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Penn researchers describe key molecule that keeps immune cell development on track

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In the latest issue of *Nature*, researchers at the Perelman School of Medicine at the University of Pennsylvania clarify the role of two proteins key to T-cell development. They found that one well-known protein called Notch passes off much of its role during T-cell maturation to another protein called TCF-1. T cells are required for many aspects of immunity, and understanding how these proteins influence the production of infection-fighting cells could improve treatments for immune-suppressed patients.

The research group, led by senior author Avinash Bhandoola, MBBS, PhD, associate professor of Pathology and Laboratory Medicine, found an important role in early T-cell development for T-cell factor 1 (TCF-1), which is turned on by Notch signals.

"Notch triggers the process of T-cell development, and turns on expression of TCF-1, but Notch itself doesn't stick around; it's more of a kiss-and-run molecule," says Bhandoola. In contrast, once induced by Notch, TCF-1 is faithfully expressed throughout T-cell maturation.

T cells 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.

Notch regulates cell-fate decisions in many cell types in addition to

immune cells. Past work at Penn helped demonstrate that Notch is active in early T-cell progenitors in the thymus of mice, and drives the differentiation of these progenitors down the T cell pathway.

Delegating Work

Co-first authors, Anthony Wei-Shin Chi, MD, PhD, and Brittany Nicole Weber, BS, were graduate students together in the Bhandoola lab. They used retroviruses to express TCF-1 in immature blood progenitor cells. "If you expose progenitor cells to Notch signals in culture, we know that they will express TCF-1 and take on other features of T cells," says Chi.

However, when they forced expression of TCF-1 in cells using retroviruses, Weber noticed expression of T-cell proteins on the surface of cells -- even when Notch signals were absent. The team further characterized these new T-lineage cells by looking at gene expression on microarrays and found they expressed many T-cell specific genes. They concluded that Notch normally turns on TCF-1 early in development, and that TCF-1 then does the job of turning on T-cell genes and keeps T-cell maturation on the right track.

"The data are telling us that Notch delegates much of its work during T-cell development to TCF-1," says Bhandoola, "But we now have many questions about what comes next."

Adds Weber, "Some of the new questions are: How is TCF-1 regulated after Notch steps off stage? What keeps it on? What is TCF-1 doing? And how is it doing it?"

In many clinical settings, early T-cell progenitors are likely to be deficient, especially in patients undergoing bone marrow or blood-cell-producing stem cell transplantation – situations in which new T cells fail to be produced for long periods of time. In some patients, especially

elderly ones, there is never true recovery of T cells, and this non-recovery can be associated with infection.

"To improve the outcome of transplant patients, the process of T-cell development needs to be better understood," says Chi. This may also be important in cancer patients who get profound immunosuppression from treatments and in AIDS patients when T cells are not made at a rate sufficient to replenish the T-cell pool.

"It's possible that one day we will use molecules like TCF-1 to improve T-cell development for people," says Weber.

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