

Functions of Spleen in Health and Disease

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ABSTRACT

Spleen is a capsulated and compartmentalized lymphoid organ with a complex vascular and cellular organization. It develops from dorsal mesogastrium. The spleen performs a number of physiological functions namely, phagocytosis of aging erythrocytes and platelets, recycling iron, inducing immune response against blood antigens, and defending against invading bacteria, fungi, viruses, prions and other infective agents. Because the spleen has only the efferent lymphatic vessels, it is therefore, involved in the filtration of blood but not lymph. The splenic functions can be affected by immune suppressant drugs, vaccines and biological products, chemo- and radiation-therapy, resulting in splenomegaly and thrombocytopenia (reduced number of platelets). Recently, it has been shown that the splenic monocytes play a significant role in the regeneration of heart tissue following a heart attack.

Keywords: Spleen structure and function, splenic blood circulation, immune functions of spleen, splenomegally

Introduction

The spleen is located in the left hypochondriac region of abdomen between the fundus of the stomach and diaphragm. In humans, it is about 12 cm long, 7 cm wide, and 3 cm in thickness, and weighs around 150-250 g. The splenic artery, splenic vein, efferent lymphatic vessels and

splenic nerve plexus pass through the hilus, which is a depressed area in the capsule [1, 2, 3]. The spleen is an organ which not only effectively uses its own immune cells but also mobilizes the body's immune cells for immune surveillance and protecting other vital organs including heart, kidney and brain [4, 5, 6, 7]. The cells which play an important role in spleen functions are Macrophages, monocytes, natural killer (NK) cells, and B- and T cells. The spleen is prone to physical injury, infections, and various immunological conditions including cancers. Enlargement of spleen or splenomegaly may occur due to anaemia, infections, inflammation, cancer, metabolic disorders, and liver diseases.

Anatomic structural organization of spleen

The spleen has four important structures, viz., capsule, red pulp (RP), white pulp (WP) and marginal zone (MZ) (Figure 1).

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Each area shows unique morphological structure and is involved in performing specific physiological functions. The capsule contains dense connective tissues, elastic and smooth muscle fibres, and sympathetic nerve fibres from the splenic nerve plexus. The RP contains numerous sinuses which are filled with blood, rich in platelets. Between the sinuses, spongy cellular cords (cords of Billroth), made up of reticular fibres and reticular cells intermingled with a number of immune cells, such as macrophages, monocytes, granulocytes, B cells, T cells and plasma cells are found. Several RP specific functions occur in the spleen including blood filtration, antigenic stimulation and proliferation of B and T cells and production of antibodies of different specifications. RP constitutes about 70 % of the total splenic volume in adult. The WP is a lymphocyte rich area which contains periaarterial lymphatic sheath (PALS) around the arterial vessels particularly around the central artery and central arterioles, follicles and loose lymphatic tissues. The PALS is a sheath of lymphocytes mostly $CD4^+$ T cells that envelope the central arterial vessels [8].

The follicles not only contain B cells but also T cells, which are found adjacent to the PALS. Significant immunological activities and cell trafficking and cross talk between various immune cells occur. Bordering the PALS and the follicles is the marginal zone (MZ) which has few lymphocytes but numerous macrophages and antigen presenting cells (APCs). Immunological activation of B cells occurs in the MZ as a result of antigenic encounter [9]. Many lymphocytes in MZ migrate into respective T- and B area. The MZ contains the highest concentration of blood antigens than any other area in the spleen because splenic arterial blood empties to the MZ. Marginal zone B cells show somatic hypermutation, clonal expansion [10] and B cell positive selection [11]. B cell clonal expansion also occurs in the germinal centre of the B cell follicle following antigenic stimulation.

Blood supply and lymphatic organization

Figure 1 illustrates the spleen's anatomical features. An important feature of spleen's central artery and arterioles is that these vessels show periaarterial lymphatic sheath

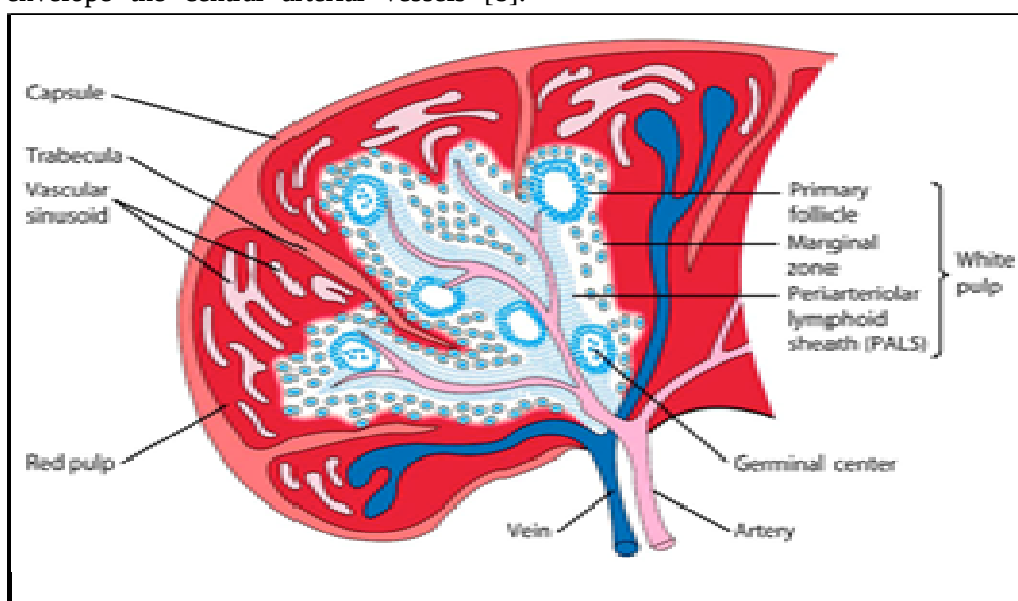


Fig. 1. Illustration of the anatomical structures of spleen

(PALS) which contains predominantly $CD4^+$ T cells, some $CD8^+$ cells, APCs,

plasma cells, interdigitating dendritic cells and fibroblastic reticular cells. The splenic

microcirculation and lymphatic organization is presented in Table 1. Spleen gets its blood supply through splenic artery and removes blood through splenic vein and lymph via efferent lymphatic vessels. Lymph carries APCs, T cells, B cells, cytokines, chemokines, growth factors and peptide hormones. Following the filtration of RBCs, the mature B- and T-cells and plasma are transported via splenic vein to the general circulation. Bone marrow differentiated B cells, thymus differentiated T cells, RBCs, platelets, and blood antigens enter the spleen through splenic artery. Venous blood from sinusoids is emptied through the trabecular vein, then to the splenic vein, and eventually to the inferior vena cava. The splenic artery divides into trabecular arteries located within the trabeculae entering the splenic parenchyma. The trabecular artery gives off central artery. The central artery branches out as central arterioles. These arterioles provide blood to the WP (Table 1). Central arterioles are surrounded by sheaths of lymphoid tissues (PALS) at different point [12]. Some of these terminate in the

marginal sinus at the junction of the white pulp and the marginal zone, others terminate within the marginal zone, and a few extend beyond the white pulp to terminate in the red pulp [13, 14, 15]. As the central arterioles continue, the white pulp wanes and they become the penicillar arteries surrounded by red pulp. Blood from the red pulp collects in the venous sinuses which enter the trabeculae and merge into the trabecular veins. The trabecular veins then converge at the hilus to form the splenic vein which drains into the hepatic portal system [1, 3]. Blood from terminal capillaries (arterioles) directly enter to venous sinus (closed circulation) or enter to the splenic cords, then to sinus (open circulation). In humans open venous circulation in spleen is favoured [1, 16].

Antigenic exposure and B cell clonal expansion

Bone marrow derived naïve B cells enter through the central artery to the PALS, MZ and to the GC of the follicle. The naïve B cells under the influence of antigen become activated and undergo clonal expansion.

Table 1. Splenic Blood Circulation

Branches of splenic artery	Supply to	Characteristic PALS
Trabecular artery	Mostly to red pulp, and also to white pulp	A very narrow sheath of lymphocytes
Central artery/arteriole	Red pulp, white pulp, germinal centre, mantle zone	Heavily sheathed with lymphocytes; (PALS)
Penicillar artery/arteriole	Red pulp	Very few lymphocytes
Sheathed arteriole (Ellipsoids)	Red pulp	Heavy sheathing with lymphocytes, platelets, macrophages
Terminal capillaries	Red pulp and MZ	Lymphocytes, macrophages, plasma cells, RBCs

These B cells may undergo somatic hypermutation at the B cell receptor (BCR)

and immunoglobulin (Ig) locus. They can also undergo class switch from IgM to IgG.

Some B cells with complementary receptor to antigenic epitope transform into plasma cells while others may become memory B cells. The long-term survival, growth and differentiation of selected B cell clones are thought to be dependent on stimulation by antigens and stromal cells. B cells that encounter blood antigens complementary to their antibody receptors develop into plasma cells and plasma cells produce antigen specific antibody. CD4⁺T cells act as supporting cells for growth and differentiation of B cells. CD4⁺T cells and CD8⁺ T cells are found in various parts of the spleen [8]. Majority of T cells in spleen are CD4⁺ T cells. Most of CD4⁺ cells are found in PALS, splenic cords, marginal zone, and marginal sinuses and in the periphery of follicles. B cells are found in the follicles, marginal zone, and splenic cords. The B cells found in MZ are tissue specific and are non-migratory (non-circulatory). However, some published data show that human MZ B cells are circulatory [17].

Role of immune cells in splenic functions

The spleen not only produces and brings together the function of various immune cells, but also helps the body to maintain the normal quality of blood, consequently protecting from adverse effects of blood borne antigens and infective agents that may cause harm to the other organs. Following antigenic stimulation, T helper cells secrete cytokines which regulate the differentiation of T helper cells to T₁ and T₂ helper cells. The naive B cells from the bone marrow enter germinal centre (GC), and under the influence of IL-21 GC-derived B cells transform into plasmoblasts, and then become mature B cells. Germinal centres are the central core of follicles both in the primary and secondary follicles. In GC, B cells following antigenic exposure undergo B cell maturation, Beta Cell Receptor (BCR) organization and genetic recombination. Mature B cells become high

affinity plasma cells which produce antibodies of certain specificities. Some of the GC-derived B cells tend to become memory B cells and not plasma cells [18, 19]. These cells are capable of becoming plasma cells only on subsequent exposure to antigens. These processes require the participation of stromal cells as well as CD4⁺ T cells. Activated T-helper cells (on exposure to antigens and also B cells) secrete a number of cytokines such as IL1, IL4, IL5, and IL6. These cytokines promote B cell proliferation and differentiation. In addition to the B cells, T cells, NK cells, spleen shows compartment and function specific macrophages particularly those found in the marginal zone [5]. The splenic monocytes are also actively involved in processes associated with tissue regeneration such as angiogenesis and vasculogenesis, either by producing pro-angiogenic factors or even by evolving to structural components of the vascular wall [5]. The spleen contains heterogeneous population of macrophages varying in morphological structures, biochemical and immunological properties [5]. Some of these cells perform phagocytic functions, while others act as antigen presenting cells (APCs) and participate in generating immune response. Those which act as APCs carry MHC II molecules on their cell receptors.

Spleen-related immune response

Antigens enter to the MZ through marginal sinus. The MZ lies between red pulp and white pulp, and contains high concentrations of blood antigens as the central arterioles empty blood to the MZ. The MZ has a unique group of B cells. The marginal zone B cells are non-circulatory (in rodents)/circulatory (in humans) and need Notch 2 and other signalling molecules for proliferation. Antigens enter germinal centres through the marginal sinus. The fenestrated nature of the marginal sinus facilitates the entry of blood-borne antigens

into the MZ. A selection process for B cells occurs in the MZ that have high affinity for antigens in question. A joint activity of APCs, CD4⁺ T cells and B cells to the antigen triggers an immune response. Some MZ-derived B cells can act as APCs after getting signals from B cell receptor but most of the APCs are macrophages or dendritic cells.

Pathophysiology of spleen:

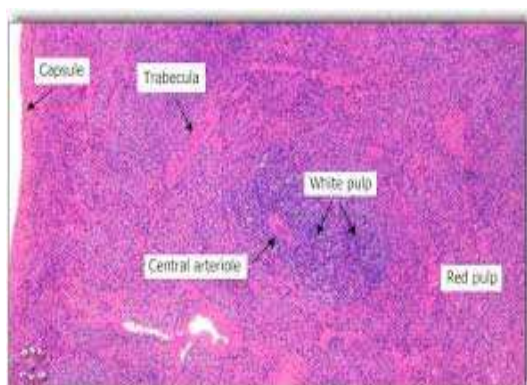


Fig. 2. Histology of normal human spleen. Source: Google

As discussed earlier, one important function of the spleen is to maintain the normal quality of blood. Spleen plays a major role in the prevention of certain diseases such as malaria, sickle cell anemia, leukemia, pernicious anemia, Hodgkin's disease, mononucleosis, Epstein-Barr virus infection and sarcoidosis. The spleen may show pathological changes [20] due to a variety of causes, whereas splenomegaly becomes a major clinical diagnosis concern. Enlargement of spleen may occur due to a wide variety of causes such as: bacterial, viral and malarial infections, mononucleosis, toxoplasmosis, endocarditis, leukemia and lymphoma of spleen, Hodgkin's lymphoma, follicular lymphoma of spleen, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia, splenic MZ lymphoma, certain inflammatory diseases, such as rheumatoid arthritis, lysosomal diseases

such as Gaucher's disease, liver disease, and sickle cell anaemia.

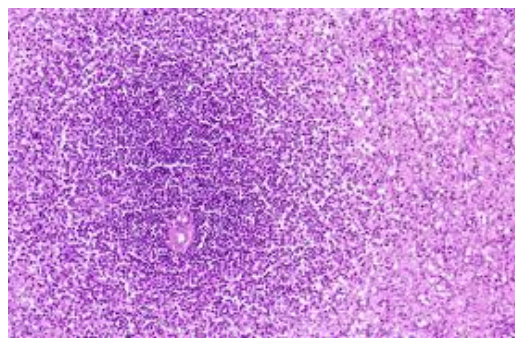


Fig. 3. Heavy cellular infiltration of lymphocytes in the mantle zone (MZ) of spleen due to lymphoma of splenic MZ.

Source: Google

One of the most common causes of splenomegaly is portal hypertension with hepatic cirrhosis. Splenic infarcts may occur as a consequence of patients with endocarditis. Congenital absence of spleen, or surgical removal of spleen predisposes an individual to infections, particularly with capsulated bacterial organism such as pneumococcus. In the fetal life, the spleen functions temporarily as a hematopoietic organ, whereas in post-natal life it acts as lymphoid organ and graveyard for red blood cells. There are some differences in the cellular composition of spleen between young compared to adults. B cells in the spleen of infant lack CD 21; IgD – and IgM⁺ compared with adult marginal zone B cells. In rare cases (< 10 %), an accessory spleen may be found without any apparent pathological implications.

Effects of immunosuppressants on splenic function

Certain immunosuppressant drugs (e.g. glucocorticoids), vaccines and biological agents, administration of antibodies and antibiotics as well as chemo- and radiation-therapy may cause either splenomegaly and/or thrombocytopenia (reduced number

of platelets) which may lead to bleeding problems.

Conclusion

The spleen has a very complex lymphatic and vascular organization. It is an organ with multiple functions. Although its primary functions are to filter blood and protect body from invading pathogens and antigens, it also plays a significant role in maintaining the immunologic homeostasis and tissue regeneration processes. When spleen is surgically removed due to the pathological conditions, Kupffer cells from the liver may act as phagocytic cells to remove aging RBCs from the circulation with limited capacity.

Conflict of interest

The authors have no conflict of interest, financial or personal.

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