor specific for a given antigen is low**
- **Recirculation of lymphocytes through lymphoid tissues optimizes productive encounters with specific antigen to initiate adaptive immune response**

High endothelial venules (HEV)

- **Venules in paracortex of spleen and lymph nodes are lined by special tall, rounded endothelial cells (in contrast to flat, cuboidal cells of blood vessels).**

- **These cells are joint by discontinuous ‘spot-welded junctions” (in contrast to tight junction of blood vessels).**

- **On exposure to antigens, cells of HEV further increase in height and expresses selectins and adhesins, which results in activation, rolling, adherence and emigration of lymphocytes from blood in paracortex**

Lymphocyte Recirculation

- **Lymph flows from tissues to lymph nodes through afferent lymphatics and leave the lymph node through efferent lymphatics**
- **Efferent lymphatics carries 75% T cells and 25% B cells**
- **Efferent lymphatics join together to form large lymph vessel**
- **Largest of them is thoracic duct draining lymph from lower body and intestine into anterior vena cava**
- **B cells are principally sequestered in secondary lymphoid organs; only 10 – 30% of circulating lymphocytes.**
- **Majority of circulating lymphocytes are T cells**

- **Primary immune response to antigens administered/ entered via i.v or i.m routes mainly occurs in spleen, followed by lymph nodes.**
- **Secondary immune response to same antigen mainly occurs in bone marrow, followed by spleen and lymph nodes**
- **This occurs because of lymphocyte (memory cells) homing phenomenon (lymphocytes activated in a particular region of the body to preferentially return to the same region).**

Lymphocyte Homing

- **For lymphocytes activated in a particular region of the body to preferentially return to the same region.**