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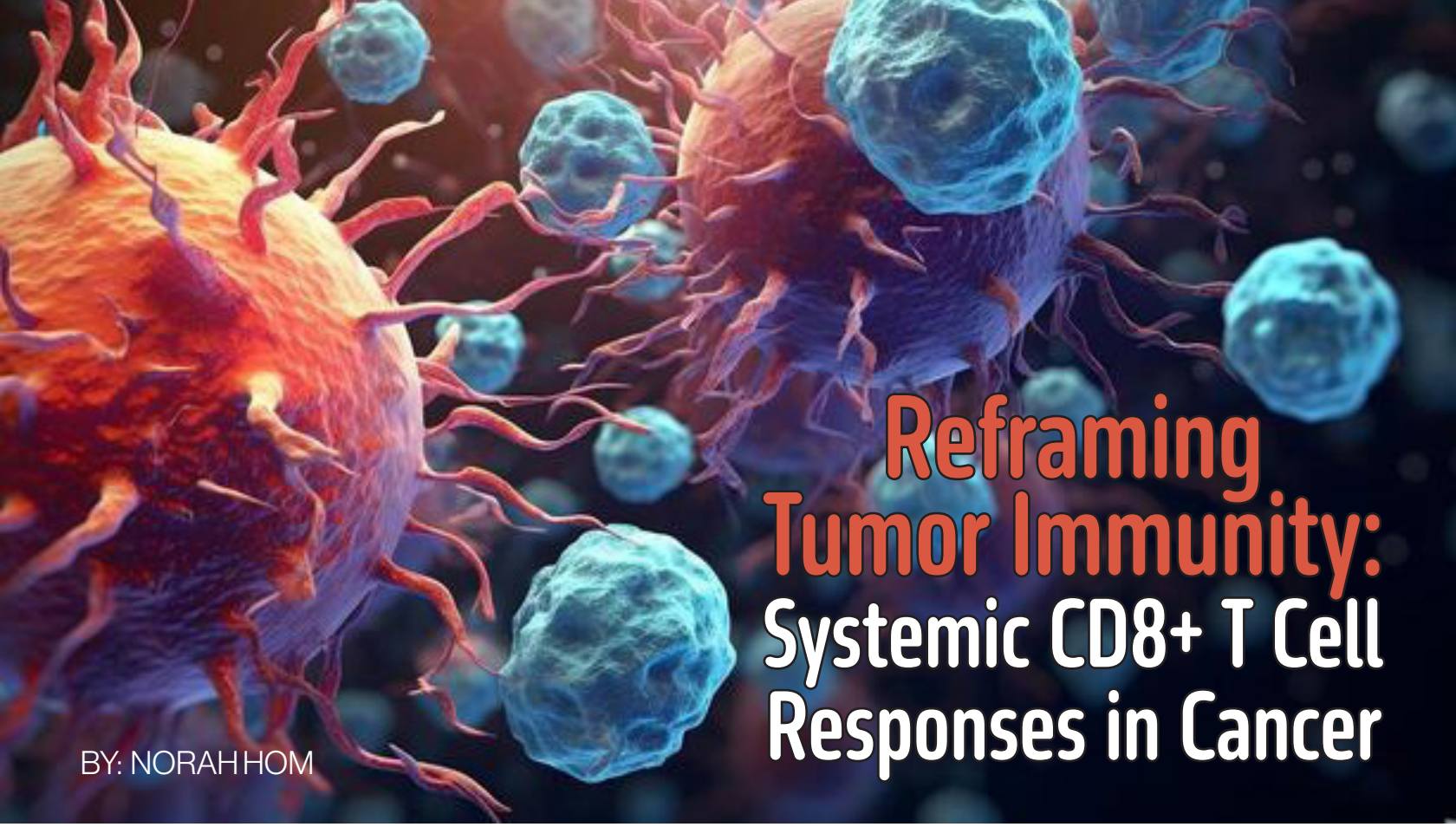
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Reframing Tumor Immunity: Systemic CD8+ T Cell Responses in Cancer

BY: NORAH HOM

INTRODUCTION: WHY THE LOCATION OF ANTI-TUMOR IMMUNITY MATTERS

For decades, cancer was treated as a localized disease—something to be cut out, treated with radiation therapy, or directly targeted with drugs. Immunotherapy disrupted that idea. Treatments like immune checkpoint blockade (ICB) showed that the immune system could be reawakened to recognize and eliminate tumors, sometimes producing long-lasting remissions. Yet the reality is uneven: only a subset of patients experience durable responses, and even within responders, outcomes vary widely. This inconsistency raises a deeper question: where in the immune system does effective anti-tumor immunity actually take place?

Historically, the answer seemed obvious. The tumor microenvironment (TME), the dense ecosystem of cancer cells, immune cells, and stromal components, was viewed as the central place. Tumor-infiltrating lymphocytes (TILs), especially $CD8^+$ cytotoxic T cells, were considered the primary agents of tumor destruction. These cells recognize peptide antigens presented on MHC class I molecules on the surface of target cells via their T cell receptors, allowing them to distinguish infected/malignant cells from healthy tissue. Once engaged, they form a tight synapse and kill target cells through perforin- and granzyme-mediated cytotoxicity or by activating apoptotic pathways through death receptors.[1]

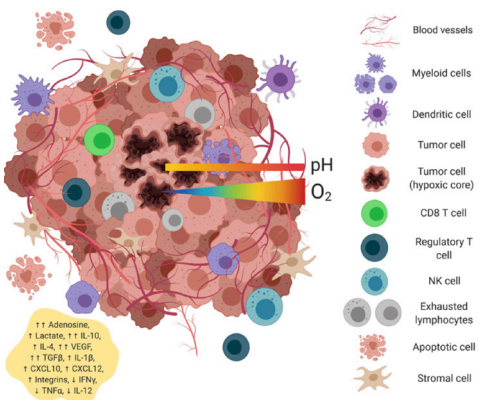


Figure 1. The tumor microenvironment as an immunosuppressive site of anti-tumor immunity. The tumor microenvironment (TME) contains diverse immune and stromal cells, including $CD8^+$ T cells that can recognize and kill cancer cells. However, hypoxia, low pH, and inhibitory signals promote T cell dysfunction and exhaustion, limiting effective anti-tumor responses and highlighting the constraints of a tumor-centric view of immunity.

However, this tumor-centric view is incomplete. Recent evidence suggests that anti-tumor immunity is not confined to the tumor itself, but unfolds across a coordinated, body-wide network. Lymph nodes are specialized immune organs that serve as key sites where naïve T cells are primed and activated upon encountering antigen-presenting cells. T cells then enter the bloodstream for systemic distribution, while tumors serve as sites of execution. $CD8^+$ T cells move through this system in a dynamic sequence of activation, expansion, migration, and differentiation. This process is encapsulated in the cancer-immunity cycle. In the context of cancer, tumor-draining lymph nodes are the specific lymph nodes that receive antigen and immune signals from the tumor microenvironment, whereas not all lymph nodes in a cancer patient are tumor-draining.

Recent work reframes immunotherapy as a fundamentally systemic phenomenon. Effective treatment depends not just on what happens inside tumors, but on how immune responses are generated, maintained, and replenished across the entire organism.

CD8+ T CELLS IN THE CANCER-IMMUNITY CYCLE

The immune response to cancer is often described as a series of linked steps that connect innate sensing with adaptive

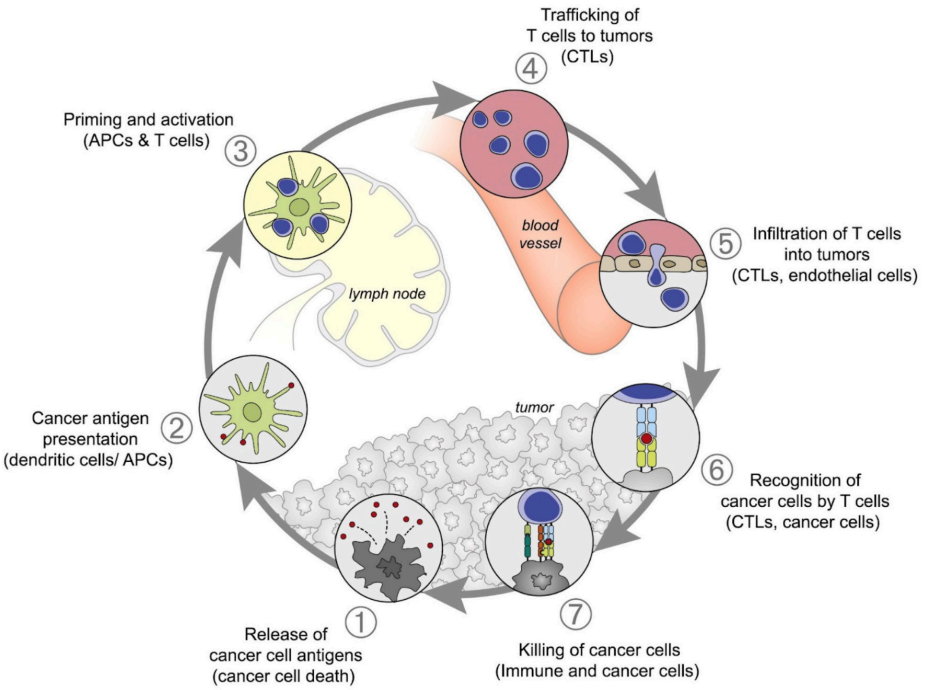


Figure 2. The cancer-immunity cycle and systemic CD8⁺ T cell responses. Tumor cell death releases antigens that are captured by dendritic cells and presented in tumor-draining lymph nodes, where CD8⁺ T cells are primed and activated. These cells expand, enter circulation, and traffic to tumors, where they infiltrate, recognize cancer cells, and mediate cytotoxic killing. Each step occurs across distinct anatomical sites, illustrating the systemic nature of anti-tumor immunity.

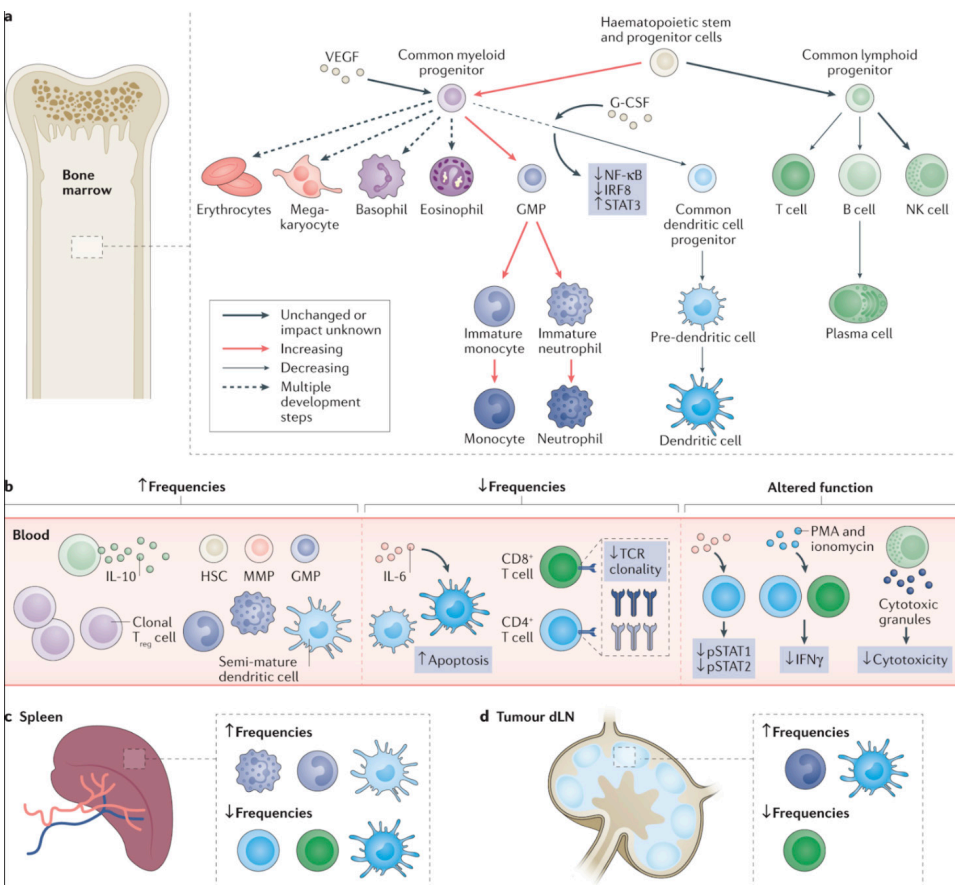


Figure 3. Systemic immune remodeling during cancer immunotherapy. Immunotherapy induces widespread changes across immune compartments, including the bone marrow, blood, spleen, and tumor-draining lymph nodes. These changes include altered immune cell development, shifts in cell frequencies, and reduced T cell function, demonstrating that anti-tumor responses depend on systemic immune regulation rather than tumor-localized activity alone.

effector function. At its core, this cycle is driven by CD8⁺ T cells. It begins with tumor cell death, which releases tumor-associated antigens and neoantigens. These antigens are captured by dendritic cells within the tumor microenvironment. Once activated, dendritic cells migrate to the tdLN, where they present antigen fragments to naïve CD8⁺ T cells. However, this encounter is not sufficient on its own. Effective priming requires co-stimulatory signals and cytokines that push T cells toward activation. Once engaged, these cells undergo clonal expansion, proliferating into a population of tumor-specific effectors. Next, they exit lymphoid tissues, enter circulation, and traffic throughout the body. Eventually, these activated T cells infiltrate tumors. There, they recognize cancer cells presenting the same antigens and initiate cytotoxic responses, killing malignant cells and releasing additional antigens to push the cycle further.[2]

This framework makes clear that anti-tumor immunity is inherently distributed. Each step occurs in a distinct anatomical location: antigen capture in tumors, priming in lymph nodes, expansion and trafficking through circulation, and killing back in the tumor. The success of immunotherapy depends on the integrity of this entire system, not just a single site.

EVIDENCE THAT SYSTEMIC IMMUNITY IS REQUIRED FOR CANCER IMMUNOTHERAPY

Early models of immunotherapy assumed that reinvigorating T cells already present in tumors would be sufficient for tumor rejection. Checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 therapies, were thought to act primarily by reversing exhaustion in tumor-infiltrating T cells. However, a pivotal 2016 study challenged this assumption by examining immune responses across multiple compartments, including tumors, secondary lymphoid organs, and circulating blood. The results pointed to a broader, systemic mechanism.

First, immunotherapy was shown to activate immune responses throughout the body, not just within tumors. Second, the majority of T cell proliferation occurred in secondary lymphoid organs rather than in the tumor microenvironment. This suggested that tumors alone are not sufficient sites for sustaining robust T cell

expansion. Notably, when researchers blocked lymphocyte migration from lymphoid tissues, thereby preventing T cells from entering circulation, tumor regression failed to occur. Even with checkpoint blockade, tumors could not be controlled without a continuous influx of recently activated T cells.[3]

These findings overturned the idea that tumor-resident T cells are self-sufficient. Instead, they established a key principle: effective cancer immunotherapy requires ongoing recruitment of T cells generated outside the tumor. The immune response must be continuously replenished from systemic sources. This raised a critical follow-up question: where are these tumor-reactive T cells being generated and maintained?

TUMOR-DRAINING LYMPH NODES AS CRITICAL IMMUNE HUBS

Tumor-draining lymph nodes (tdLNs) have emerged as central players in this process. These structures act as hubs where adaptive immune responses are initiated and organized. Within tdLNs, dendritic cells present tumor-derived antigens to naïve CD8⁺ T cells, triggering their activation. These T cells then proliferate, differentiate, and form both effector and memory populations. Lymph node architecture created a dense network of antigen-presenting cells, with defined cellular niches, and supportive cytokine environments, which are the ideal conditions for this process of priming T cells.

Despite their importance, lymph nodes have historically been understudied in human cancer immunology. Clinical research has largely focused on tumor biopsies, leaving the dynamics of lymph node responses during immunotherapy less well understood. Recent advances have begun to close this gap. By analyzing immune activity across tumors, lymph nodes, and blood simultaneously, researchers are uncovering how these compartments interact. This shift has been particularly important for understanding how CD8⁺ T cell populations are generated and sustained over time.[4]

CD8+ T CELL DYNAMICS IN HUMAN LYMPH NODES DURING IMMUNOTHERAPY

A 2023 study examining patients with head and neck squamous cell carcinoma provided some of the clearest insights yet into how systemic T cell responses are organized. By combining single-cell RNA sequencing, T cell receptor (TCR) sequencing, and spatial profiling, researchers were able to track individual T cell clones across tissues.

One of the most important findings was the identification of progenitor-exhausted CD8⁺ T cells (Tpex cells) within uninvolved lymph nodes. Unlike terminally exhausted T cells found in tumors, these cells retain stem-like properties. They can proliferate, self-renew, and give rise to downstream effector and exhausted populations. In contrast, tumors were dominated by terminally exhausted T cells with limited capacity for expansion. This distinction suggests a division of labor where lymph nodes act as reservoirs of renewable T cell populations, while tumors are sites where these cells carry out their effector functions.

TCR sequencing revealed a direct clonal relationship between lymph node and tumor T cells. Identical T cell clones were found in both compartments, indicating a shared lineage. This supports a developmental pathway in which tumor antigens drain to lymph nodes, activate T cells, and generate populations that later migrate into tumors and differentiate further. Immunotherapy appears to amplify this process. During anti-PD-L1 treatment, Tpex cells in lymph nodes engaged with dendritic cells, expanded, and produced intermediate populations that entered circulation. These cells then trafficked to tumors, which replenished the pool of tumor-infiltrating T cells.[5]

Notably, the study also found that

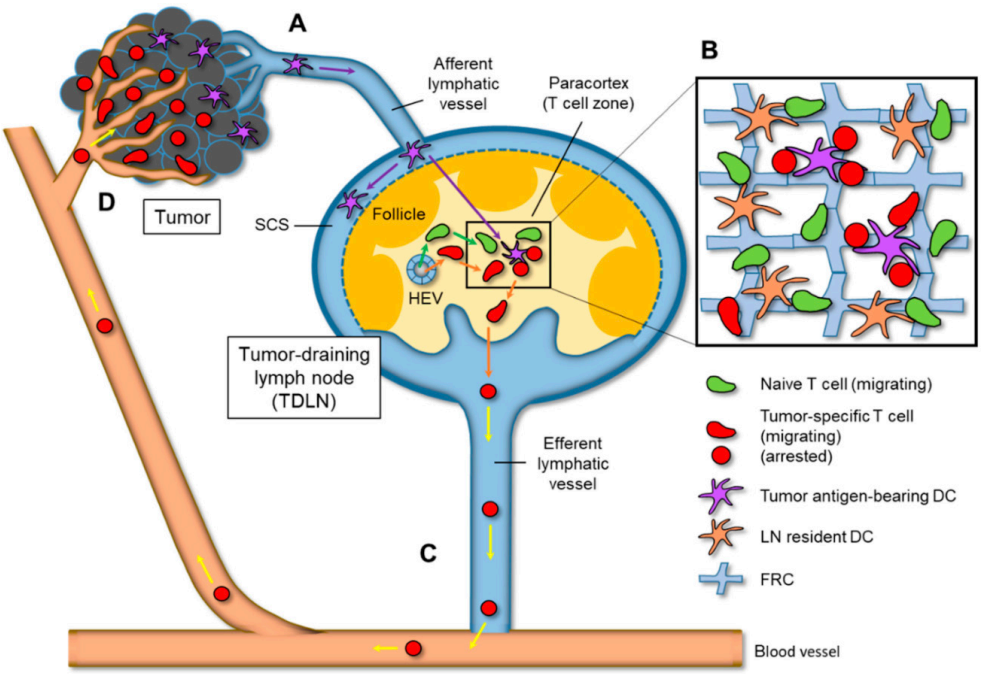


Figure 4. Tumor–tumor-draining lymph node (tdLN) axis of CD8⁺ T cell priming. Tumor antigens are transported by dendritic cells via lymphatics to the tdLN, where naive T cells are activated within specialized niches and differentiate into tumor-specific populations. Activated T cells then exit through efferent lymphatics and recirculate to the tumor.

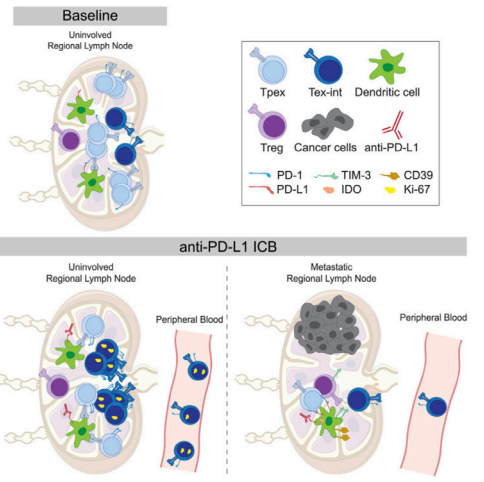


Figure 5. CD8⁺ T cell dynamics across lymph nodes, blood, and tumor during anti-PD-L1 immunotherapy. At baseline, progenitor exhausted (Tpex) cells reside in uninvolved lymph nodes. Following checkpoint blockade, Tpex cells expand through interactions with dendritic cells, generate intermediate populations, and give rise to circulating and tumor-infiltrating T cells. In contrast, metastatic lymph nodes exhibit disrupted architecture and impaired T cell responses.

metastatic lymph nodes disrupt this system. In nodes infiltrated by tumor cells, immune architecture was altered: Tpex populations were reduced, immunosuppressive cells increased, and T cell expansion was impaired. This suggests that metastasis to lymph nodes may actively undermine systemic immunity, limiting the effectiveness of immunotherapy.

INTEGRATING THESE FINDINGS INTO A SYSTEMIC CANCER-IMMUNITY CYCLE

Taken together, these studies point to a revised understanding of the cancer-immunity cycle as a spatially distributed process spanning multiple tissues. tdLNs serve as sites of initiation and renewal, where tumor-specific T cells are primed and expanded. The circulatory system acts as a conduit, distributing these cells throughout the body. The tumor microenvironment, in turn, is where cytotoxic activity is executed. Immunotherapy operates across this entire network. Rather than simply reactivating T cells already present in tumors, it enhances upstream processes—expanding progenitor populations, strengthening antigen presentation, and promoting the continuous recruitment of new effector cells.

In this model, tumor control depends on the integrity of all compartments. Disruption at any stage (e.g., impaired priming in lymph nodes, blocked trafficking, or suppression within tumors) can compromise the overall response.

FUTURE DIRECTIONS OF CANCER IMMUNOTHERAPIES

Future therapies will likely extend beyond the tumor itself, aiming to strengthen the broader immune system that supports lasting anti-tumor responses. This includes strategies to enhance T cell priming in tdLNs, such as targeted cancer vaccines or approaches that improve dendritic cell activation and antigen presentation. Therapies may also focus on expanding and sustaining progenitor $CD8^+$ T cell populations with stem-like properties, which can continuously replenish the pool of effector cells.[6]

Cancer immunology is now undergoing a conceptual shift. What was once viewed as a localized battle within tumors is now understood as a coordinated, system-wide process. $CD8^+$ T cells move through this network, from priming in lymph nodes to circulation and ultimately to tumor sites where they exert their effects. The success of immunotherapy depends on this entire trajectory. By recognizing the importance of systemic immunity and the central role of lymph nodes in sustaining it, researchers are beginning to discover why some treatments succeed while others fail.

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