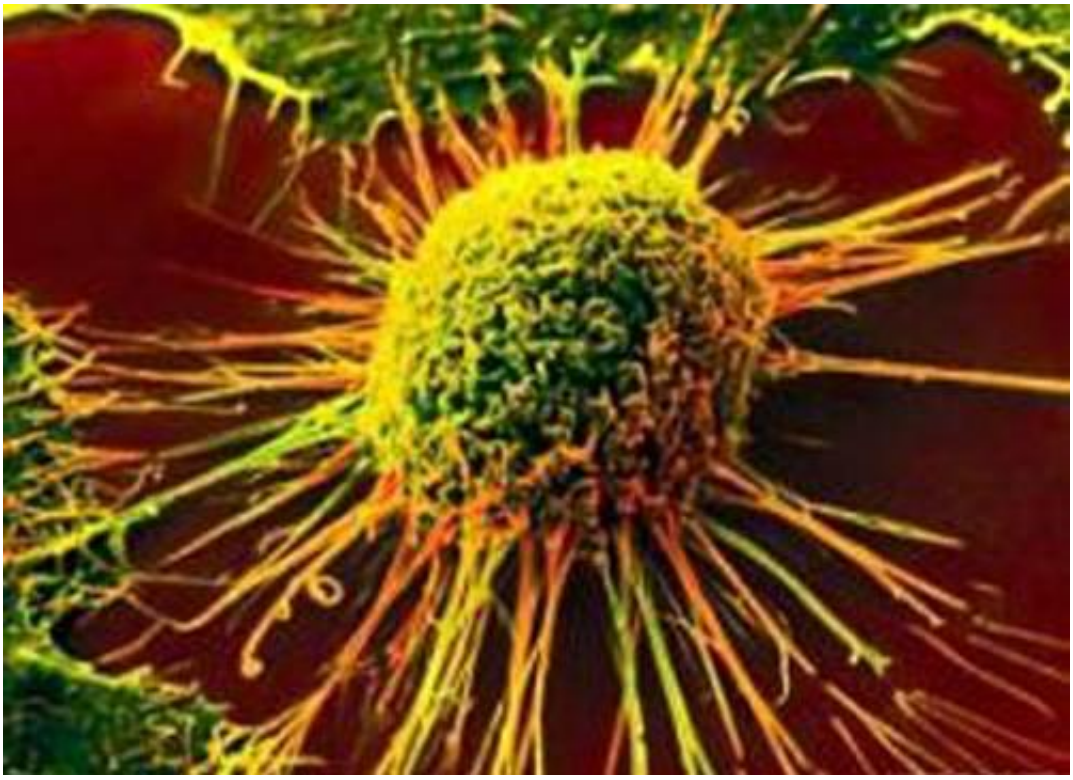
Blood cancer treatment may age immune cells as much as 30 years

September 1 2016



Certain cancer treatments are known to take a toll on patients, causing side effects like fatigue, nausea and hair loss. Now, scientists are investigating whether some treatments can cause another long-term side effect: premature aging of important disease-fighting cells.

University of North Carolina Lineberger Comprehensive Cancer Center researchers, by tracking a molecular marker that has been shown to increase in white blood cells as people age, have uncovered clues that suggest that stem cell transplant is linked to a marked increase in the "molecular age" of these immune cells in a group of patients with blood cancer.

The researchers report in the journal *EBioMedicine* that patients treated with an autologous stem cell transplant - a procedure that uses a reserve of a patient's own stem cells to regenerate healthy, non-cancerous blood cells - had elevated levels of expression of messenger RNA (mRNA), a type of genetic code used to make proteins, for this age-related marker. Strikingly, they found expression levels increased to a degree comparable to an additional 30 years of chronological age.

Despite the risk for significant short- and long-term side effects, the researchers say stem cell transplant is an extremely important treatment option. They believe their findings could lay the foundation for future studies into using this age marker to enable physicians to better quantify a patient's potential risk and benefit associated with a stem cell transplant.

"We know that transplant is life-prolonging, and in many cases, it's life-saving, for many patients with blood cancers and other disorders," said the study's lead author William Wood, MD, a UNC Lineberger member and an associate professor in the UNC School of Medicine Division of Hematology and Oncology. "At the same time, we're increasingly recognizing that survivors of transplant are at risk for long-term health problems, and so there is interest in determining what markers may exist to help predict risk for long-term health problems, or even in helping choose which patients are best candidates for transplantation."

Researchers are interested in objective measures of molecular or

functional age as a person's age in years is not always a good indicator of his or her health or fitness to receive a treatment. UNC Lineberger researchers examined mRNA levels for a protein called p16. MRNA expression of the gene coding for the p16 protein has been found to exponentially increase with chronological age.

"It's a well-known concept in geriatric oncology that different people age biologically at different rates and that their overall health status may or may not correspond with chronological age," Wood said. " On the one hand, we would not want to use chronological age itself to exclude patients from transplant since there are now patients up to the age of 80 who would benefit from transplant if they are otherwise appropriate candidates. A measure of biological age could help us to identify appropriate older candidates who might have previously been excluded from transplant. On the other hand, there are other, potentially younger patients who may be less physiologically fit because of prior treatment or comorbid illness, for whom transplant carries increased risks."

UNC Lineberger researchers studied the impact of two different transplant types: autologous stem cell transplant, which uses a patient's own stem cells, and allogeneic stem-cell transplant, which uses a stem cells from a donor, on 63 patients treated at UNC Hospitals for myeloma, lymphoma or leukemia.

The researchers reported higher expression of mRNA coding for p16 in the T-cells of both patients who received allogeneic and autologous transplant, but patients receiving autologous transplant had a larger increase—three times their pre-transplant levels.

They also noted that autologous stem cell transplant, as measured by p16 mRNA expression, had the strongest impact on molecular aging of T-cells—even greater than cytotoxic chemotherapy. A previous study had found that cytotoxic chemotherapy in breast cancer led to an

approximately two-fold increase in p16 mRNA expression, equivalent to about 10 years of chronological aging.

To try to explain why autologous stem cell transplant might age T-cells faster, they speculated that the forced regeneration of bone marrow that accompanies re-engraftment may contribute to stem cell aging. Chemotherapy prior to transplant may also contribute to increased p16 mRNA expression - so recipients of autologous transplant are in effect aged twice.

While the researchers did not have data showing a clear connection between changes in p16 mRNA expression levels and the actual function of the T-cells, they did argue that expression of this marker is "arguably one of the best in vivo marker of cellular senescence and is directly associated with age-related deterioration."

"Many oncologists would not be surprised by the finding that stem cell transplant accelerates aspects of aging," said the study's senior author Norman Sharpless, MD, director of UNC Lineberger and the Wellcome Distinguished Professor in Cancer Research. "We know that years after a curative transplant, stem cell transplant survivors are at increased risk for blood problems that can occur with aging, such as reduced immunity, increased risk for bone marrow failure, and increased risk of blood cancers. What is important about this work, however, is that it allows us to quantify the effect of stem cell transplant on molecular age."

More information: William A. Wood et al, Chemotherapy and Stem Cell Transplantation Increase p16INK4a Expression, a Biomarker of T-cell Aging, *EBioMedicine* (2016). DOI: 10.1016/j.ebiom.2016.08.029

Provided by UNC Lineberger Comprehensive Cancer Center