Extrathymic T-Cell Development in the Mesenteric Lymph Nodes of Mice

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T-cells are a class of lymphocytes that play an essential role in adaptive immunity and are known to develop in the thymus. However, functional T-cells are also found in animals lacking a thymus, suggesting extrathymic development. We used experimental data from control and genetically modified mice, and flow cytometric analysis to locate and characterize this extrathymic T-cell development pathway. By analyzing the frequencies of double-positive (DP; CD8+ CD4+) T-cells in the thymus, mesenteric lymph nodes (MLN), peripheral lymph nodes (PLN), and spleen, we show that the MLN, and to a lesser degree the PLN, support T-cell development. To determine if extrathymic T-cell development is dependent on Notch signaling, a critical signaling pathway for early T-cell differentiation, we analyzed frequencies of DP cells in mice injected with antibodies against Notch Delta-like-ligands Dll1 and Dll4. We found that T-cell development in the MLN is dependent on both Dll1 and Dll4, unlike the thymus which is dependent on Dll4 alone. We also identified fibroblastic stromal cells to be the source of Dll4 in the MLN. Additionally, we found that MLN support the development of both gamma-delta (innate immunity) and alpha-beta (adaptive immunity) T-cells with equal efficacy, surprising considering the thymus primarily produces alpha-beta T-cells. This was confirmed through analysis of Rag-1 expression and detection of gamma-delta T-cell precursors in the MLN. Understanding extrathymic T-cell development may enable interventions aimed at increasing their production under conditions where the thymus is compromised e.g., after radiation treatment for cancer, infection, or thymic involution with age.

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