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Paths not taken: Notch signaling pathway keeps immature T cells on the right track

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One protein called Notch, which has well-known roles in the development of multiple tissues, plays an essential role in triggering T-cell development. Notch signaling induces expression of genes that promote the maturation of T cells and discourage alternative cell fates. Deficiency of the Notch target gene Hes1 in blood stem cells results in extremely low T-cell numbers, and could shed light on how normal cells are transformed in the context of cancer.

The lab of Avinash Bhandoola, PhD, professor of Pathology and Laboratory Medicine, has studied the origins of T cells for many years. One protein called Notch, which has well-known roles in the development of multiple tissues, plays an essential role in triggering T-cell development. T cells are immune cells that are made in the thymus, a small organ situated under the breastbone near the heart. However, T cells, like all blood-cell types, originate from blood-producing stem cells in the bone marrow. Immature T-cell progenitors leave the bone marrow, settle within the thymus, and eventually give rise to T cells.

With graduate student Maria Elena De Obaldia, Bhandoola describes in *Nature Immunology* this month how Notch signaling induces expression of genes that promote the maturation of T cells and discourage alternative cell fates. Deficiency of the Notch target gene Hes1 in blood stem cells results in extremely low T-cell numbers, but the underlying mechanism is unknown. Keeping in mind that Notch signaling gone awry induces leukemia, De Obaldia notes that "understanding the Notch pathway on a molecular level can shed light on how normal cells are

transformed in the context of cancer."

The current study describes the mechanism of action of Hes1, a repressor protein that acts in the nucleus of immature T cells in the thymus. De Obaldia and Bhandoola found that Hes1 turns off genes such as C/EBPalpha, which promote the myeloid-cell fate and antagonize the T-cell fate. Whereas Hes1-deficient mice show severe T-cell defects, deleting the myeloid gene C/EBPalpha could restore normal T-cell development. This provided evidence that Hes1 keeps immature T cells on track by preventing them from defaulting to a myeloid developmental pathway, which controls non-lymphocyte cell maturation.

Because of this "policing" function, De Obaldia likens Hes1 to the traffic cop of T-cell development: "T-cell leukemias are addicted to Hes1, perhaps because it keeps progenitor cells on the path to producing more T cells, as opposed to myeloid cells. Bhandoola adds, "Our findings establish the importance of constraining myeloid developmental programs early in T-cell development, and this knowledge may provide clues about how to stop T-cell leukemias." Future studies will address whether Hes1 serves a similar function in Notch-dependent, T-cell leukemias by repressing myeloid genes, as it does during normal T-cell development.

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