

Investigators Pinpoint Keys to Cell Therapy Response for Leukemia

Dana-Farber researchers sought to learn more about what factors contribute to the success of donor lymphocyte infusion, a standard therapy.

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Dana-Farber Cancer Institute researchers have identified factors that determine whether donor lymphocyte infusion (DLI), a standard therapy for patients with acute myeloid leukemia (AML) who have relapsed after allogeneic hematopoietic stem cell transplant, will successfully move the patient into remission. The team identified that a key cell type in the DLI product and features of the tumor microenvironment in patients both play a role.

The findings were published in *Science Immunology*.

“Relapse of AML after stem cell transplant is a major challenge,” says first author Katie Maurer, MD, PhD. “There are few effective therapies, and patient outcomes after relapse are poor.”

For patients with AML, a stem cell transplant holds the potential for a cure. The goal of the transplant is to replace the patient’s hematopoietic stem cells – cells that rejuvenate supplies of blood and immune cells – with donor stem cells that are not cancerous. In addition, the donor cells also include active immune cells that can attack leukemia cells that remain in the patient after the transplant. This phenomenon is called the graft versus leukemia effect.

However, approximately one in three patients with AML relapse after allogeneic stem cell transplant. DLI is a follow-on treatment that can help stave off or treat relapse. It involves an infusion of white blood cells, called lymphocytes, from the donor of the stem cell transplant into the patient.

DLI is successful in only about 15-20% of patients with AML. Further, exactly how the cells in the DLI product help move leukemia into remission are not known, making it difficult for investigators to improve the treatment.

Maurer and principal investigator Catherine Wu, MD, chief of Dana-Farber’s Division of Stem Cell Transplantation and Cellular Therapies, wanted to learn more about what factors contribute to the success of DLI. To do this, they examined cells from the bone marrow of 25 patients with relapsed leukemia who had been treated with stem cell transplant and DLI. The sample included patients

who responded to DLI and patients who did not.

They employed single cell sequencing techniques to deeply profile multitudes of cells from each patient. This enabled the team to learn not only the range of cell types in the bone marrow, but also how those cells were interacting and driving immune responses in the patient.

The found that patients who responded to DLI therapy had notably different cellular populations in their bone marrow compared to patients who did not respond. The finding suggests that there might be forms of AML that are “hot,” meaning they respond to immune therapy, or “cold,” meaning they do not, similar to the “hot” and “cold” paradigm seen in some solid tumors.

The team also identified a single immune cell type that appears to mediate the graft versus leukemia effect in patients that respond to DLI. The cell type, CD8+ cytotoxic T lymphocytes that express a transcription factor called ZNF683/Hobit at high levels, appear to coordinate with other immune cells to expand and attack leukemia cells. In patients who did not respond, these T cells had lower levels of expression of ZNF683/Hobit and higher levels of markers that inhibit their activity.

Further, the team found that this cell type originates in the DLI product. That is, it is present in the donor’s original graft and re-infused during DLI.

“The goal of our research is to identify the ways in which some patients respond, in the hopes that uncovering these mechanisms can help us create improved therapies that are more effective for a greater number of patients,” says Maurer. “In this project, we identified a specific subset of activated T cells that have anti-leukemic activity. This discovery paves the way for creation of T cell therapies with improved efficacy in treating AML.”

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