

# 1-6 The Lymphoid System and Lymphocyte Circulation

## There are two types of lymphoid tissues

The lymphoid system is traditionally divided into primary and secondary lymphoid tissues. **Primary lymphoid tissues** are the tissues in which lymphocytes are generated and differentiate into mature naïve lymphocytes: these are the bone marrow for B cells, and the bone marrow and the thymus for T cells; they will be discussed in Chapter 7. **Secondary lymphoid tissues** are the tissues in which immune responses are initiated, and the **lymphatic vessels** that connect them to the tissues and the bloodstream and thus to sites of infection (Figure 1-18).

## Secondary lymphoid tissue brings antigen together with lymphocytes

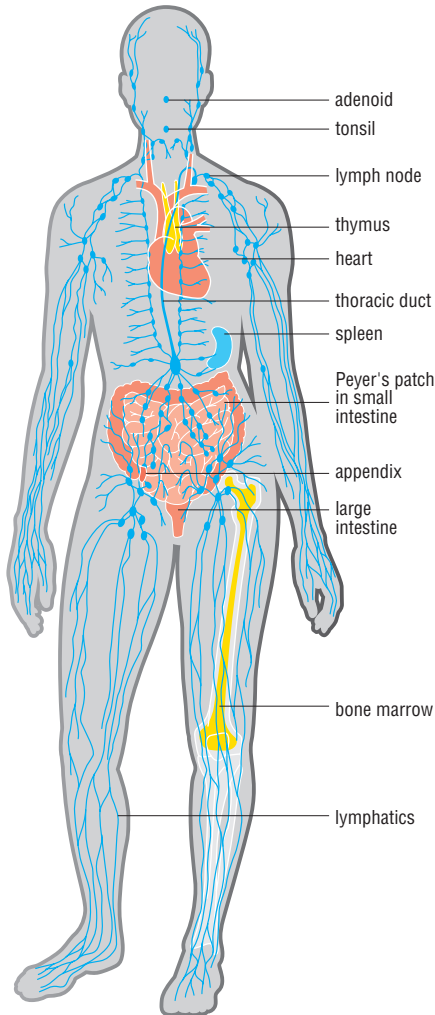
The adaptive immune system pays two penalties for the extraordinary diversity of the antigen receptors of lymphocytes. First, unlike those on cells of the innate immune system, the antigen receptors of lymphocytes do not distinguish microbial products from harmless ones; and second, only a very small number of lymphocytes express receptors of any given specificity. The first of these disadvantages is overcome by the requirement for cells of the innate immune system, and in particular dendritic cells, that have been activated by microbial products. The second disadvantage is overcome by the specialized architecture of the secondary lymphoid tissues, which are organized to collect antigen and antigen-presenting cells and ensure that each naïve lymphocyte is continually brought into contact with them, so that clonal selection can occur, with expansion in numbers of antigen-specific lymphocytes.

Secondary lymphoid tissues (Figure 1-19) consist of the **lymph nodes**, which are clustered at sites such as the groin, armpits and neck and along the small intestine, and collect antigen from the tissues; the **spleen**, which collects antigen from the bloodstream; and the **mucosa-associated lymphoid tissues (MALT)**, which collect antigen from the respiratory, gastrointestinal and urogenital tracts and are particularly well organized in the small intestine, in structures known as **Peyer's patches**. The lymph nodes are connected to the tissues and the bloodstream by a system of lymphatic vessels. The **afferent lymphatics** drain extracellular fluid (**lymph**) from the tissues, including mucosal tissues, into the lymph nodes; and the **efferent lymphatics** carry the lymph out of the secondary lymphoid tissues and ultimately into a collecting vessel known as the **thoracic duct** (or for lymph nodes in the neck, the **cervical duct**), and thence through the heart and into the bloodstream.

When mature naïve lymphocytes leave the bone marrow and thymus, they enter the bloodstream and then circulate continuously through the lymph nodes, which they enter by migrating through the walls of specialized blood vessels, leaving via the efferent lymphatic vessels, which ultimately return them to the bloodstream. Antigen is collected in secondary lymphoid tissues both directly through the blood, from which antigen reaches the spleen, and through the afferent lymphatic vessels, which drain infected tissues and deliver antigen to the lymph nodes; and more indirectly by three specialized cell types (including dendritic cells) that we discuss in the next section.

## Chemokines direct the migration of lymphocytes and determine the specialized microenvironments in which they are activated

Secondary lymphoid tissues provide a highly structured microenvironment adapted to foster the cell–cell interactions required to initiate an adaptive immune response. All secondary lymphoid tissues have distinct regions specialized to support the activation of T cells and B cells, although



**Figure 1-18 The lymphoid organs** The lymphatic vessels and secondary lymphoid tissues are shown in blue, with primary lymphoid organs in yellow.

### Definitions

**afferent lymphatics:** lymphatic vessels entering lymph nodes from tissue spaces.

**efferent lymphatics:** lymphatic vessels leaving lymph nodes and returning lymph to the bloodstream.

**follicle:** (of lymphoid tissue) B cell area of secondary lymphoid tissue.

**germinal center:** site of vigorous proliferation of B cells

in the B cell follicles of secondary lymphoid organs.

**lymph:** fluid drained from the tissues and flowing through lymphatic vessels.

**lymphatic vessels:** system of vessels draining fluid (lymph) from the tissues and in which dendritic cells and antigens are delivered to lymph nodes.

**lymph nodes:** secondary lymphoid organs distributed widely in the body but especially in the groin, the axilla and the neck, and along the small intestine.

**lymphoid chemokine:** constitutively expressed chemoattractant molecule that directs the migration of lymphocytes and dendritic cells into specialized regions of the secondary lymphoid tissues. Also known as *homeostatic chemokine*.

**MALT:** see **mucosa-associated lymphoid tissues**.

**mucosa-associated lymphoid tissues (MALT):** secondary lymphoid tissue in the walls of the gastrointestinal, respiratory and urogenital tracts.

**PALS:** see **periarteriolar lymphoid sheath**.

this is most clearly seen in the lymph nodes (see Figure 1-19a). B cells are usually concentrated in relatively well defined areas known as **follicles**, adjacent to or surrounded by T cell areas that may be more diffuse: in the lymph nodes, the T cell area is sometimes called the **paracortical area**; in the spleen, the bulk of which is formed from highly vascularized tissue known as the **red pulp**, the lymphoid tissue is known as the **white pulp** and each T cell area takes the form of a cuff, known as the **periarteriolar lymphoid sheath (PALS)**, round an arteriole from which antigen is delivered (see Figure 1-19b). In lymphoid tissue actively responding to infection, the B cell follicles are enlarged and have a perceptible central region known as the **germinal center** composed of rapidly proliferating B cells.

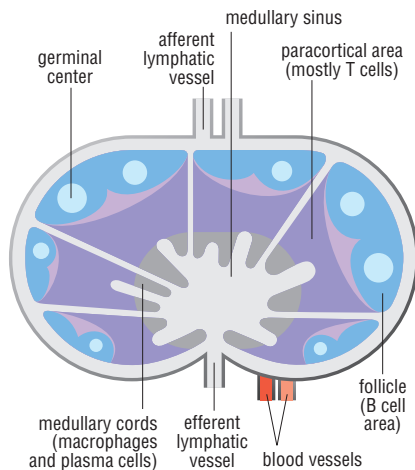
The specialized architecture of the secondary lymphoid tissues is determined by **lymphoid chemokines**, chemoattractant molecules that are differentially expressed in the T and B cell zones and direct the migration of dendritic cells as well as T and B lymphocytes to these areas. Lymphoid chemokines and other specialized homing molecules also direct the migration of circulating lymphocytes through the specialized blood vessels through which they enter the lymphoid tissues, and regulate their exit, ensuring continued recirculation and surveillance of all lymphoid tissues in which antigen may be present. These processes are described in Chapter 2, and the control of lymphocyte homing is discussed in more detail in Chapters 5 and 6.

## Secondary lymphoid tissue is sustained and can be induced by signals from immune cells

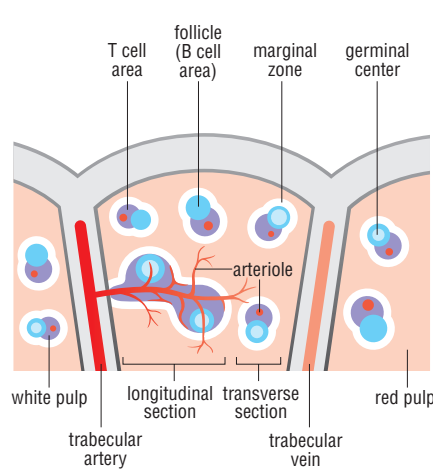
The chemokines that establish the architecture of the secondary lymphoid tissues, unlike the chemokines produced in the course of an immune response, are expressed constitutively. Once established however the lymphoid architecture may be maintained in part by normal lymphocyte traffic and interactions. This may explain why, in acquired immunodeficiency disease (AIDS), in which an entire class of T lymphocytes is destroyed, the organized architecture of the lymph nodes collapses. Conversely, at sites of chronic inflammation, organized lymphoid tissue may form: this is known as *tertiary lymphoid tissue*.

**Figure 1-19 Secondary lymphoid tissues** The specialized sites of T cell activation are colored purple; the sites of B cell activation are blue. In lymph nodes (a), spleen (b) and the Peyer's patches of the small intestine (c), the B cell zones are seen as defined follicles; functionally equivalent areas, not all as well defined, are found in all mucosal lymphoid tissues. Proliferating B cells are concentrated in the germinal centers. The T cell regions (purple) are adjacent to the B cell follicles. In the spleen, these form the periarteriolar lymphatic sheaths (PALS) and are surrounded by a region known as the *marginal zone*, which we describe in the next section. In the lymph nodes, the T cell zones are separated from the medullary sinus, which forms the exit route into the efferent lymphatic vessels, by a region known as the *medullary cords*, which are rich in macrophages and plasma cells secreting large quantities of antibody.

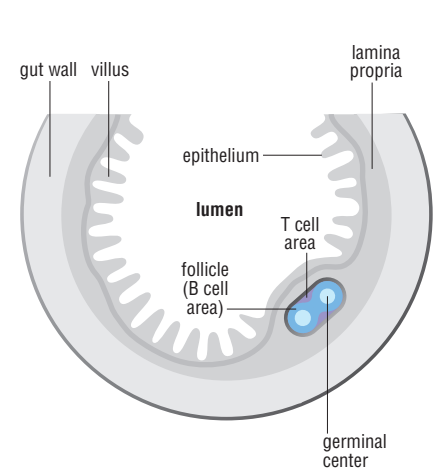
(a) Lymph node



(b) Spleen



(c) Peyer's patch



**paracortical area:** (of **lymph node**) area beneath the outer regions of the lymph node and where T lymphocytes accumulate.

**periarteriolar lymphoid sheath (PALS):** T cell area in the **spleen**, formed around arterioles.

**Peyer's patches:** organized regions of **secondary lymphoid tissue** in the wall of the small intestine.

**primary lymphoid tissues:** bone marrow and thymus, in which lymphocytes differentiate and mature.

**red pulp:** site of destruction of senescent red blood cells in the **spleen**.

**secondary lymphoid tissues:** tissues in which lymphocytes are brought together with antigen and adaptive immune responses are initiated.

**spleen:** secondary lymphoid organ in the abdomen collecting antigen from the bloodstream.

**thoracic duct:** main vessel collecting **lymph** for delivery to the heart.

**white pulp:** lymphoid area of the **spleen**.

## References

- Cyster, J.G.: **Chemokines, sphingosine-1-phosphate, and cell migration in secondary lymphoid organs.** *Annu. Rev. Immunol.* 2005, **23**:127–159.
- Picker, L.J. and Siegelbaum, M.H.: **Lymphoid tissues and organs** in *Fundamental Immunology* 4th ed. Paul, W.E. ed. (Lippincott-Raven, New York, 1999), 449–531.