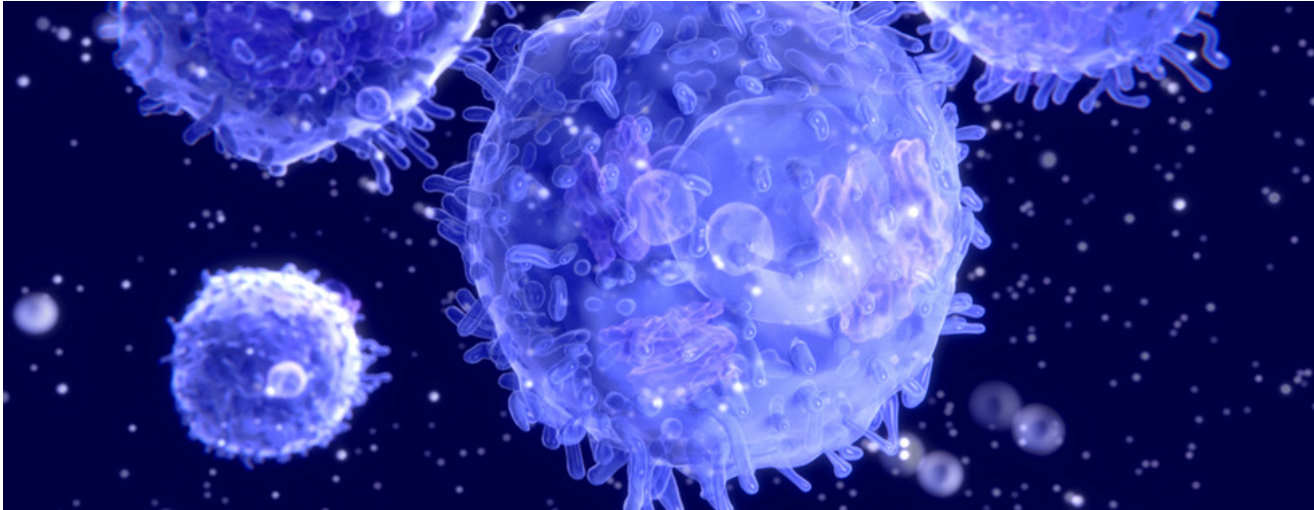


## The Effect of Aging On Our Immune System: A Review

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The thymus plays a key role in the production and maturation of T-lymphocytes, a type of white blood cell that identifies and kills cancer cells, virus-infected cells, or cells that are damaged in other ways. Hormones released by the thymus, such as thymosin, stimulate the maturation of T-cells before they are expelled into the bloodstream. Some T-cells migrate to lymph nodes where they become activated when they are presented with antigens by MHC class II molecules by antigen-presenting cells (APCs). Active T-cells then divide and help identify and kill pathogens, activate B cells to produce antibodies, and build an army of memory T-cells to respond quickly to secondary exposure to the infection. While most organs grow with us as we age, the thymus slowly shrinks after puberty and is replaced with fatty tissue. Therefore, aging is associated with the deterioration of the thymus that leads to the decreased production of new T-lymphocytes and thus, decreased immune function. Thome et al. from Columbia University recently published a paper in *Science Immunology* describing how compartmentalization of T-cells in lymph nodes allows for naive T-cells to be maintained throughout the human lifespan.

While most immunological studies rely on blood samples to identify circulating T-cells, which contain only 3% of the total T-cells



in the body, Thome et al. used human tissue to analyze cell composition. While some T-cells are found in circulating blood, they are mostly found in lymphoid tissues located at various submucosal membranes throughout our body, such as those associated with our lungs and eyes. Analyzing human tissue allowed scientists to characterize the other 97% of total T-cells in the body, uncovering more information about T-cell lineage and sustenance. Human tissues were obtained from organ donors through the organization LiveOnNY, and from discarded tissue from patients undergoing pediatric cardiac surgery through the Human Studies Core of the Columbia Center for Translational Immunology. Lymphocytes were then isolated from the various lymphoid tissues obtained, including the thymus, lymph nodes, and spleen.

To identify how the production of T-cells changes over time, researchers studied the presence of T-cells in tissue samples from a large range of ages. In order to measure thymic output of T-cells, researchers marked the differences between immature T-cells, cells that had recently exited the thymus, and long-lived naïve cells in the periphery. The team identified new naïve

T-cells by looking for episomal circular DNA (TRECs) formed during recombination of a gene in the T-cell receptor. TRECs are stable and not duplicated during mitosis, so they diminish with each cellular division. By determining TREC content using a PCR-based approach, the researchers determined that different sites had concentrations of naïve T-cells that varied based on the age of the donor. For instance, pediatric patients had more T cells in the thymus, while older children had more T cells in the lung-draining lymph nodes. Furthermore, there was a decline in the thymic production of naïve T-cells after the age of 40. This supports the age-related regression of the thymus and the correlated decrease in naïve T-cell output.

This finding suggests that naïve T-cells are selective about where in the body they travel to as we age, although the mechanism for this is unclear. More interestingly, the study found that naïve cells are not as mobile as previously thought. Instead, they travel only to specific sites where they nest and receive signals to expand in the vicinity of these “nests”. Thus, T-cells observed to be circulating in high numbers during childhood are naïve T-cells in transit to their lymphoid homes

rather than naïve T-cells migrating between tissues.

Understanding how T-cells differentiate and populate different tissue sites, such as lymph nodes, after leaving the thymus may allow us to personalize immunotherapies and vaccines. Furthermore, studying how aging correlates with the shrinkage of the thymus and the reduction in T-cell diversity may help us address increased susceptibility to autoimmune diseases, infection, and cancer in older individuals. In fact, it may even be possible to preserve T-cell functionality by slowing, stopping or reversing thymic recession. Continued research on the mechanisms and spatiality of our immune system will help advance new approaches for extending immune competency in older individuals.

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