

Fork in the Road? Penn Researchers Find That Cells on Path to Becoming Mature T-Cells More Flexible Than Commonly Thought

Findings may shed light on T-cell leukemias and immunodeficiencies

PHILADELPHIA – Contrary to the currently accepted model of T-cell development, researchers at the **University of Pennsylvania School of Medicine** have found that juvenile cells on their way to becoming mature immune cells can develop into either T cells or other blood-cell types versus only being committed to the T-cell path. The findings appear in this week's issue of *Nature*, and have implications for better understanding how T-cell leukemias and other disorders arise.

“It is critically important to understand the life history of the T-cell lineage and to define the steps that multipotent progenitor cells take to mature to T cells,” says lead author **Jeremiah Bell, PhD**, Postdoctoral Fellow in the Department of Laboratory Medicine and Pathology. “Whether you're trying to understand T-cell immunodeficiencies, T-cell cancers, or other T-cell-related disorders, you first need to know the steps in T-cell development, and the signals acting at each step.”

The life of a T cell, and all other blood cells, begins in the bone marrow as a hematopoietic stem cell (HSC). HSCs have the potential to become all the different types of cells in the blood, including red blood cells, platelets, white blood cells, and all the cells involved in defending the body against pathogens and foreign proteins. The first stage in the process leading to such diversity is for the HSCs to become the precursor cells called multipotent progenitor (MPPs) cells.

The accepted version of what happens next is that there is a fork in the road to becoming a mature blood cell. Each MPP commits to becoming either a precursor of red cells and non-lymphoid white blood cells (called the myeloid pathway) or a precursor of T and B cells (called the lymphoid pathway). The T-cell precursors then go to the thymus, a small organ located under the breastbone, where they are called early thymic progenitors (ETPs).

“If the currently accepted model of T-cell development is correct, then early thymic progenitors, the ETPs, should be able to make T cells, but unable to make myeloid cells,” explains senior author **Avinash Bhandoola, PhD**, Associate Professor of Pathology and Laboratory Medicine. “Jeremiah instead found that progenitor cells that make it to the thymus have not yet committed to either the myeloid or T-cell pathway.”

In order to determine the potential of ETPs, the team first had to separate ETPs from all the other cells in a mouse thymus. This was accomplished by sorting the cells based on surface tags that are characteristic of the ETP cell type.

Next, single ETP cells were painstakingly placed into culture so that each container received only one cell. “We really wanted to examine single cells,” says Bell. “Otherwise, even if you do see T cells and myeloid cells, you can't be certain that they all came from the same progenitor cell.” After growing and dividing for several days, the

cells from each container were examined, again by surface tags, to see whether T cells or myeloid cells were present.

To the surprise of Bell and Bhandoola, most of the cultures begun with single cells had become a mixture of T cells and myeloid cells. This means that the majority of early thymic progenitor cells do not commit to becoming T cells by the time they get to the thymus gland. ETP cells retained the ability to become either T cells or myeloid cells.

Since ETPs showed the potential to give rise to myeloid cell types, the team also asked whether some of the myeloid cells in the thymus normally arise from ETPs. The process of T-cell development in the thymus requires progenitor cells to rearrange pieces of DNA. This process of DNA rearrangement is required to build the antigen receptor used by T cells, and permanently marks ETPs. Bell and Bhandoola found that permanent marks of past DNA rearrangements were present in myeloid cells within the thymus, but not in myeloid cells at other sites. This showed that ETPs give rise to myeloid cells in the normal thymus. “It’s very hard to accommodate these data with our old way of thinking about T-cell development,” notes Bhandoola.

“Now, we want to understand how ETPs make the decision to become myeloid cells or T cells within the thymus,” says Bell. “Although our research is focused on basic science, it is relevant to figuring out how T-cell leukemias develop from early progenitor cells.”

“We’re also wondering about the myeloid cells in the thymus that arise from ETPs,” adds Bhandoola. “Are they doing something we need to know about, and what could that be?”

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