Undesirable rejection mechanism identified in stem cell transplantation

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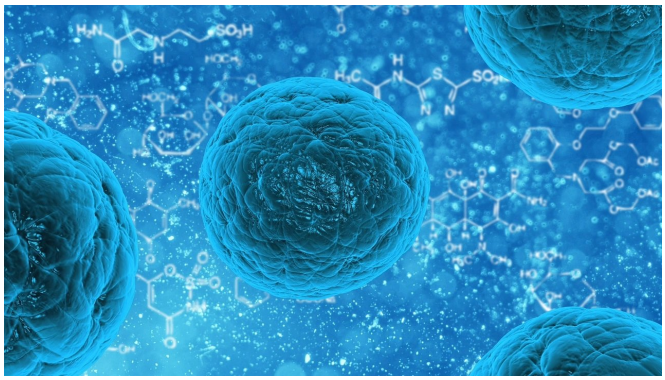

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In the treatment of leukemia, stem cell transplantation subsequent to chemotherapy and radiation can often engender severe adverse inflammatory reactions—especially in the skin or in the gut, since these so-called barrier organs are more frequently affected. Up until now, the reason for this was unclear. A MedUni Vienna team led by Georg Stary and Johanna Strobl from MedUni Vienna's Department of Dermatology, the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases has now identified an immune mechanism that is partially responsible for this. The results have now been published in the leading journal *Science Translational Medicine*.

The term leukemia is used to describe a group of malignant diseases of the haematopoietic system, in which precursors of the white blood cells (leucocytes) proliferate uncontrollably. Chemotherapy and radiotherapy are used to destroy the abnormal blood cells, which are then replaced by means of a stem cell transplant. In leukemia, the transplantation of healthy bone marrow stem cells or haematopoietic stem cells is often the only hope of recovery for patients. The process involves "replacing" all the recipient's blood cells that were previously destroyed by the treatment with donor cells.

However, the MedUni Vienna dermatologists have now found that there are so-called skin-resident and inactive T cells in the endogenous immune system that survive chemotherapy and radiotherapy intact and go on to survive for a further ten years between and beneath the epithelial cells of the skin, while the circulating T cells are destroyed.

"We were able to demonstrate that T cells surviving in the skin tissue are responsible for the inflammatory reaction following a stem cell transplant. These phenomena often occur within the first 100 days and can cause anything from mild eczema through to extensive fibrosis, hardening of the tissue, or blistering on the surface of the skin. In other words, the endogenous T cells attack the recipient (host) following stem cell transplantation." In specialist jargon, the condition is also referred to as Graft versus Host Disease (GvHD), and, for the first time, this study identified an inverse "Host-versus-graft reaction."

There were also cases in which the donor T cells further "supported," and thus intensified, this reaction. Affected patients are treated with cortisone, which causes an additional burden for patients who are already immunosuppressed following the transplantation. The study found that in patients who do not develop graft-versus-host disease, tissue-resident T cells remaining after treatment even proved to be beneficial to the recipient, in that they assumed their role in immune defense and protecting against infection.

In the future, the exemplary study results could lead to new treatment strategies that help to avoid, or at least to minimize, undesirable and violent inflammatory reactions following stem cell

transplants by manipulating the recipient's inactive T cells in advance. In addition, the manipulation of tissue-resident T cells might lead to new therapeutic approaches for other chronic inflammatory skin diseases, such as psoriasis or neurodermatitis.

More information: Johanna Strobl et al. Long-term skin-resident memory T cells proliferate in situ and are involved in human graft-versus-host disease, *Science Translational Medicine* (2020). DOI: 10.1126/scitranslmed.abb7028