Understanding the tricks of lymphomas

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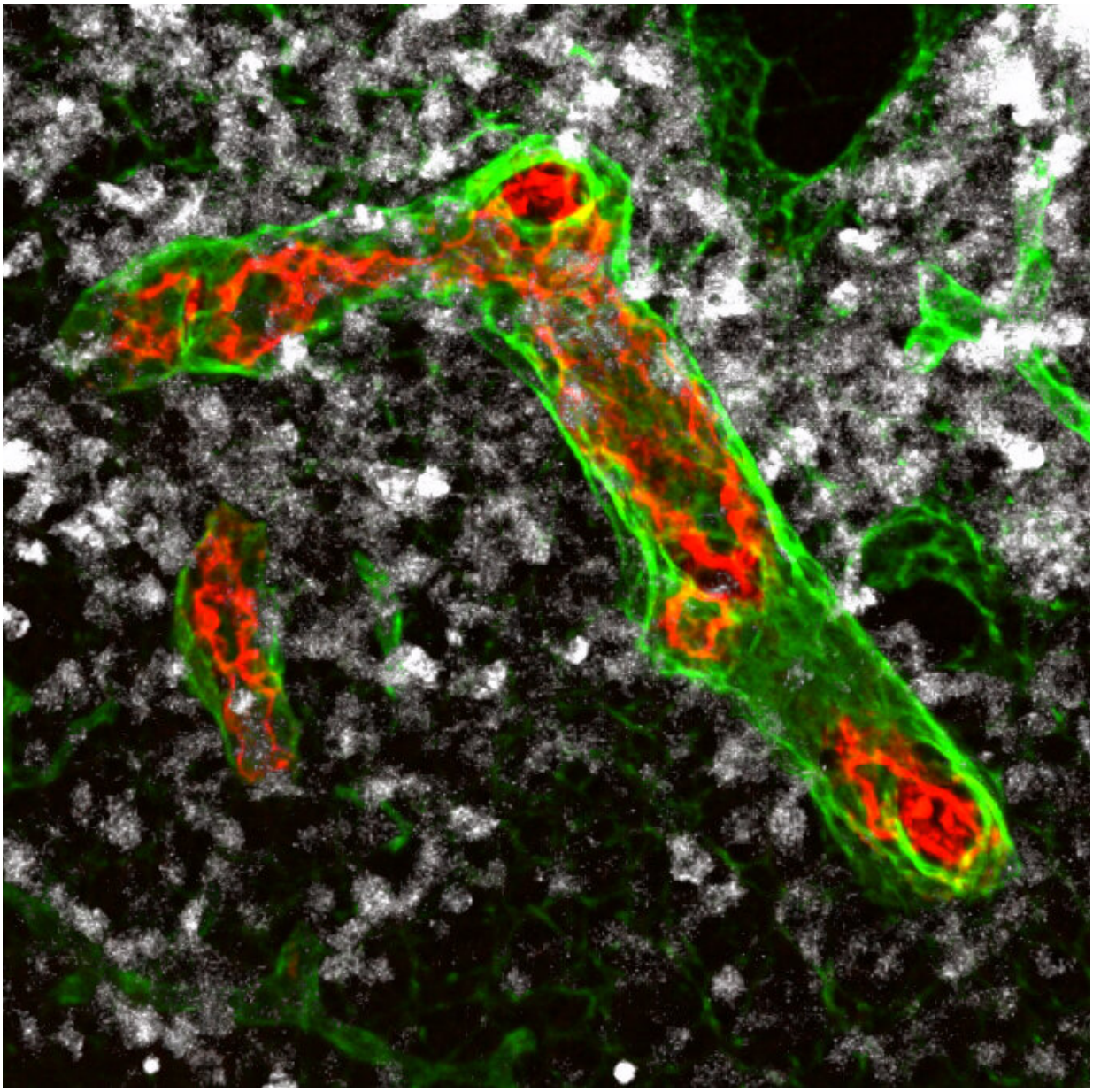

Immune cells can migrate into the lymph nodes via particularly large blood

vessels (red and green in the picture) and destroy existing tumor cells (white). These vessels are gradually remodeled in aggressive non-Hodgkin's lymphomas. This is probably why cell-based immunotherapies have so far not been effective against this type of tumor. Credit: Rehm Lab, MDC

Cellular immunotherapies have so far not been very effective against non-Hodgkin's lymphoma. A team led by Armin Rehm of the MDC has discovered a possible reason. As the they describe in *Cell Reports*, this cancer induces changes in the large blood vessels through which immune cells normally migrate to the lymph nodes.

Immunotherapies have become an indispensable part of modern cancer treatment. They are particularly effective against cancers like Hodgkin's disease, a type of blood cancer that attacks the lymphatic system. When it comes to aggressive non-Hodgkin's lymphomas, however, comparable approaches that employ various strategies to incite the immune system to attack the tumor cells typically end in failure.

Lymph node architecture is disrupted

The probable reason for this failure has now been uncovered by a team led by Dr. Armin Rehm, head of the Translational Tumor Immunology Lab at the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) in Berlin. "In experiments with mice and human tumor tissue, we were able to show that the cancer cells disrupt the delicate architecture of the lymph nodes," explains Dr. Lutz Menzel, first author of the *Cell Reports* paper and a researcher in Rehm's lab.

This ultimately leads to a group of large blood vessels—the high endothelial venules—losing one of their most important functions. "Without these intact vessels, immune cells cannot migrate into the

lymph nodes on their patrols to track down tumor cells," explains Menzel. Several research groups at the MDC were involved in the German Cancer Aid-funded study, including the Microenvironmental Regulation in Autoimmunity and Cancer Lab led by Dr. Uta Höpken.

Identical findings in mice and humans

"We knew from a previous study that aggressive lymphomas, such as diffuse large B-cell non-Hodgkin's lymphoma, stimulate the growth of small capillary-like vessels in the lymph nodes," says Rehm. In this way the tumor cells ensure that they are optimally supplied with nutrients during their rapid growth. "At the same time, microscopic examinations showed us that there were very few blood vessels with larger diameters in the affected lymph nodes," reports Rehm, adding that the findings in mice were identical to those in humans with aggressive lymphomas.

In the current study, the researchers first used mice to investigate how the loss of high endothelial venules occurs, a situation that allows lymphomas to evade attack by the cellular immune system. "We discovered a complex cascade of changes which include the scaffold structures in the lymph nodes being disrupted," says Menzel. "Such disruption causes changes in the pressure and volume ratios, both of which influence gene expression."

This, he says, eventually leads to high endothelial venules being transformed into completely normal blood vessels, thus cutting off the immune cells' access to the cancer cells. The team was then able to confirm these observations in human cancer tissue. They examined nearly 80 tissue samples from patients with aggressive non-Hodgkin's lymphoma to validate the results.

Cancer cells create protective niches for themselves

"Many types of tumors employ strategies to evade an attack by the immune system," says Rehm. "For example, cancer cells develop special surface molecules or produce signaling molecules that shut down immune cells." Little research had been done previously on how lymphomas protect themselves from the body's defenses as they grow. "Our study now provides deeper insights into the methods tumor cells use to create protective niches in lymph nodes," notes Rehm.

"It is crucial to know what is happening in the tumor microenvironment, especially when it comes to cancer immunotherapy, " adds Menzel. "Only in this way can we devise strategies that enable therapeutic T cells to reach the tumor site, where they can fight the tumor directly."

Easing immune cell immigration

The team plans to use the new findings to develop targeted strategies to halt or even reverse the process responsible for the disappearance of high endothelial venules. "One thing we are trying to do is specifically alter the vessels in the lymph nodes with the help of various drugs," says Rehm. The goal here, he says, is to ease immune cell immigration and prevent tumor cells from shielding themselves against attack in their niches. In this way the researchers hope that immunotherapeutic approaches like CAR T-cell therapy may also become more effective against aggressive non-Hodgkin's lymphomas.

More information: Lutz Menzel et al, Lymphocyte access to lymphoma is impaired by high endothelial venule regression, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.109878

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