Lymphocyte Recirculation and Homing

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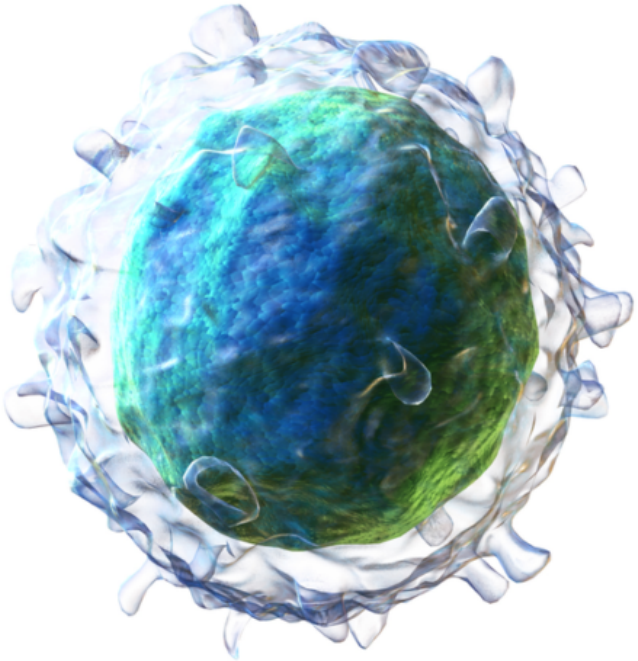
Lymphocytes have a miraculous ability to get attracted to the site of pathogen attack. This complex process is the interplay of a wide variety of molecules and processes within the body. Read on to find out what constitutes these mechanisms of lymphocyte circulation.



Introduction

The human body operates on two basic types of immunity:

Innate immunity: it is the immunity that a person is born with and comprises of the skin, the acid in the stomach, the enzymes in tears, the enzymes in saliva, the complement system, etc.

Adaptive immunity: Once the barriers constituting the innate immunity are breached by an **invading organism**, the adaptive immunity comes into play. It is comprised of the highly specific **B- and T-lymphocytes**, which operate in two distinct modes. Thus, adaptive immunity is of two types: the antibody-mediated or immunity of B-cells, and the **cell-mediated immunity** of T-cells. Lymphocytes are produced from the CLP or the **committed lymphoid progenitor cells**.

Lymphocyte Recirculation Through Blood and Lymphatic Vessels

White blood cells are the cellular component of immune responses. The function of immunity being largely dependent on lymphocytes that are either T-cells or B -cells. T-cells are in highest proportion of all lymphocytes (80 %), followed by B-cells (10 %) and **natural killer cells** (10 %). The proportions of lymphocytes in the **lymph** and **blood** vary continuously.

This is due to the **constant circulation** of lymphocytes among the lymph vessels, the blood and sites where **antigens** may be found like tissues, spleen, and mucosal surfaces; but why do they circulate?

There are two types of circulation:

- Circulation stimulated by an antigen invasion
- Normal circulatory pathways.

During an **invasion**, the antigen presenting cells in the tissue take up the foreign invader and its antigen. The antigen presenting cells include the B-cells, **macrophages** and the **dendritic cells**. These cells then circulate through the **lymphatic vessels** to the **lymph nodes** where they present the antigen, using their **MHC class II molecules,** to the T-Cells.

The T-cells and B-cells have specific **TCR and BCR receptors** on their membrane, which are highly specific to a specific antigen. They are developed during maturation of these cells in the **thymus** and **bone marrow,** respectively.

During this activation, APCs also secrete **costimulatory molecules** that will cause T-cells and B-cells clone to proliferate. These costimulators include the **chemokines** and **cytokines**, which are produced by macrophages and activated T-cells.

There is a small group of T-cells and B-cells that are specific for each antigen. The specificity is so great that immunologists believe that there are 107 different specificities in the total of 1012 cells in the body. The group that is specific for the antigen is then selected and activated.

Hence, the B-cells, T helper cells and the dendritic cells all interact together to stimulate an immune activation. This results in the recruitment and multiplication of a specific clone which will be released into the blood, a process called the **adaptive immune response**.

The entire system starts with the identification of foreign antigen, which is the reason why lymphocytes keep patrolling the entire body. They do so to seek out any foreign invaders, so that they could alert the lymphocytes in the nodes to trigger an adaptive immune response.

By birth, normal adults possess **1012 lymphocytes**, of which, those in the circulation represent only 10%. The circulation starts when the lymphocytes enter the lymph vessels from the lymph nodes. These, then, pass through the **efferent lymphatic duct** and collect in the **main thoracic duct**, which drains into the **subclavian artery** to the hand.

Lymph and lymphocytes from other parts of the body are collected in lymph channels. Then they are coalesced via progressively larger vessels to drain via the **afferent lymphatics** to the **peripheral lymph nodes.** From there they enter the thoracic duct

and ultimately the blood.

The **naive lymphocytes** go through the **lymphoid organs,** while the activated ones enter the blood to reach the site of **infection**. This circulation is specific for the T-cells because their job is to seek out and attack foreign invaders. B-cells, on the other hand, convert into **plasma cells** and secrete their antibodies from within the lymph nodes.

High Endothelial Venules

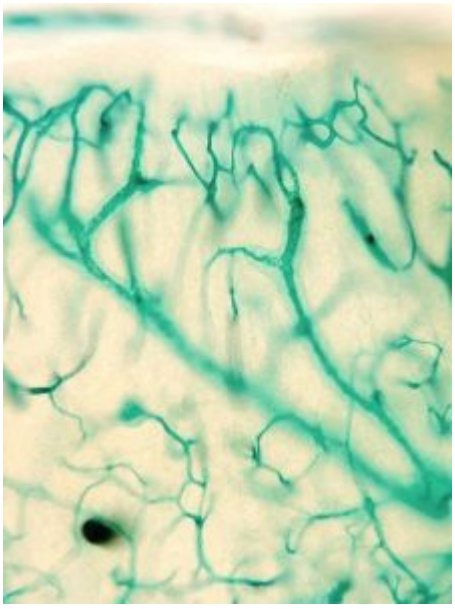


Image: “High endothelial venules in a lymph node.” by Art Anderson. License: CC BY-SA 3.0

An essential role in this entry of cells into the lymph node is taken by the **high endothelial venules**. These are simple blood vessels with cuboidal, plump endothelial cells instead of the regular flat ones.

They are present in the post-capillary location in the lymph nodes and house the receptors to bind these lymphocytes. The role of high endothelial venules is to provide a site of attachment for the lymphocyte to home. It is these venules that possess the specific ligands for the **T-cell homing receptors**. The ligands include the **CCL21** and the **L-selectin ligand,** which are called the **cell adhesion molecules**.

There are basically 5 groups of these molecules, including the **cadherin**, the **Ig-superfamily CAMS**, **Mucin-like CAMS**, **Selectins**, and **Integrins**. The integrins play a vital role in the **cell-to-cell interactions** and the **cell-extracellular matrix interactions**. These will bind to the naive lymphocytes and help them enter the lymph nodes, thus playing a vital role in procuring lymphocytes. This process of adhesion is called **lymphocyte homing**.

Lymphocyte Homing to Skin and Peripheral Tissues

Homing is the process by which circulating lymphocytes adhere to specialized endothelial cells within lymphoid organs. The process is facilitated by two main mediators which include:

1. Tissue specific adhesion molecules on lymphocytes (homing receptors.)

2. Adhesion molecules on endothelial cells (vascular addressing)

T-cells attach to the **endothelia**, cells within the dermis of the skin. Using their **selectins** and **integrins** they attach to the endothelial cells. They, then, enter the tissue by **diapedesis**.

Afterwards, aided by the **chemokine gradient**, the cells spread out towards the site of infection in both the **dermis** and the **epidermis**. There they fight against the invading organism along with the natural killer cells, macrophages, and other WBCs.

Similarly, these cells home to peripheral tissues like the lungs, heart, and GIT, aided by their special homing receptors that include CLA, CD43, CD44, LFA-1, VLA-4, P- and L-selectins.

“Lymphocyte Homing to Peripheral Tissues” Image created by Lecturio

Trafficking to Mucosal Tissues

During this process, antigens present in the gut are taken to the **Peyer’s patches**. Here, antigen processing and presentation to T-cells result in their activation. Activated T-cells are then taken by **afferent lymphatics** to the **mesenteric lymph nodes.** There they undergo proliferation and are then distributed via the **efferent lymphatics** to the **blood.** The blood, in turn, distributes all these cells to the **mucosal tissues**, ensuring lasting and effective immunity.

T-Cell Homing Receptors

These are special receptors present on the T-cell membrane hat, allowing it to attach to the blood vessels, home and enter the tissues to perform its action. These receptors are specific for certain molecules on the endothelial cells themselves.

There are 5 types of homing receptors, but the most common are the **selectins** and **integrins.** The selectins offer temporary weak attachment, while the integrins offer strong attachment that actually allows homing. Naïve T-cells have L- selectin, CCR7, and LFA-1, while the activated T-cells, both effector and central, have E- and P-selectin ligands, CXCR3, CCR5, LFA-1 and VLA4.

“T-cell Homing Receptors” Image created by Lecturio

Integrin Signalling

Integrins bind the ECM outside a cell to the **cytoskeleton** (specifically, the **microfilaments**) within the cell. The ligand in the ECM that a specific integrin can bind to, is highly dependent on the α and β subunits that make up the integrin.

Included among the ligands of integrins are **fibronectin, vitronectin, collagen, and laminin**. The association between the cell and the ECM strengthens the cell, preventing it

from being torn out of the ECM.

Cellular connection to the ECM is essential in the construction of a multicellular living being. Integrins are not just snares, but rather, they give the cell important notifications about its surrounding cells and the environment.

Along with signals that stimulate receptors via the help of soluble molecules like VEGF, EGF, and numerous others, they implement a cell's choice of what natural move to make, be it connection, development, death or separation. In this way, integrins lie at the heart of numerous **cell organic procedures**.

The cells connect via an arrangement of **intercellular bonds**, which comprise of integrins and numerous cytoplasmic proteins, for example, **talin, vinculin, paxillin, and alpha-actinin**.

These exert their effects by controlling **kinases**, for example, FAK (central attachment kinase) and Src kinase relatives to phosphorylate substrates. These bond buildings join to the **actin cytoskeleton**. The integrins serve to connect the two systems over the plasma film: the **extracellular ECM** and the **intracellular actin filamentous framework**.

Integrin alpha6beta4 is an exemption: it has connections to the keratin part of the fiber framework in epithelial cells.

Focal adhesions are big complexes, produced by the grouping of several integrin-to-ECM associations. The groups likely give adequate intracellular restricting destinations to allow the arrangement of stable signaling molecules on the cytoplasmic side of the cell layer. Thus, the focal adhesions contain the **integrin ligand**, **integrin atom**, and **partner plaque proteins**.

Binding is stimulated by **changes in free energy**. As expressed before, these buildings associate the extracellular network to actin packs. **Cryo-electron tomography** uncovers that the attachment contains particles on the cell layer with a distance across of 25 +/ – 5 nm and separated at roughly 45 nm. Treatment with **Rho-kinase inhibitor Y-27632** diminishes the span of the molecule, and it is greatly mechanosensitive.

One imperative capacity of integrins on cells in tissue culture is their part in **cell relocation**. Cells stick to a substrate through their integrins. Amid development, the cell makes new connections to the substrate at its front and simultaneously discharges those at its back.

After release, integrin atoms are reclaimed into the cell by **endocytosis**; they are transported through the cell to its front by the **endocytic cycle**, where they are added back to the surface. Thus, they are cycled for reuse, empowering the cell to make crisp connections at its driving front, aiding in **chemotaxis**.

Once the T-cells are activated, they result in the formation of three types of cells, the **helper T-cells**, the **cytotoxic T-cells** and the **suppressor T-cells**, each with their own function. Once these cells enter the blood, they are directed towards the site of infection.

Small molecules called chemokines are responsible for controlling the direction of migration of the lymphocytes by a process called **chemotaxis**. These chemokines create a **gradient** for the white blood cells to follow. The white blood cells detect the chemokines and move towards their higher concentration, which draws the cell to the very location of the infection.

Function of Chemokines

There are 4 families of chemokines, organized according to the arrangement of **cysteine** in their molecules. They include the **C family**, the **CC family**, the **CXC family** and the **CX_3C family**.

The different chemokine molecules are detected by the 7-transmembrane g protein-coupled **chemokine receptor** that results in the activation of the actin filaments and the locomotion of the cells to the site of infection. This can occur in the **Peyer's patches** of the GIT, in the skin or any other place. Wherever the infection is, lymphocytes have the ability to seek it out and destroy it.

"Chemokines" Image created by Lecturio

The chemokines function in the activation of both T-cells and B-cells. They also play a vital role in chemotaxis, where they direct the white blood cells towards the site of infection. It is these chemokines which help create a gradient for the lymphocytes to follow, guiding them to the actual infection site.

Memory T-Cells Migration (Central and Effector)

Besides the cells that are actually involved in the immune response, antigen presentation also results in the production of memory T-cells. These cells possess **specificity against the one specific antigen**. This helps create a **secondary immune response** of higher severity if the antigen happens to invade the body again.

There are 2 types of memory T-cells: the **central memory T-cells,** which are present in the lymph nodes, ready to be activated if the same antigen enters the body again; and the **effector T-cells,** which are present in the blood and spleen and in the tissues.

These T-cells play the role of the **immediate attackers**. As soon as the antigen is detected, these cells are activated and serve to eliminate the invading organism without having to migrate from the lymph nodes.

"Migration of Central Memory and Effector Memory T-Cells" Image created by Lecturio

References

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Notes