

Why Cell Therapy Cancer Treatment Sometimes Fails

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Chimeric Antigen Receptor (CAR) T-cell therapy is one of oncology's most powerful ideas: Harvest a cancer patient's own immune cells, genetically engineer them to recognize tumor cells, multiply them in a laboratory and reinject them as a living drug.

For some patients, the treatment produces extraordinary, durable remissions. For many others, however, it produces nothing, and a Rutgers [study](#) in Cell Reports may finally identify one of the contributing factors: the poor initial quality of the patient's cytotoxic T lymphocytes, or CD8+ T cells, that are used to build the treatment.

"Many of their T-cells are in a defective state called senescence, which means they can't proliferate in the lab, they can't migrate to tissue effectively, and they can't kill very well," said [Ricardo Iván Martínez-Zamudio](#), an assistant professor at [Rutgers Robert Wood Johnson Medical School](#) who was a senior author of the study.

The study focused on CD8+ T cells, the immune system's front-line killers of cancerous and virus-infected cells. As people age, an increasing share of these cells enter senescence, which researchers describe as a kind of permanent retirement. The cells stop dividing but refuse to die, instead releasing low levels of inflammatory molecules that contribute to chronic inflammation. In young adults, about 20% to 30% of circulating CD8+ T cells are senescent. In people ages 55 and older, the figure can reach 55% to 80%.

That matters for CAR T manufacturing, which depends on robust cell multiplication. When the researchers grew CD8+ T cells from donors with high senescence burdens under standard CART culture conditions, those cells expanded significantly less than cells from donors with lower senescence levels.

Using gene signatures from their senescent cells, researchers then analyzed published clinical data from lymphoma patients who had received CAR T-cell therapy. Patients whose starting T-cells and finished products carried strong senescence signatures were significantly more likely to fail treatment. Those with more youthful profiles were significantly more likely to respond.

The analysis was retrospective and will need to be confirmed in a prospective clinical study.

To understand what controls the transition into senescence, the researchers obtained blood from younger and older donors, isolated CD8+ T cells and sorted them using a fluorescent dye that glows green in senescent cells. They then mapped the gene expression and “chromatin landscape” of both groups. (Chromatin is the physical packaging of DNA inside cells; its structure determines which genes can be switched on or off.)

The central finding was that senescence itself, not chronological age, was the primary driver of molecular differences. The proteins controlling the senescence program – known as transcription factors and functioning as switches that activate or silence specific genes – were nearly identical in younger and older donors. The machinery for immune cell aging thus appears to be built into T cells in early adulthood and simply gets activated over time.

“The senescence program is essentially precoded,” said Martínez-Zamudio, who is a member of the Genomic Instability and Cancer Genetics Program Cancer Pharmacology Program at Rutgers Cancer Institute, the State’s only National Cancer Institute-designated Comprehensive Cancer Center, together with RWJBarnabas Health. “It’s not that older people develop some new dysfunctional program. The capacity is there from the beginning.”

The researchers identified three transcription factors at critical control points in the network. When they reduced levels of these proteins using chemical inhibitors and genetic tools, they could partially dial back the inflammatory gene expression of senescent T cells. Reducing one of them partially restored gene expression patterns associated with normal T cell activation, though the actual recovery of cell division was modest.

Members of the study team hope to soon determine whether senescence profiling before CAR T-cell manufacturing can predict which patients will and won’t respond to treatment through a planned collaboration with [Rutgers Cancer Institute](#).

More broadly, the work connects to a basic problem in aging biology, Martinez-Zamudio said. Senescent immune cells aren’t just a concern for cancer therapy. Their accumulation contributes to the decline of immune function with age and to the chronic, low-grade inflammation linked to conditions from cardiovascular disease to autoimmune disorders.

The researchers found that their senescence signatures also were enriched in patients with active lupus, suggesting the program may be relevant beyond oncology.

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