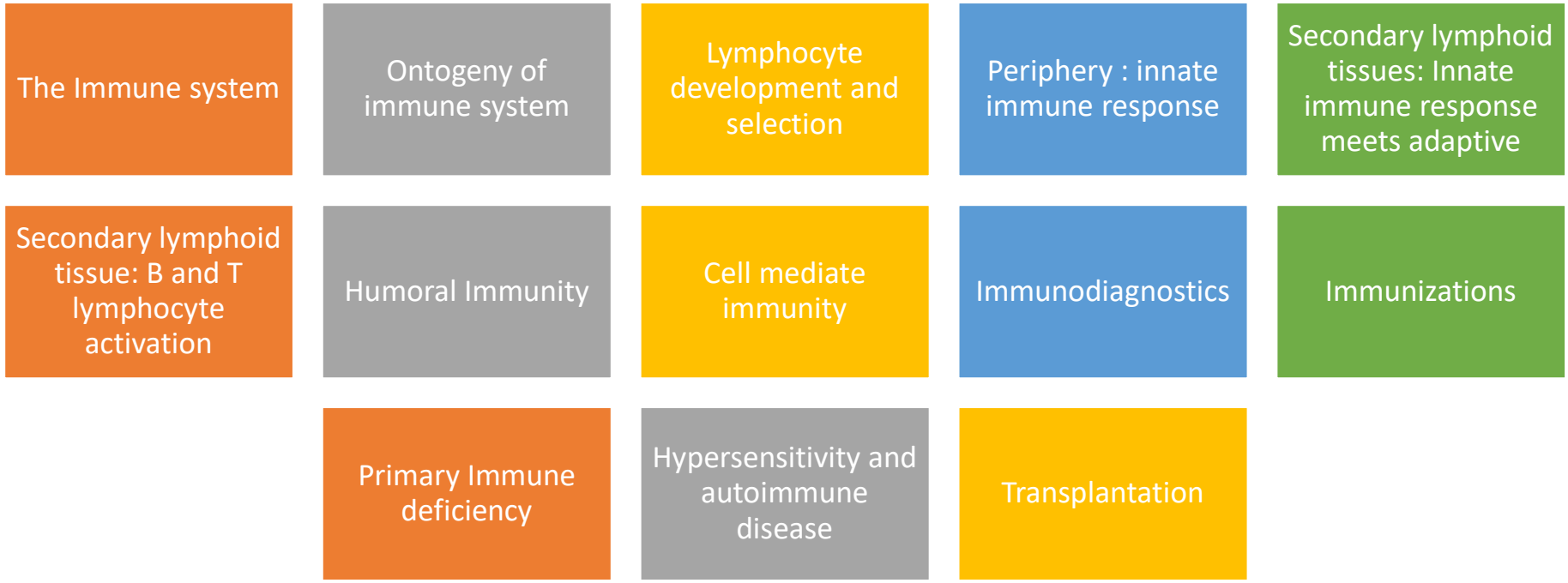
IMMUNOLOGY


The Immune system
Ontogeny of immune system
Lymphocyte development and selection
Periphery : innate immune response
Secondary lymphoid tissues: Innate immune response meets adaptive
Secondary lymphoid tissue: B and T lymphocyte activation
Humoral Immunity
Cell mediate immunity
Immunodiagnostics
Immunizations
Primary Immune deficiency
Hypersensitivity and autoimmune disease
Transplantation

Immunology

IMMUNOLOGY

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Learning objective

- Demonstrate understanding of inflammatory response
- Solve problems concerning structure of and migration to secondary lymphoid tissue

Secondary Lymphoid Tissues : Innate immune response meets adaptive

MIGRATION TO THE SECONDARY LYMPHOID TISSUE

- Within a few hours of the initiation of the acute inflammatory response, the professional
- APCs that have phagocytosed and processed the invading antigen begin to leave the area via lymphatic vessels. Dendritic cells are probably the most efficient of these cells and retract their membranous processes to round up and begin the journey to the closest lymph node (Figure I-5-1).

Secondary Lymphoid Tissues : Innate immune response meets adaptive

- As discussed earlier, dendritic cells and other phagocytes such as macrophages bind to antigens via PRRs, with a limited diversity, such as the TLRs. The activation of the TLRs induces an acute inflammatory response in the tissue, leading to the production of pro-inflammatory cytokines. These cytokines cause a change in the phenotype of the phagocyte which eventually alters their migration pattern and enhances their function.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

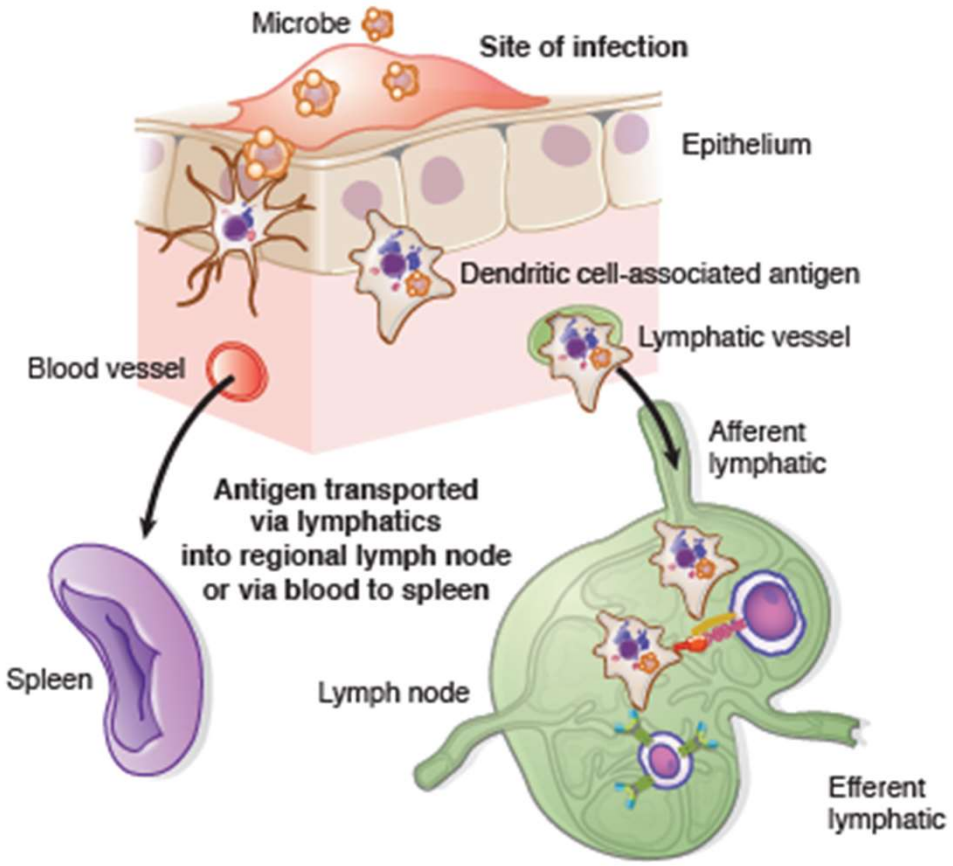
- Activated dendritic cells will begin to express a chemokine receptor called CCR7. CCR7 is activated by chemokines that are produced by the endothelium.
- Chemokines bind to CCR7 on DCs, allowing them to exit the tissue.
- Upon activation, DCs switch focus from antigen-capture to antigen presentation.
- Activated DCs concentrate in draining lymph nodes and become trapped in the paracortex.
- Naive T cells expressing CCR7 bind to chemokines on HEVs and migrate to the paracortex.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

- Considering the vast number of pathogens that enter the body, it would be a nearly impossible task for the lymphoid cells to travel to all body sites to protect the host. Thus, the antigens are taken to the secondary lymphoid tissues where the lymphocytes constantly recirculate in order to come into contact with their specific antigen.
- If the initial tissue damage is sufficient, these cells can also be flushed into blood vessels, ultimately becoming trapped in the vascular sinusoids of the spleen. Regardless, the secondary lymphoid organs (lymph nodes and spleen) are the sites where naive, mature lymphocytes will fi st be exposed to their specific antigens.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Transport of antigen to secondary Lymphoid organ



Secondary Lymphoid Tissues : Innate immune response meets adaptive

STRUCTURE OF THE SECONDARY LYMPHOID TISSUE

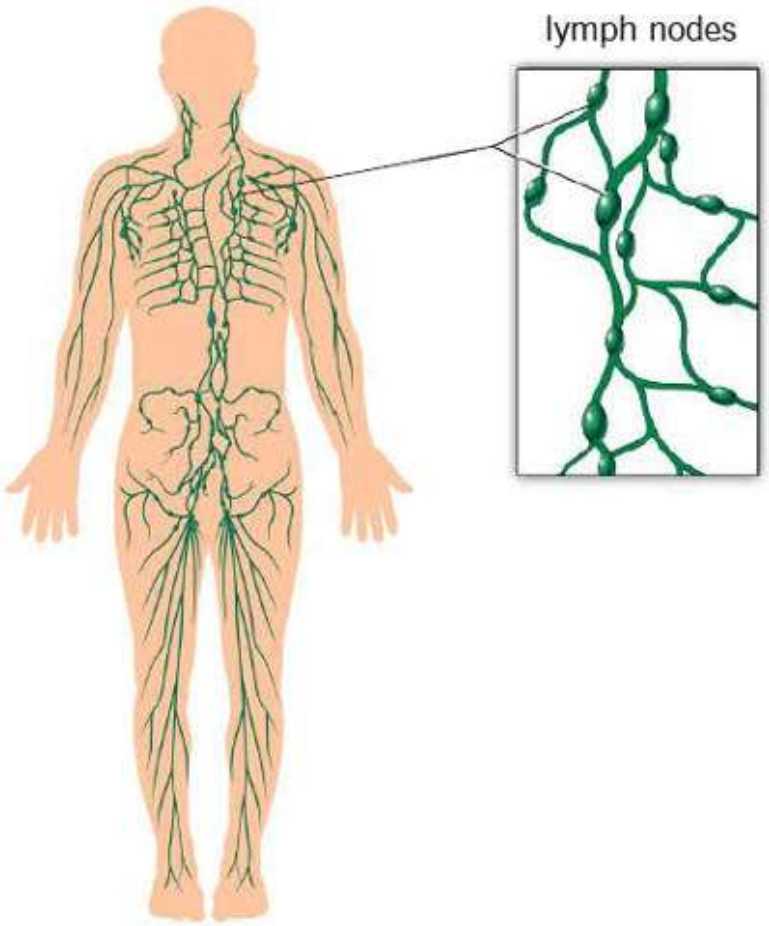
- Lymph nodes are small nodular aggregates of secondary lymphoid tissue found along the lymphatic channels of the body. They are designed to initiate immune responses to tissue-borne antigens.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

- Each lymph node is surrounded by a fibrous capsule that is punctured by afferent lymphatics, which bring lymph into the subcapsular sinus.
- The fluid percolates through an outer cortex area that contains aggregates of cells called follicles.
- The lymph then passes into the inner medulla and the medullary sinus before leaving the node through the hilum in an efferent lymphatic vessel.
- Ultimately, lymph from throughout the body is collected into the thoracic duct, which empties into the vena cava and returns it to the blood.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

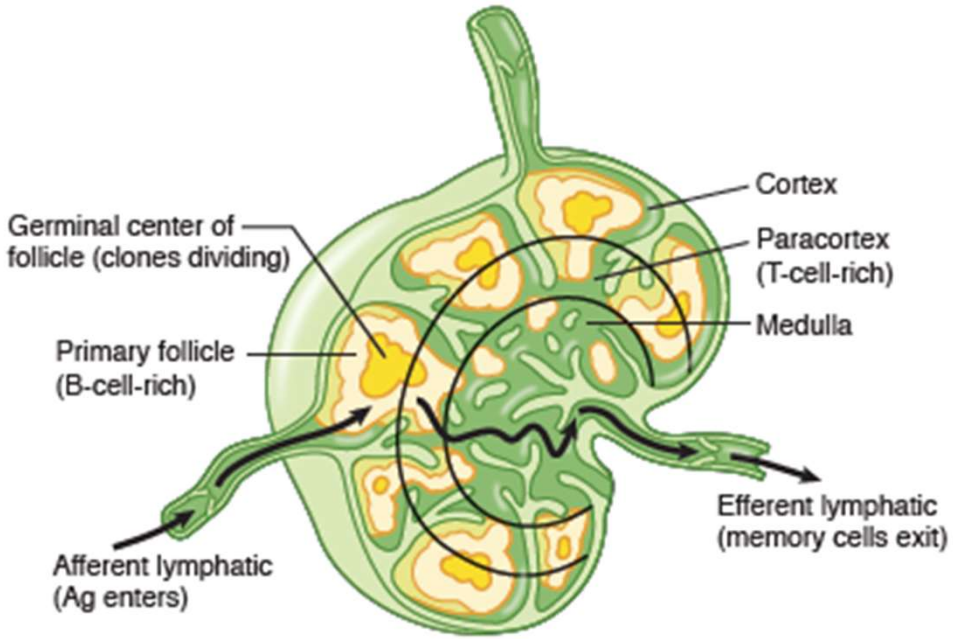
Lymphatics and Lymph Node



Secondary Lymphoid Tissues : Innate immune response meets adaptive

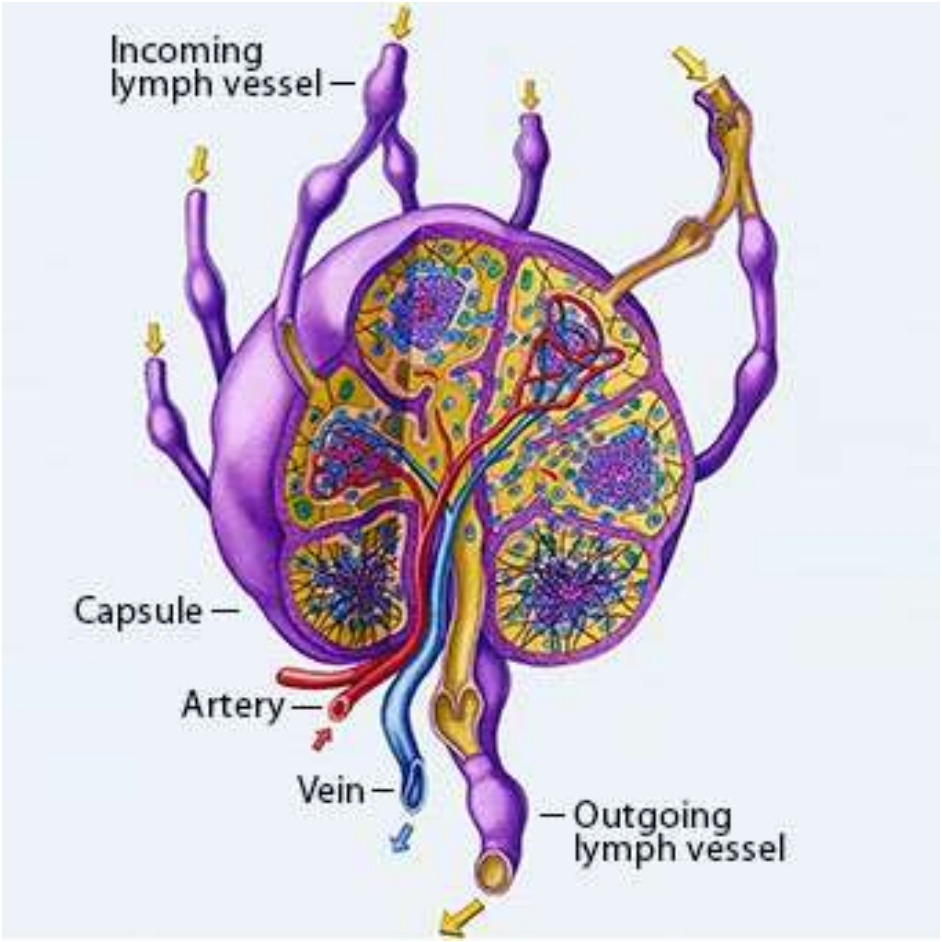
Lymph node

Schematic diagram



Secondary Lymphoid Tissues : Innate immune response meets adaptive

Lymph Node

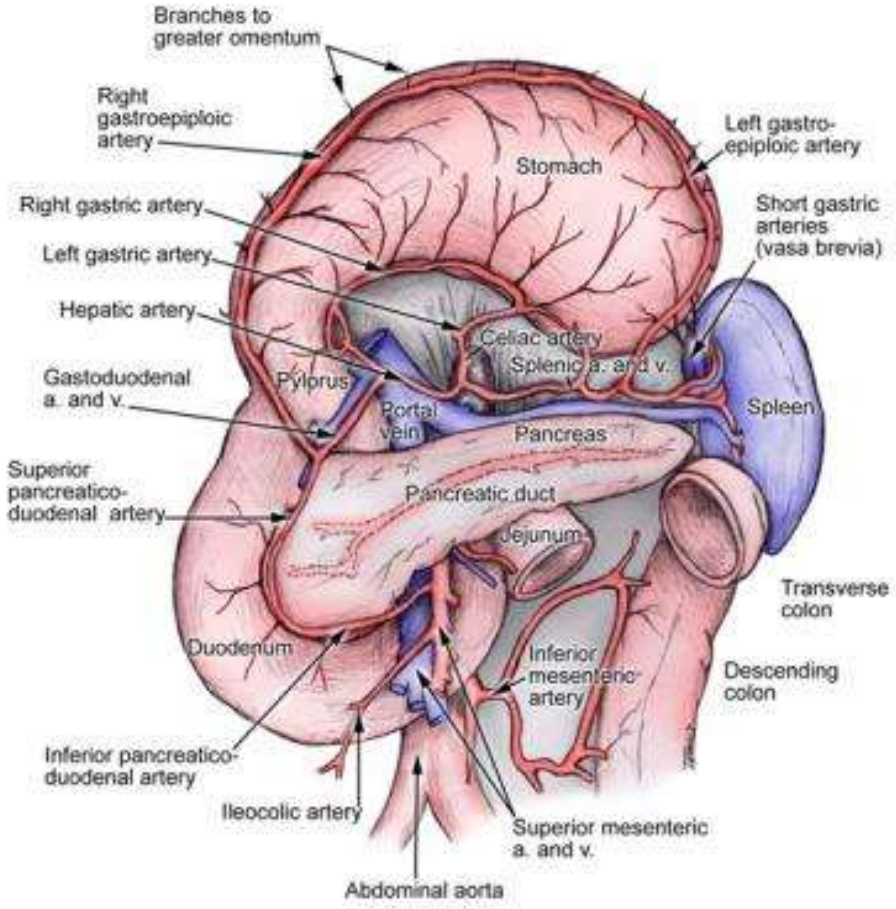


Secondary Lymphoid Tissues : Innate immune response meets adaptive

- The spleen is the secondary lymphoid organ that initiates immune responses to blood-borne antigens. A single splenic artery enters the capsule at the hilum and branches into arterioles, which become surrounded by cuffs of lymphocytes known as the **periarteriolar lymphoid sheaths (PALS)**. Lymphoid follicles surrounded by a rim of lymphocytes and macrophages are attached nearby. This constitutes the white pulp. The arterioles ultimately end in vascular sinusoids, which make up the red pulp. From here, venules collect blood into the splenic vein, which empties into the portal circulation.

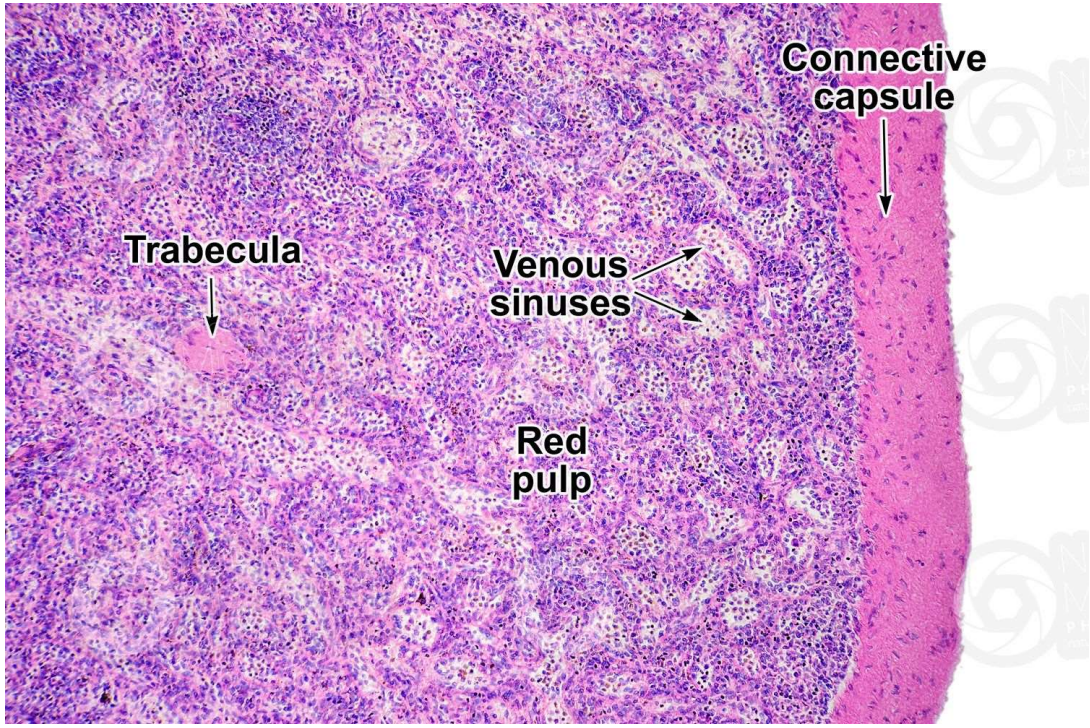
Secondary Lymphoid Tissues : Innate immune response meets adaptive

Spleen



Secondary Lymphoid Tissues : Innate immune response meets adaptive

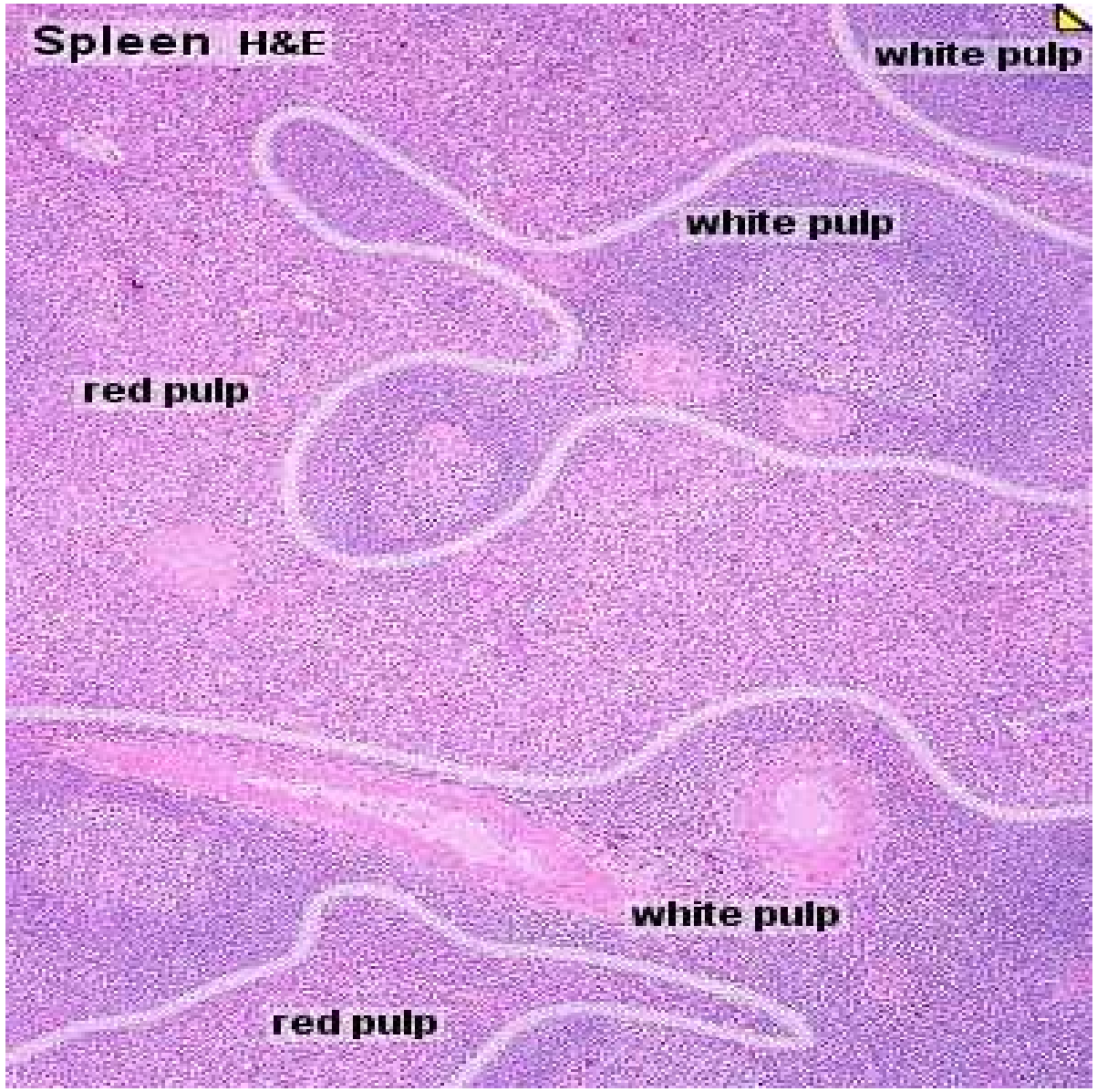
Spleen Histology



Secondary Lymphoid Tissues : Innate immune response meets adaptive

Spleen

Red and White pulp



Secondary Lymphoid Tissues : Innate immune response meets adaptive

ANTIGEN PROCESSING AND PRESENTATION

- **Exogenous Pathway of MHC Loading**
- **Endogenous Pathway of MHC Loading**

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Exogenous Pathway of MHC loading

- Although some small, easily digestible antigens are almost totally degraded and exocytose by phagocytes, the critical fi st step in the elicitation of the adaptive immune response to a primary antigenic challenge is the processing of antigen for the presentation to naive T lymphocytes.
- Professional antigen-presenting cells (APCs) include dendritic cells, macrophages, and B cells; their job is to load partially degraded peptides into the groove of the MHC class II molecules.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

The APCs have slightly different functions to help elicit unique immune responses required to eliminate various types of pathogens.

- **Dendritic cells** are the most prolific of the APCs, as they do not have to be activated in order to present antigen to T cells. They constitutively express the co-stimulatory molecules needed to activate the T cells.
- **Macrophages** help activate the Th1 response by digesting microbes and presenting them to the T cells to elicit a cell-mediated immune response.
- **B cells** present specific protein antigens to T cells to help elicit a humoral immune response or a Th2 response (*see* chapter 7). B cells are unique, as they are the only APCs that specifically recognize antigen via the B cell receptors (of surface bound antibody).

Secondary Lymphoid Tissues : Innate immune response meets adaptive

APC	Expression of Co-stimulatory Molecules	Expression of HLA Class II	Major Function
Dendritic cells	Constitutive: B7 (B7.2)*, CD40	Constitutive but upregulated by IFN-γ	Activation of naïve Th cells
	Inducible: IFN-γ, TLR's		
Macrophages	Constitutive: B7 (B7.2), CD40	Negative or low level expression but induced by IFN-γ	Initiation and effector phase of the T_h1 response for cell mediated immunity
	Inducible: IFN-γ, TLR's		
B cells	Constitutive: CD40	Constitutive but upregulated by IL-4	Initiation of the T_h2 response for humoral immunity
	Inducible: T cells, B7		

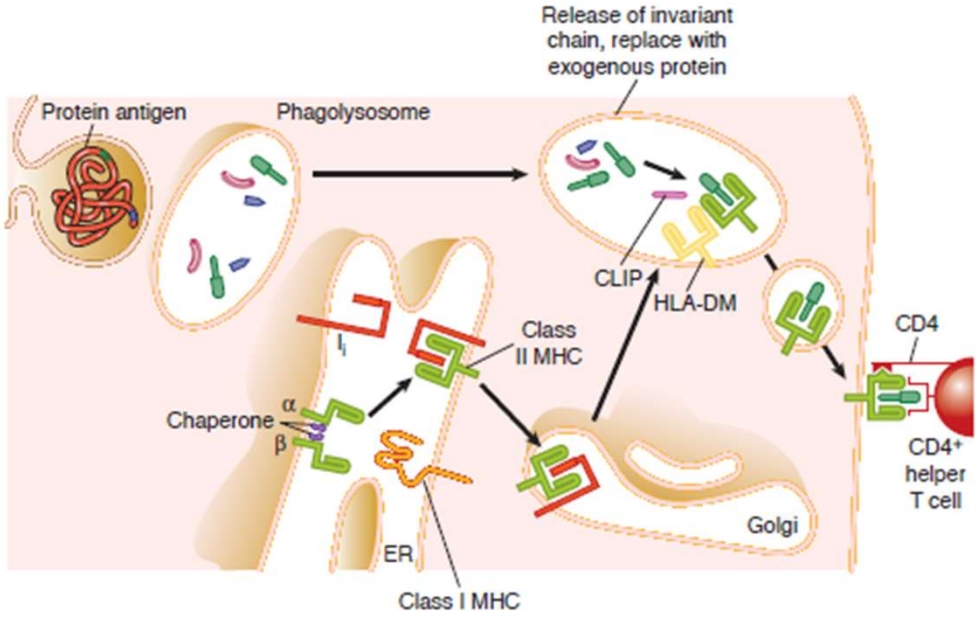
APC Expression of Co-stimulatory Molecules, Class II MHC, and Function

Secondary Lymphoid Tissues : Innate immune response meets adaptive

- When MHC class II molecules are produced in the endoplasmic reticulum of an APC, a protein called the invariant chain (Ii) is synthesized at the same time. The Ii has a class II invariant chain peptide (CLIP) that binds with high affi ty to the peptide binding cleft of newly synthesized MHC class II molecule. The Ii with its associated CLIP blocks the peptide-binding groove so no normal cellular peptides can accidentally be attached. The CLIP + Ii is transported in a vesicle to the location of endocytic vesicles containing the ingested, internalized peptides.
- A molecule called HLA-DM is found within the late endosome (lysosomal compartment). It is the job of HLA-DM to exchange the CLIP for a phagocytosed peptide that will bind to the MHC class II molecule with even higher affi ty than the CLIP. Once exchanged for the CLIP, the peptide is loaded on the MHC class II molecule and the complex is transported to the cell surface, where it will be accessible for interaction with any T lymphocyte with a complementary TCR. If, however, the class II molecule does not fi d a peptide that it can bind with even higher affi ty than the CLIP, the empty class II molecule is unstable and degraded, and will thus nevermake it to the cell surface.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Exogenous pathway of antigen presentation



Secondary Lymphoid Tissues : Innate immune response meets adaptive

Endogenous Pathway of MHC Loading

The endogenous pathway of antigen-processing handles threats to the host which are intracellular. These might include viruses, altered/mutated genes (from tumours), or even peptides from phagocytosed pathogens that may escape or be transported out of phagosomes into the host cell cytoplasm. Intra cellular proteins are routinely targeted by ubiquitin and degraded in proteasomes.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

- The peptides from these proteins are transported through a peptide transporter known as the **TAP complex (transporter of antigen processing)**, and into the endoplasmic reticulum, where they have the opportunity to bind to freshly synthesized MHC class I molecules.

• The TAP complex includes the TAP proteins that form the tunnel through which the proteins travel and a bridging protein called tapasin.

• Tapasin bridges the TAP transporter to the MHC class I molecule so that as these peptides enter the endoplasmic reticulum, they are easily bound by the newly synthesized and empty class I molecules.

• The peptide-MHC class I complexes are then transported to the cell membrane where they may be presented to CD8+ T lymphocytes (*see* chapter 8).

Secondary Lymphoid Tissues : Innate immune response meets adaptive

- Just as with the MHC class II molecules, MHC class I is unstable without the addition of peptide and will not be expressed at the cell surface without the addition of peptide.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Clinical Correlate

Proteasome Inhibitors in the Treatment of Cancer

By their very nature, oncogenic cells are overly proliferative, requiring a higher rate of protein synthesis than their normal cell counterparts. A majority of cellular proteins are degraded via the ubiquitin proteasome pathway, including many proteins that play a role in maintaining cellular homeostasis. These include proteins that regulate the cell cycle, apoptosis, etc.

- Proteasome inhibitors induce apoptosis in tumor cells by interfering with the degradation of these regulatory proteins. For example, proteins that regulate the cell cycle such as p53 may be inactivated in transformed cells. This leads to a dysregulation of cell cycle control and a progression of the tumorigenesis.

- Proteasome inhibitors will produce an accumulation of p53 as well as other regulatory proteins, and therefore eventual cell death via apoptosis.

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Drug Name	Use
Bortezomib	Currently approved to treat multiple myeloma and mantle cell lymphoma (clinical trials for leukemia)
Carfil omib	Currently approved to treat multiple myeloma (clinical trials for leukemia and lymphomas)

Proteasomes in Cancer

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Cross Presentation (Cross Priming)

- In addition to presenting antigens on MHC class II molecules to CD4+ T cells, dendritic cells also have a role in presenting antigens to CD8+ T cells in a process called **cross presentation**. As professional phagocytes, dendritic cells are able to ingest a virally MHC class I infected cell in toto and present viral antigens within a molecule to CD8+ T cells. Therefore, DCs may activate or prime both CD4+ T cells and CD8+ T cells specific for the same pathogen. Th s activation may occur in close proximity, which is important for the activation of naïve CD8+ T cells into activated CTLs and memory cells. Th s occurs via the activation of CD4+ Tcells and the production of cytokines such as IL-2 (*see* chapter 8)

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Cross Presentation or Cross Priming

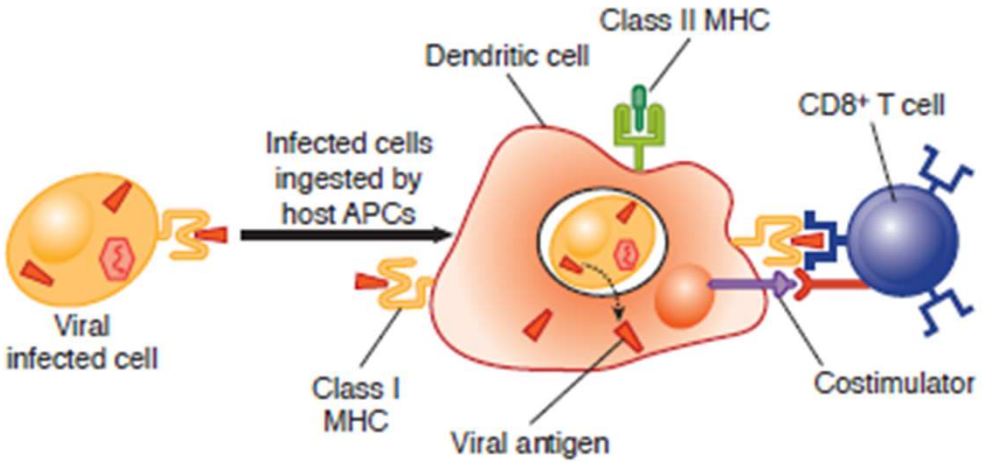


Figure I-5-7. Cross-Priming

Secondary Lymphoid Tissues : Innate immune response meets adaptive

Chapter summary

- APCs migrate to the secondary lymphoid organs, where they present this processed antigen to recirculating naive lymphocytes.
- Lymph nodes are designed to filter antigens from the tissue fluids.
- Lymph enters through afferent lymphatics and percolates through an outer cortex and inner medulla before leaving through the efferent lymphatic in the hilum.
- The spleen is designed to filter antigens from blood; blood enters through a single splenic artery, which branches into arterioles that become surrounded by cuffs of lymphocytes (periarteriolar lymphoid sheaths) with follicles and macrophages nearby.
- MHC class I molecules are loaded with peptides via the endogenous pathway.
- Partially digested peptides are loaded into the groove of class II MHC molecules on antigen-presenting cells by the endosomal (exogenous) pathway.
- Dendritic cells may activate both CD4+ T cells and CD8+ T cells (cross priming) which is essential in the development of CTL's and CD8+ memory cells.

Secondary Lymphoid Tissues : Innate immune response meets adaptive