Human Autoimmunity and Associated Diseases

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PREFACE

The immune system is a complex system that forms the defense mechanism against diseases in a living thing, recognizes and destroys pathogens and tumor cells, and protects the body from foreign and harmful substances. Autoimmunity is the impairment of immunological tolerance and an immune response against one's own antigens. Autoimmunity is still not fully understood for its reasons and treatment possibilities. We examined the immune system and autoimmunity in terms of its causes, mechanism of occurrence and its relationship with various diseases and treatment approaches. New studies on immunity and autoimmunity are constantly being carried out, and new diagnostic and therapeutic protocols are emerging. For this reason, it is important to follow and compile current studies. This book will examine current, emerging, and cutting edge approaches to autoimmunity. This book discusses the issue of immunity and autoimmunity in different aspects such as epigenetics, genetics, pregnancy, microbiota, male and female infertility, anesthesia applications, HIV, covid-19, foods and more.

The Editors

CHAPTER ONE

INTRODUCTION TO THE IMMUNE SYSTEM

KEMAL BİLGİN

Introduction

The body's ability to defend itself against foreign substances, especially infectious agents, is called “immunity”, and all reactions to protect the body from these elements are called the “immune response”. Immunology is the branch of science that examines the immune system and its response to pathogens and the consequences of this response (Us 2016).

The immune system enables us to live in harmony with the environment in preventing the factors that can cause infections by working coherently with organs, tissues, cells and soluble molecules. However, a deficiency in the immune system may result in the deterioration of this balance (Titiz 2014; Us 2016).

The immune system has to deal with many different pathogens developing new ways to prevent recognition or elimination (Trowsdale and Parham 2004). Simultaneously, the immune system must eliminate antigens by separating them from the self structures. Antigens are biological and chemical molecules that can induce antibody formation (Camcıoğlu and Deniz 2007; Us 2016).

The host defence mechanism includes innate and adaptive (acquired) immunity that work with each other in a very delicate balance and cooperation (Turul and Ersoy 2004; Takeda and Akira 2005; Vatansever and Kahraman 2012).

While innate immunity prevents the entry of microbes, it recognizes and distinguishes non- and self-antigens. Innate immunity mechanisms are the defence system that is always present in healthy individuals and destroys microbes that succeed in entering tissues during the first encounter with the pathogen from birth (Turul and Ersoy 2004; Camcıoğlu and Deniz 2007).

The adaptive immune system has slower-acting mechanisms. However, this immune system adapts itself to invading microorganisms and provides

a more effective defence. Especially in recurrent encounters, it has faster and more robust responses (Turul and Ersoy 2004; Camcıoğlu and Deniz 2007; Bonilla and Oettgen 2010).

Innate and adaptive immune mechanisms are in continuous interaction (Beutler 2004; Iwasaki and Medzhitov 2015). For example, antibodies, which are a component of adaptive immunity, bind to microbes, and microbes coated with antibodies can be easily digested and destroyed by phagocytes, a member of innate immunity (Camcıoğlu and Deniz 2007).

1. Innate immunity

Innate immunity is the first line of defence that prevents microorganisms from entering. Unlike the adaptive immune system, it provides an immediate immune response when faced with pathogens (Turvey and Broide 2010; Vatansever and Kahraman 2012).

Compared to the adaptive immune system, the innate immune system has a limited repertory of receptors that recognize pathogens (e.g. toll-like receptors) and several molecular structures common to pathogens. Thus, it can initiate the defence by identifying the self and non-self (Turul and Ersoy 2004; Takeda and Akira 2005; Vatansever and Kahraman 2012).

Inflammation is stimulated by the release of cytokines and chemokines when the innate immune response occurs. At this stage, the interferon-γ (IFN-γ) produced by the activated natural killer (NK) cells plays a vital role (Borish and Steinke 2003; Vatansever and Kahraman 2012; Duque and Descoteaux 2014).

The innate immune system elements are the epithelial layer, phagocytic cells, NK cells and the complement system (Janeway and Medzhitov 2002; Titiz 2014).

1.1. Epithelial layer

The protection created by the immune system against pathogens first begins with the epithelial layer located in the body parts open to the outside. The epithelial layer physically prevents the entry of microorganisms and chemically produces peptide antibiotics that kill bacteria (Camcıoğlu and Deniz 2007; Turvey and Broide 2010; Vatansever and Kahraman 2012; Titiz 2014). There are intraepithelial lymphocytes in the epithelial layer carrying receptors with γ and δ chains (Camcıoğlu and Deniz 2007). Simultaneously, IgA, produced in the submucosal lymphoid tissue and secreted into the lumen, also acts as a humoral assistant (Titiz 2014).

1.2. Phagocytic cells

Neutrophils and monocytes are cells that perform intracellular destruction by phagocytosing microorganisms at the site of infection. Neutrophils are the most profound cells in the circulation that play a part in responding to several infections, especially those that are bacterial and fungal in origin. The reproduction of neutrophil precursors in the bone marrow is stimulated by cytokines (colony-stimulating factors) produced by many cell types during infection (Camcıoğlu and Deniz 2007).

Monocytes, like neutrophils, are effective against microorganisms in the circulation and tissues. Unlike neutrophils, monocytes live longer in extravascular tissues. Monocytes located in tissues differentiate and are called macrophages (Camcıoğlu and Deniz 2007). These cells express CD14 as the characteristic surface marker (Us 2016). Macrophages and monocytes are crucial effectors and regulators of inflammation and innate immunity (Geissmann et al. 2010; Varol et al. 2015). The secretion of cytokines such as interleukin (IL)-1, IL-12 and tumour necrosis factor (TNF) is triggered by a microorganism's phagocytosis of monocytes/macrophages, and inflammatory reactions start. IFN-γ is produced by NK or T cells, enhancing the lethal effect of macrophages. Thus, chemokines secreted by activated macrophages attract immature dendritic cells, activated T cells, neutrophils, and NK cells to the region, strengthening the inflammatory reaction (Borish and Steinke 2003; Us 2016).

1.3. Natural killer (NK) cells

Natural killer (NK) cells, a component of the innate immune system, are a special lymphocyte series that activates macrophages by secreting cytokines (IFN-γ) (Cooper et al. 2001; Borish and Steinke 2003). However, they do not express the antigen receptors, found in B and T lymphocytes (Camcıoğlu and Deniz 2007). NK cells are determined by positive CD56 and CD16 markers, without CD3 expression (Cooper et al. 2001). The CD16 molecule is a receptor that binds to the Fc portion of IgG antibodies. In this way, NK cells can bind to targets coated with antibodies and kill them (Us 2016; Kumar 2018).

NK cells are involved in anti-tumour activity, and against infectious pathogenes (Freud et al. 2017). NK cells' surface inhibitor and activator receptors control the killing of target cells without damaging normal body cells. The interaction between normal cell surface MHC-I molecules and NK cell inhibitory receptors prevents NK cells from killing normal body

cells (Janeway and Medzhitov 2002; Kumar 2018). However, virus-infected cells and tumour cells have generally lost MHC-I molecules. Therefore, activator receptors on the surface of NK cells come into play. As a consequence of direct contact with the target cells, cytotoxic proteins (perforin and granzymes) found in NK cells' granules are secreted. Thus, the killing of target cells is achieved by inducing apoptotic pathways (Us 2016).

Complement system

The complement system, consisting of a protein network, plays a vital role in host defence and inflammation. Many of the complement proteins are proteolytic enzymes, activating the system in tandem. With the activation of the system, pathogens are removed by phagocytes as a result of opsonization, and lysis of the microorganism cell and stimulation of inflammatory responses can occur (Hoebe et al. 2004; Camcıoğlu and Deniz 2007; Sarma and Ward 2011).

Complement activation can occur in three different ways: alternative, classical and lectin pathways (Hoebe et al. 2004; Sarma and Ward 2011).

The alternative pathway; This is activated when some complement proteins encounter amino and hydroxyl groups found in the bacterial wall. As a result, the membrane attack complex is formed, and cell death occurs due to pore formation in the cell wall (Titiz 2014).

The classical pathway; The binding of antibodies to microorganisms or other antigens activates the classical pathway, and the system develops like the alternative pathway in the next steps (Sarma and Ward 2011; Titiz 2014).

The lectin pathway; The attachment of a plasma protein called mannose-binding lectin to mannose found in many pathogens activates the lectin pathway (Titiz 2014).

Although the complement pathways' initial activations differ, they follow a similar flow after a particular stage and merge at C3, forming C3a, C3b, C5a and the membrane attack complex (Sarma and Ward 2011).

2. Adaptive immunity

In the case that innate immunity mechanisms are insufficient to destroy the harmful antigen, the adaptive immune system is activated with the innate immunity stimulus (Titiz 2014).

The most crucial feature of adaptive immunity is that it shows specificity to antigens that are structurally different from each other, and formed due

to the clonal selection of lymphocytes with antigen-specific receptors (Camcıoğlu ve Deniz 2007; Bonilla and Oettgen 2010; Vatansever and Kahraman 2012). Thus, adaptive immunity can peculiarly target the immune system and maximize the effectiveness of the immune response while minimizing the redundant secondary detriment (Palm and Medzhitov 2009). Another critical feature of adaptive immunity is immunological memory that develops from previous encounters with the antigen (Bonilla and Oettgen 2010; Vatansever and Kahraman 2012; Titiz 2014).

There are two types of adaptive immune systems. One is **humoral immunity**, which is designed to recognize extracellular microbial antigens using antibodies produced by B lymphocytes, and the other is **cellular immunity**, which plays a role in defence against intracellular microbes by T lymphocytes (Camcıoğlu and Deniz 2007).

2.1. Humoral immunity

Humoral immunity is regulated by proteins called **antibodies** generated by B lymphocytes (Us 2016). Antibodies; opsonize antigens making them ready for phagocytosis, neutralize viruses and activate the complement system's classical pathway (Titiz 2014).

IgM and IgD molecules found on the B lymphocyte surface, act as B-cell receptors (BCR) by interacting with the Fab parts of antigens. The most crucial surface marker of B lymphocytes is BCR (monomeric IgM), and the transmembrane α and β chains associated with BCR ensure the intracellular transmission of the received signal (Us 2016).

B lymphocytes possess negative and positive selection mechanisms like T lymphocytes. Through this mechanism, B cells that produce reactive BCR against their self-antigens or fail to form a functional Ig molecule undergo apoptosis, while others proliferate and mature (Us 2016).

The humoral immune response's developmental stages can be listed as a primary and secondary immune response. **The primary immune response** is generated by naive lymphocytes that encounter the antigen for the first time. **The secondary immune response** emerges when re-encountering the same antigen and it is faster, broader, and more capable of eliminating the antigen than the primary response. Memory lymphocytes with a long life span are formed during the primary immune response and they eventually become effectors during the secondary response. Here, immune system mechanisms respond to foreign antigens, but not to the host's antigens (self-antigens) (Camcıoğlu and Deniz 2007).

2.2. Cellular immunity

Antibodies that constitute humoral immunity cannot reach microorganisms within the infected cell. **Cellular immunity** formed of T lymphocytes is the immune mechanism that provides defence against intracellular microbes (Camcıoğlu and Deniz 2007).

While B-cell receptors can directly recognize the native antigen, T-cell antigen receptors can only recognize peptide antigens. Peptides are bound to specific peptide-presenting molecules called the major histocompatibility complex (MHC) found in antigen-presenting cells (APC). T cells can recognize antigen fragments processed by APCs and presented with MHC molecules (Bancherau and Steinman 1998).

T cells are called helper T cells ($CD4^+$) and cytotoxic T cells ($CD8^+$) according to their functions in the immune system (Bonilla and Oettgen 2010; Titiz 2014).

T cells with the characteristic surface marker CD4 molecule are called **helper T cells**. These cells help B lymphocytes to make antibodies and phagocytes to destruct ingested microbes. Those with characteristic surface marker CD8 molecules are called **cytotoxic T cells**. These cells function to eliminate virus-infected cells and tumour cells (Bancherau and Steinman 1998; Camcıoğlua and Deniz 2007).

Two types of peptide binding proteins, MHC class I and II induce cytotoxic T cells and helper T cells, respectively. Cytotoxic T cells that can directly kill a target cell upon activation recognize the intracellular antigens that split into peptides in the APC cytosol bound to MHC-I molecules. Extracellular antigens enter the APC endocytic pathway to be processed here and are usually presented to T helper cells by MHC class II molecules (Bancherau and Steinman 1998).

3. Immune system organs

The organs that play a role in the immune response are divided into primary and secondary lymphoid organs. The bone marrow and thymus are the primary lymphoid organs, in which lymphocytes differentiate, develop and mature. Lymph nodes, mucosal and cutaneous lymphoid tissues and the spleen form the secondary lymphoid organs. Lymphocytes encounter antigens and respond to antigenic stimuli in these organs (Bonilla and Oettgen 2010; Us 2016; Nikolich-Žugich and Davies 2017).

4. Cytokines

Cytokines are secreted proteins that play a role in immune system cell inter-communication and regulate immune reactions. A series of responses can be seen as a result of cytokine activity, and there may be situations where several cytokines are required for this response (Borish and Steinke 2003).

Cytokines can act on cells from which they are synthesized (autocrine), nearby cells (paracrine) and rarely on distant cells (endocrine) (Us 2016).

Cytokines can be classified according to their functions; innate immunity regulators (e.g. IL-1, IL-6, IL-12, IFN-α/β, IFN-γ, TNF-α), adaptive immunity regulators (e.g. IFN-γ, IL-2, IL-4, IL-5, IL-10) and hematopoiesis regulators (e.g. IL-7, IL-3, GM-CSF) (Us 2016).

Conclusion

We have a robust defence system against the infectious agents we encounter using natural and adaptive immunity mechanisms. Various problems that may occur in these immune mechanisms can lead to the emergence of serious diseases. Getting to know the immune system better contributes to finding solutions to the problems that may occur.

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CHAPTER TWO

IMMUNE SYSTEM EMBRYOLOGY

RÜMEYSA GÖÇ

Introduction

The lymphatic system is responsible for both providing a healthy structure and protecting the body in pathological conditions by maintaining the osmotic pressure level and keeping it at a certain intensity. The lymphoid tissue is the main organ of the immune system. The main cells of the tissue, however, are lymphocytes which are divided into three types according to their morphological structures: null cells, T lymphocytes and B lymphocytes. Null cells are the source of natural killer (NK) cells and stem cells (Moore et al. 2016).

Development of the lymphatic system

The development of the lymphatic system is associated with the cardiovascular system. At the 5th week of pregnancy, the cardiovascular system first begins to form. The lymphatic system occurs approximately two weeks after this development (Vladareanu et al. 2016). Although there is not enough information about the origin of lymphatic vessels, two hypotheses are emphasized;

1. The development of sacs directly from in situ mesenchyme
2. The formation of sacs from the endothelium of blood vessels.

Lymph sac formation first begins with six primary sacs. These are located as follows;

Two jugular; At the junction of the anterior cardinal and subclavian veins

Two iliac; At the intersection of the posterior cardinal and iliac veins

One retroperitoneal; Close to the root of the mesentery vein

One cisterna chyli; Dorsal to the retroperitoneal sac (Figure 2.1) (An and Rockson 2004).

The sacs are connected to each other by means of numerous channels, thus draining the lymph collected from the head, neck, limbs and body wall. The two jugular lymph sacs and the cisterna chyli sac are joined by the right and left thoracic ducts, then a new anastomosis is formed between these main canals (Kraus et al. 1990). The thoracic duct, which will then develop, originates from the anastomosis, the cranial section of the left thoracic duct, and the distal section of the right thoracic duct. The right lymphatic duct is formed from the cranial part of the right thoracic duct (Nussenbaum et al. 2000). Both channels maintain their original connection with the venous system. In this way, they drain into the junctions of the subclavian and internal jugular veins. Numerous variations in the final form of the thoracic canal are formed by the many anastomoses obtained in this process (Patton 1996; Carlson 2014).

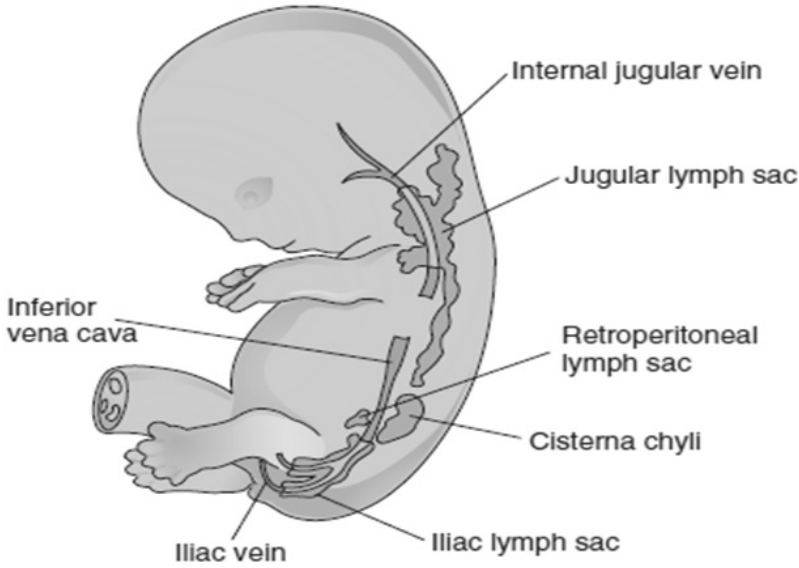

Figure 2.1: Development of lymph sacs (Moore et al. 2016)

Development of lymph nodes

Lymph nodes that develop from primary lymph sacs are of mesenchymal origin. Mesenchymal cells found in the structures of all lymph sacs form the contents of the sac, turning into groups of lymph nodes (Figure 2.2). The cavities located in the middle of the sacs form lymph channels that will form the lymph sinuses in the future. In addition, another part of the mesenchymal cells forms the outline of the connective tissue and the capsule structure. The only exception that does not show this development process is the superior part of the cisterna chyli (Moore et al. 2016).

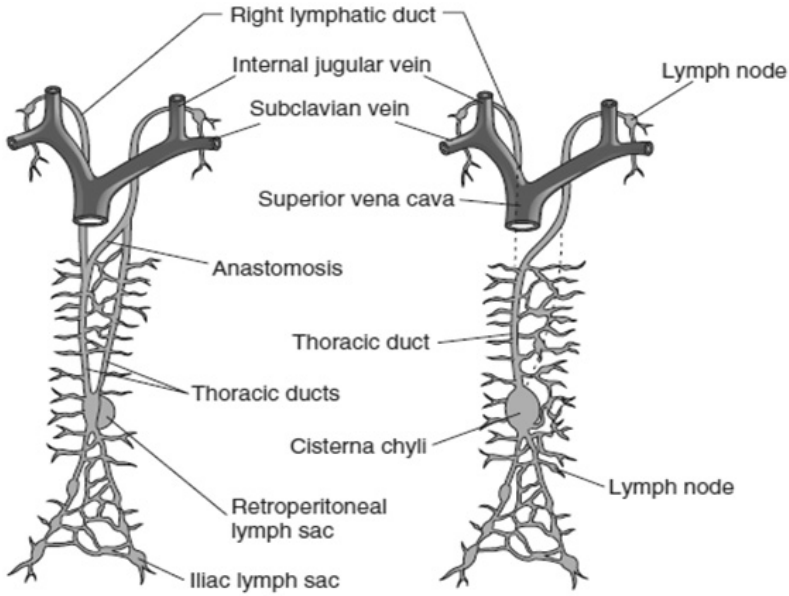

Figure 2.2: Development of lymph nodes (Moore et al. 2016)

Development of lymphocytes

In the early stages of the embryo, lymphocytes first originate from the mesenchymal stem cells of the yolk sac. In later periods, the spleen and liver perform this task. Lymphocytes produced at an early stage migrate to the bone marrow to form lymphoblasts. Looking at the lymph nodes in the last trimester, it is clear that the lymphocytes here come from the thymus. The mechanism is that small lymphocytes separated from the thymus

reach other lymphoid organs via the circulation. Some mesenchymal cells in the lymph nodes it reaches also turn into lymphocytes. During pregnancy, lymph nodes do not come into contact with foreign antigens, so lymph nodes are not seen in the fetus (Dudek 2015).

Development of tonsils

The tonsilla palatina develops bilaterally from the endodermal surface of the second pharyngeal pouch. At the beginning of the twelfth week of their development, the tonsil stroma starts to form with the stimulation of the mesoderm located under the pouch epithelium. The stroma grows to form buds. During this growth, it is observed that the cells located in the center die and harden over time. Hardened structures are destroyed by lymphoid tissue and crypts are formed. They are formed by the coming together of all tonsillar lymph nodes except the palatine tonsil (Moore et al. 2016). They are also named according to the important structure in the area where they come together. Lymph nodes located around the nasopharyngeal opening of the eustachian tube are called tubal tonsils. The communities formed in the posterosuperior region of the pharynx wall are called pharyngeal tonsils or adenoids. The nodules located at the root of the tongue in the last third of the tongue are expressed as lingual tonsils. In addition to the tonsils, lymph nodes are also observed in the mucous membranes of the respiratory and gastrointestinal systems (Schoenwolf et al. 2015).

Development of the thymus

In the intrauterine fifth week, the ventral part of the epithelium of the third pharyngeal pouch differs from the thymus, and the dorsal part from the inferior parathyroid gland (Tubbs et al. 2016). Thymic precursors on both sides begin to form by making endodermal proliferations in the ventral area in the fourth week. These proliferations spread over time into the mesenchymal tissue they come into contact with, forming solid and branching cords here. Over time, the cords transform into hollow tubes and make the precursors of further thymic lobules. Towards the seventh week, the primary structures of the thymus and inferior parathyroid glands are separated from the pharyngeal wall (Figure 2.3). The thymus then moves in the medial and caudal direction and pulls the inferior parathyroid with itself (Sadler 2018).

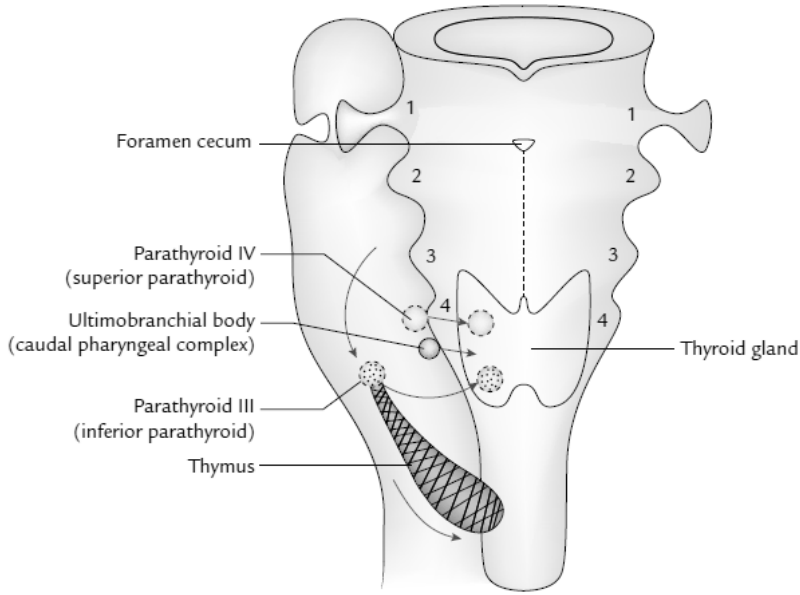

Figure 2.3: Development of the thymus (Singh 2012)

The main parts of the thymus coming from the right and left pouches converge in the final position of the anterior thorax. Sometimes during this transport, the tail part of the thymus is embedded in the thyroid gland or can remain in the form of isolated thymic tubers. The thymus in the thorax; This is located behind the sternum in front of the pericardium and great vessels. At this stage, while the thymus is still in the epithelial structure, the septa and capsule structure are formed by the arrival of neural crest cells. The epithelial reticular cells in the structure of the thymus are obtained from the endoderm of the third pharyngeal pouch, and lymphocytes (thymocytes) are obtained from the mesoderm of the third pharyngeal arch. By the twelfth week of the fetus, lobule sizes reach 0.5 to 2 mm in diameter (Moore et al. 2016). In addition, the separation of the cortex and the medulla appears. The spiral structures of the Hassall corpuscles in the medulla originate from the ectodermal cells of the third pharynx. It is thought that the signals produced by the Hassall corpuscles are necessary for the formation of regulatory T cells. The development of epithelial reticular cells, especially in the medulla of the thymus, depends on the formation of lymphotoxins. If lymphotoxins are not produced, the thymus cannot develop or function correctly. The thymus continues to grow and develop until adolescence. It occupies a large place in children

before puberty. In the elderly, it undergoes atrophy and leaves in its place adipose tissue, so it is difficult to recognize (Singh 2012).

Development of the spleen

This develops from a mesodermal origin between two layers in the dorsal part of the mesogastrium in the fourth week. All parts of the spleen originate from the mesoderm. The reticular network structure consists of septa and connective tissue forming the capsules also composed of mesodermal cells. Mesenchymal cells developing from here make splenic tissue lobules, which were previously many mesenchymal masses (Figure 2.4). These lobules are concentrated to form a single mass of the spleen (Cortes et al. 1996).

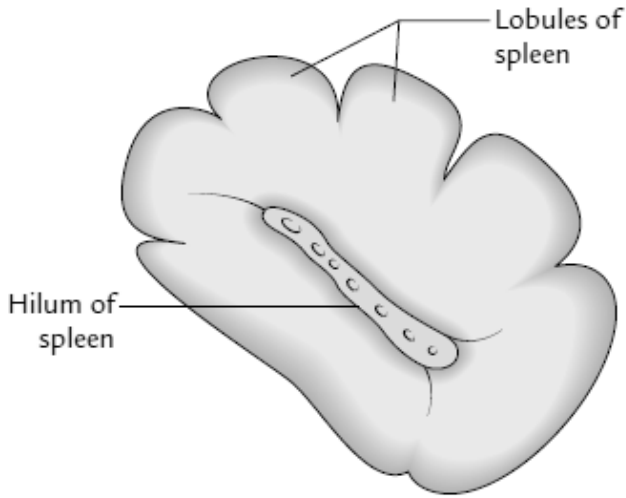

Figure 2.4: Development of the lobules and hilum (Singh 2012)

In the fifth week, this concentration differentiates into the spleen, which is a lymphatic organ with vascular structures. It forms null cells with cords branching from primordial spleen tissue. Some of the null cells form lymphoblasts, and others make hemopoietic cells. Blood formation starts in the early embryonic period and continues in fetal life. While blood production stops after birth, lymphocyte production continues after birth. Meanwhile, small concentrations around the hilum of the primary spleen can also form an accessory spleen (Singh 2012). Due to the turns of the stomach and the enlargement of the dorsal mesogastrium, the spleen

takes its main place on the left side of the abdominal cavity. At this time, permanent ligaments form: one of the ligaments is the gastrosplenic ligament, which forms the link between the greater curvature of the stomach and the splenic hilum. The other is the splenorenal ligament (lienorenal ligament) located between the spleen and the left kidney (Figure 2.5) (Ernst 2019).

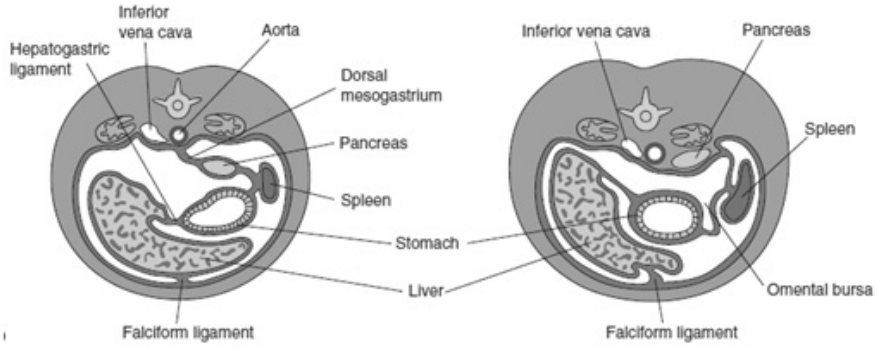

Figure 2.5: Ligaments of the spleen (Moore et al. 2016)

Conclusion

The lymphatic vessel network develops through the venous system. Therefore, the lymphatic system can change to the venous system about two weeks before this. After the formation of sacs, lymph nodes develop along the lymphatic network. The lymphatic processes are completed after birth. Since the body is not stimulated with a foreign antigen during pregnancy, the lymph nodes and the thymus cannot be formed.

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CHAPTER THREE

IMMUNE SYSTEM HISTOLOGY

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Introduction

The lymphoid system is responsible for the immunological defence of the body hence it is called the immune system. The system is composed of lymphoid organs and tissues. Lymphoid organs contain a three-dimensional mesh-like structure called reticular tissue, formed by reticular fibrils and epithelial reticular cells. Free cells settle into the network interspaces. Lymphoid organs and tissues are formed by the gathering of epithelial reticular and immune cells (Ross et al. 2011).

Lymphoid organs, as a component of the immune system, are responsible for protecting the body against pathogens or antigens. The basis of this defence mechanism or immune response is the ability to distinguish between self and foreigner (Leslie et al. 2016).

Two key components of the immune system are lymphocytes and helper cells. Lymphocytes are divided into two subgroups: B cells that are cell-independent and responsive to cell-bound antigens and T cells responsive to cell-bound antigens presented by specific molecules. After mature T and B cells leave the two primary organs (the bone marrow and the thymus), they travel in the blood circulation until they reach the secondary lymphoid organs (lymph nodes, spleen, and tonsils). Helper cells can interact with lymphocytes, present antigens to lymphocytes or regulate immune responses. Monocytes, macrophages, granulocytes, reticular cells, dendritic cells, follicular dendritic cells, Langerhans cells and epithelioreticular cells are examples of helper cells (Esrefoglu 2016).

Lymphoid organs are divided into two main groups; the primary lymphoid organs – the bone marrow and the thymus – produce cellular components of the immune system. The secondary lymphoid organs – the lymph nodes, spleen, tonsils, and the digestive system's mucosal lymphoid

tissues, Peyer plates and respiratory tract mucosa – are the places where the immune response occurs (Leslie et al. 2016).

Lenfoid tissue and organs

Lymphoid tissue and organs contain free cells located in the interspaces of the basic structure known as reticular connective tissue consisting of reticulum fibres and reticulum cells (Ross et al. 2011).

Lymph vessels begin as a blind capillary network in loose connective tissue. This removes substances and fluids from the extracellular spaces of the connective tissue. Thus, lymph is produced. As lymph vessels are more permeable than blood capillaries, they allow the passage of antigens and large molecules more easily (Esrefoglu 2016; Ross et al. 2011). The lymph travels within the lymph vessels and enters the lymph nodes via the afferent lymph vessel. Antigens are cleared within the lymph nodes. The lymph leaves the lymph nodes by the efferent lymph vessel which opens into the right lymphatic trunk or thoracic duct and then both join the bloodstream at the junction of the internal jugular vein and the subclavian vein (Kierszenbaum et al. 2019).

1. Lymphoid tissue

This is the area that protects the body against pathogenic substances and where the first immune response occurs. Lymphoid tissue exists in the organism in two forms, diffuse and nodular lymphoid tissue (Junqueira et al. 2003).

a. Diffuse Lymphoid Tissue: This consists of lymphocytes, plasma cells and macrophages settled on the primary network formed of the reticulum fibre and reticulum cells. It does not form follicles. It is found in the paracortex and medulla of the lymph nodes, the periarterial lymphoid sheath of the spleen and between the follicles in the lymph node cortex and the Peyer plates. The reason why it is named as diffuse lymphoid tissue is that all cells are homogeneously distributed in the area (Junqueira et al. 2003; Eroschenko 2008).

Like nodular lymphoid tissue, diffuse lymphoid tissue protects the organism from infectious agents and toxins. When the lymphocytes in this tissue encounter the antigen, they go to the lymph follicles to multiply, where they turn into effector T and B lymphocytes or memory cells. Then these cells return to the diffuse lymphoid tissue and take part in the immune response. Diffuse lymphoid tissue is vital for the following reasons; for the plasma cells to produce antibodies, and for the eosinophils to play an influential role in chronic inflammation and allergic reactions (Ross et al. 2011).

Diffuse lymphoid tissue is found in the digestive tract, respiratory system and genitourinary system and is located in the lamina propria layer. It is unencapsulated with no clear borders. Diffuse lymphoid tissue is collectively referred to as mucosa-associated lymphoid tissue (MALT). There are two types of MALT: bronchial-associated lymphoid tissue (BALT) and gut-associated lymphoid tissue (GALT). MALT's primary function is to produce and release antigen-specific IgA from the mucosal surface (Cesta 2006).

b. Nodular Lymphoid Tissue (lymph follicles, lymph nodules): This consists of lymph follicles. It is unencapsulated and has clear borders. Nodular lymphoid tissue has an oval or round-shaped structure consisting of tightly clustered lymphocytes located on reticular connective tissue formed by the reticulum cell and fibre network. Lymph follicles are found in the outer cortex of the lymph node, the white pulp of the spleen, the tonsils, the appendix, and the lamina propria of the digestive and respiratory tract (Junqueira et al. 2003; Eroschenko 2008).

If a lymphoid follicle only consists of small and newly developed lymphocytes, and the appearance of the central and peripheral parts is the same namely displaying a homogeneous appearance, this follicle is called a primary lymphoid follicle (nodule). The primary lymphoid follicle has no germinal centre and includes resting B-memory lymphocytes, plasma cells, macrophage dendritic cells, and reticular cells. A secondary lymphoid follicle (nodule) is more frequently seen, and the follicle centre and the periphery differ from each other. The middle part of the secondary follicle is called the germinal centre, and this part is stained paler and looks looser. This area becomes apparent when the lymphocyte recognizes an antigen and comes to the lymph follicle to proliferate. Numerous mitoses are observed in the germinal centre as an indicator of cell proliferation. In this area, lymphocytes proliferate, turn into plasma cells and synthesize antibodies (Hamel et al. 2012). The reason for the pale staining of this region is that it contains large immature lymphocytes. Large lymphocytes are stained paler because their nuclei are more euchromatic and there is more cytoplasm than in small lymphocytes. The presence of a germinal centre in a follicle is an indicator of an antigenic reaction. Macrophages also increase during the immune response in this region. Apart from their usual role in immune responses, macrophages also phagocytize and eliminate malformed lymphocytes. In the region, among the B lymphocytes, there are also follicular dendritic cells. The dark basophil stained, tight-looking peripheral (outer) part surrounding the germinal centre like a ring is called the mantle zone (Huang 2020). Newly formed small B lymphocytes are found in the mantle layer (Huang 2020).

Nodules are usually spread randomly and one by one. Nevertheless, there are nodule groups found in some specific areas of the digestive tract (Ross et al. 2011). These are;
Tonsils: these are the lymphoid tissue groups forming a lymphoid tissue ring at the entrance to the oropharynx.
Peyer's plaques: these are found in the ileum and consist of multiple lymph node groups.
Appendix: this contains multiple lymph nodes in the caecal lamina propria.

2. Lymph nodes

These are secondary lymphoid organs. Lymph nodes are round or kidney-shaped, encapsulated organs with a diameter of 1 mm to 2 cm, located throughout lymph vessels. These organs, which filter and cleanse the lymph of antigens, also add a large number of lymphocytes to the lymph content, allowing these cells to be transported in the body (Kierszenbaum et al. 2019).

Lymph nodes are common throughout the body and found as groups in the armpits, groin, neck, chest and abdominal cavity. A large number of afferent lymph vessels enter the organ from the convex edge of the lymph node (hilum). One or two efferent lymph vessels leave the organ from the hilum, which is a concave pit. Also, the blood vessels and nerves, enter and exit the organ through the hilum. A capsule from the fibrous connective tissue surrounds the lymph nodes. Extensions detaching from this capsule proceed forward as trabeculae and divide the organ into noncomplete parts (Ross et al. 2011).

The lymph is carried to the lymph nodes by afferent lymph vessels and leaves the organ via efferent lymph vessels, being transferred through the lymph sinuses that show continuity within the organ. Afferent lymph vessels at first open into the irregular space located between the capsule and the cortex called the subcapsular or marginal sinus. The subcapsular sinus continues with the subtrabecular or intermediate lymph sinuses that advance towards the medulla around the trabeculae. Intermediate sinuses continue with the medullar sinuses in the medulla. Medullary sinuses drain into efferent lymph vessels in the hilus region (Willard-Mack 2006). Sinuses (sinusoids) are lined with endothelium. The endothelium of the capsule or trabecula is continuous on the side facing the connective tissue, while it is discontinuous on the side facing the lymphoid tissue. With the help of these discontinuations, lymphocytes and macrophages can easily migrate in between the lymphoid tissue and lymph. Although macrophages are located in the lymphoid parenchyma, they send pseudopods that pass through discontinuous parts of the sinus endothelium, creating a barrier for particles to catch onto (Esrefoglu 2016).

The parenchyma of the lymph nodes consists of two parts, the cortex and medulla (Figure 3.1). The cortex is generally examined in two parts, namely the outer cortex and the inner cortex (paracortex) (Zeppa et al. 2018).

Outer cortex: This is found just below the capsule and is easily recognized due to the presence of lymph follicles. Lymphoreticular tissue in the cortex is organized as nodular or diffuse; namely, diffuse lymphoid tissue extends between the lymph follicles (nodular lymphoid tissue). The germinal centre located in the middle of the lymph follicles is stained lighter than the peripheral part (Figure 3.1). Several undifferentiated lymphoblasts, plasma cells, macrophages and follicular dendritic cells are encountered in the germinal centre. Germinal centres disappear when mitotic activity stops and can be regenerated with a new stimulus (Zeppa et al. 2018). Follicular dendritic cells, found with lymphocytes in germinal centres, are cells located between B lymphocytes and having numerous thin branching extensions. Antigen-antibody complexes can remain in this state for months or even years by being presented to the cytoplasmic extensions of these cells via the antibody's FC receptor. Although this phenomenon is similar to the mechanism of antigen-antibody complexes' attachment to macrophages, the antigen is not usually taken into the cytoplasm of these cells. Therefore, follicular dendritic cells not expressing MHC 2 receptors on their surface are generally not examined within the context of antigen-presenting cells (Esrefoglu 2016; Kierszenbaum et al. 2019).

Inner cortex (Paracortex): This consists of diffuse lymphoid tissue not containing lymph follicles. Lymphocytes are homogeneously distributed over the basic structure formed by the reticulum cell and fibre network in this region. The paracortex of lymph nodes is mainly an area where T lymphocytes are densely found (Junqueira et al. 2003; Eroschenko 2008).

Besides T lymphocytes, macrophages and dendritic cells are also found in the paracortex. Dendritic cells are bone marrow-derived, protrusive cells and sensitive to foreign antigens in the environment. As they capture and process antigens and present them to T lymphocytes, they are examined within the scope of antigen-presenting cells. Their ability to present antigens in a protein structure bound to MHC 1 and MHC 2 molecules is more potent than that of other antigen-presenting cells. Their MHC 2 levels are very high and also contain many molecules required for the activation of T lymphocytes (Ross et al. 2011).

The paracortex is a unique area due to the high content of endothelial venules (postcapillary venules). These vessels, lined with single-layered cubic epithelium instead of single-layered squamous epithelium, are the transition area of circulating lymphocytes to lymphoid tissue. High endothelial venules are found not only in the paracortex region but also in