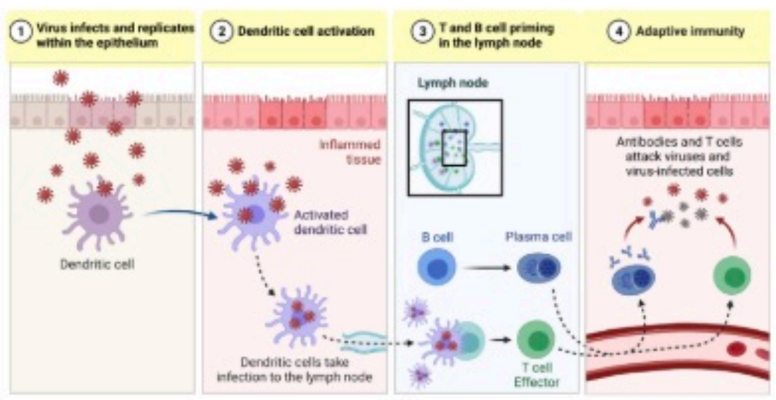
Effector Mechanisms in Cell-Mediated Responses

Learning Outcomes

- Describe the signals involved in T cell priming by dendritic cells
- Understand the regulation of CD8+ T cell homing to skin and intestine
- Explain the mechanism of CD8+ T cell mediated target cell killing
- Outline the major subsets of effector T cells, including the cytokines involved in their differentiation and function

Overview of Infection Process

When an infection occurs, such as in the skin, the virus replicates within the skin cells, particularly keratinocytes. This leads to the release of foreign antigens, which are then processed into peptides. These peptides are loaded onto Major Histocompatibility Complex (MHC) class I and II molecules.



Dendritic Cell Activation

Dendritic cells (DCs) play a crucial role in the immune response. Upon encountering antigens, they become activated and change shape, developing long protrusions that enhance their ability to capture and process antigens. Activated dendritic cells then migrate to the draining lymph node, where they facilitate the activation of T cells.

Lymph Node Functionality

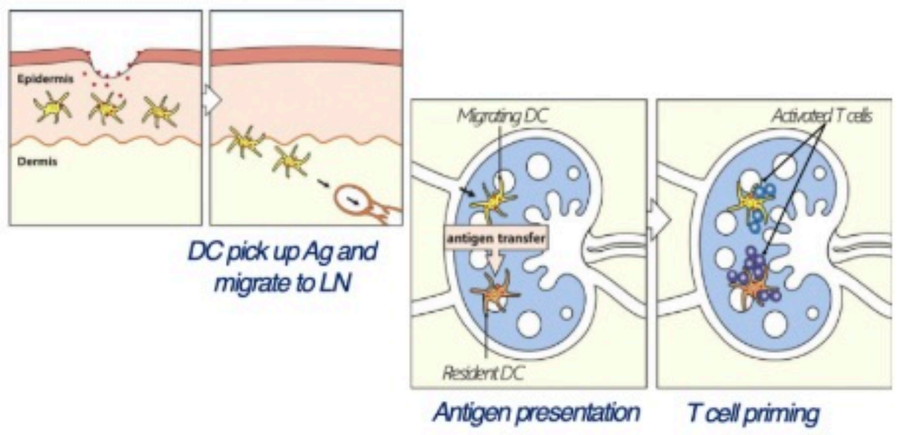
The lymph node is highly compartmentalized, allowing for efficient T cell activation. Dendritic cells utilize chemokine gradients to locate T cells in the T cell zone, where they present antigens and provide necessary signals for T cell activation. This process is essential for initiating the adaptive immune response.

Adaptive Immune Response

Once activated, T cells exit the lymph node and travel to the site of infection, guided by chemokine gradients. Some T cells differentiate into long-lived memory cells, which enhance the immune response upon re-exposure to the same pathogen.

Dendritic Cell Subsets

Dendritic cells can be categorized into two main subsets: resident DCs, which remain in the tissue, and migratory DCs, which transport antigens to lymph nodes. This antigen handover is critical for T cell priming and activation.

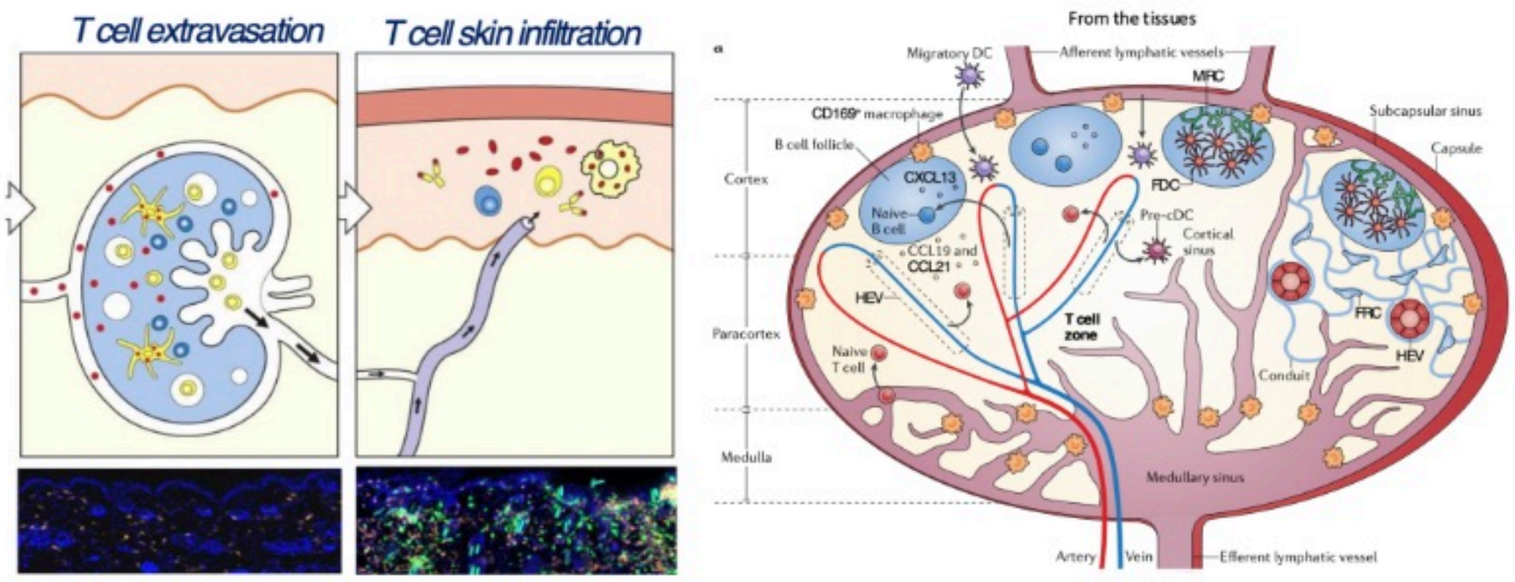


T Cell Nomenclature

In immunology, terminology can vary. Activated T cells are often referred to as effector T cells. The terms naive, activated, and memory T cells are commonly used, with some variations in terminology across different texts. For example, CD8 T cells may be referred to as cytotoxic T lymphocytes (CTLs).

Real-Life Observations

In experimental models, such as mice, the dynamics of T cell infiltration can be observed. Initially, the skin may show few T cells, but by five days post-infection, activated T cells flood the area, demonstrating the effectiveness of the immune response.

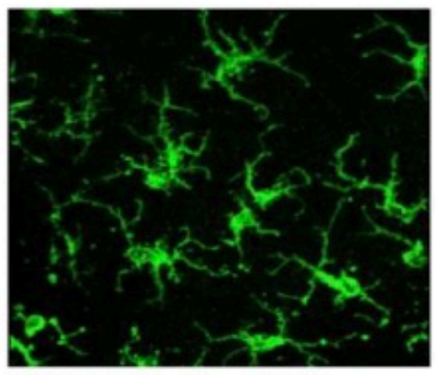


Homing Mechanisms

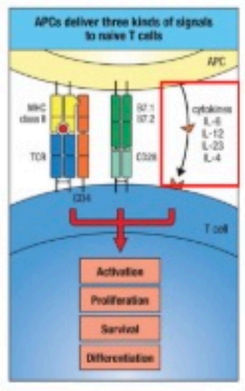
T cells utilize specific molecules for homing to lymph nodes, primarily chemokine receptors like CCR7. This receptor is essential for T cell priming and response efficacy. Other markers, such as L-selectin, also play a role in T cell trafficking.

Dendritic Cell Network in the Skin

Dendritic cells in the skin are strategically positioned to capture antigens. Upon activation, they migrate to lymph nodes, where they interact with T cells, providing co-stimulatory signals and cytokines that dictate T cell differentiation.



DC (GFP⁺) network in murine skin



Cytokine Signaling and T Cell Differentiation

Dendritic cells not only present antigens but also secrete cytokines that influence the type of immune response. For instance, during a viral infection, cytokines like IL-12 promote the differentiation of CD8 T cells, leading to a type 1 immune response characterized by interferon-gamma production.

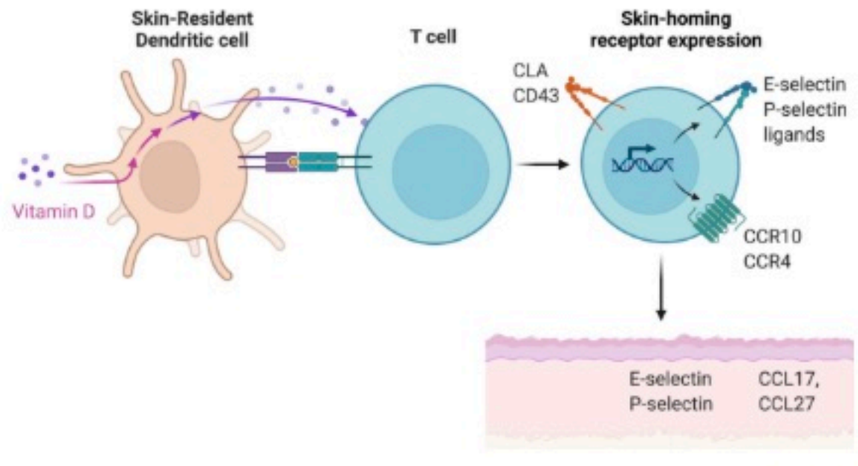
Types of Immune Responses

Immune responses can be categorized based on the cytokines produced:

- **Type 1 Response:** Characterized by interferon-gamma, typically associated with viral infections.
- **Type 2 Response:** Involves IL-4 production, often related to allergic reactions.
- **Type 17 Response:** Associated with IL-17 production, relevant in conditions like psoriasis.

Role of Dendritic Cells in T Cell Guidance

Dendritic cells (DCs) play a crucial role in directing T cells to specific tissues. In the epidermis, DCs are exposed to high levels of vitamin D, which they process and use to signal T cells. This interaction leads to the upregulation of skin-homing molecules on T cells.



Vitamin D and T Cell Homing

When T cells are exposed to vitamin D, they increase the expression of various skin-homing markers, including:

- CCR10
- CCR4
- E-selectin
- P-selectin
- CLA

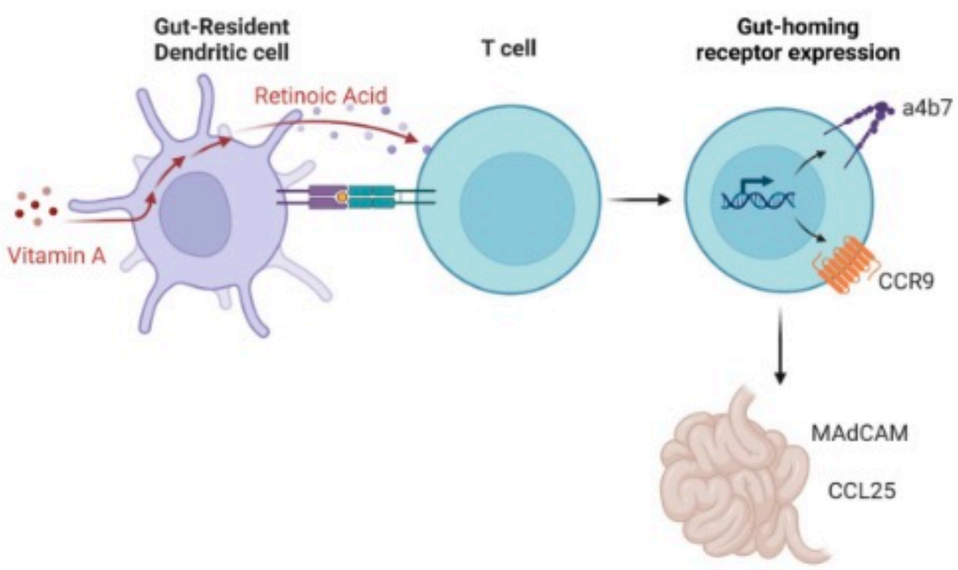
These markers facilitate the migration of T cells back to the skin, where their corresponding ligands are present, effectively providing a "postcode" for the T cells.

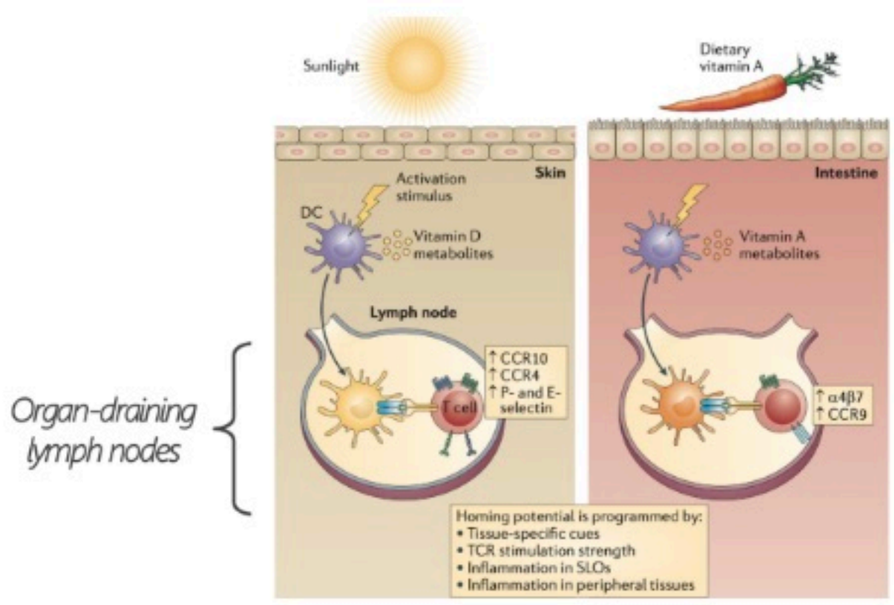
Similar Mechanism in the Gut

In the gut, a similar process occurs with vitamin A. Dendritic cells in the gut convert vitamin A into retinoic acid, which induces the expression of specific markers on T cells, such as:

- CCR9
- Alpha 4 Beta 7 integrin

These markers guide T cells to the gut, ensuring they reach the appropriate location for immune response.





Experimental Evidence

Recent studies, such as those conducted by Brian Sheridan, demonstrate the importance of the route of infection in T cell priming. For example, when mice are infected with Listeria through food, the gut-resident dendritic cells become activated and promote the expression of gut-specific markers on T cells. In contrast, if Listeria is introduced via the bloodstream, T cells are primed in the spleen and do not express the necessary markers to migrate to the gut.