Novel combination of antibodies leads to significant improvement in cancer immunotherapy

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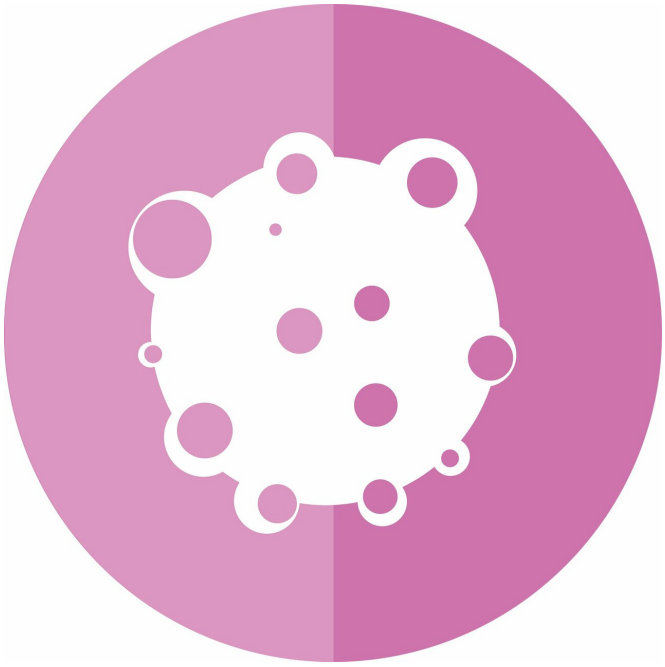

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The simultaneous use of antibodies based on two differing mechanisms of action leads to a more effective destruction of tumors. This has been demonstrated by a study in animal models by medical oncologists and scientists at the University of Basel that has been published in the scientific journal *PNAS*. Patients who do not respond to current immunotherapy options could benefit most from this new treatment.

In recent years, immunotherapies against cancer have raised great hopes. These novel therapies recruit the body's immune system to destroy cancerous tissue. An antibody that activates the CD40 receptor on the surface of immune cells and thus stimulates the production of natural killer T-cells showed a promising effect in preclinical studies.

However, in subsequent clinical trials, the success of the CD40 antibody fell far short of expectations—less than 20% of patients responded. The research group, Cancer Immunology, at the University of Basel has now shown in animal models that the effect of the anti-CD40 antibody can be increased significantly by combining it with two other antibodies that attach to tumor blood vessels.

Open the way to the tumor

The starting point for the study was the observation that the administration of anti-CD40 antibodies leads to an increase in killer T-cells as intended—but these can then only be detected in the peripheral areas and not in the interior of the tumor. The researchers suspected that this was due to the nature of the tumor's blood vessels.

"Normally, the blood vessels of a tumor are leaky or stunted. Therefore, there is no good way for killer T-cells to get inside," says study leader Dr. Abhishek Kashyap. "Our hypothesis was that the killer cells are able to invade the tumor and destroy it only if there are enough healthy blood vessels."

Therefore, they combined the anti-CD40 antibody with two other anti-angiogenic antibodies that are able to stabilize the tumor blood vessels. One of the anti-angiogenic antibodies is already approved for cancer therapy under the name Avastin, while the other is still in clinical development. All antibodies were provided by Roche.

New combination destroys tumor tissue

The researchers then tested this new combination

of antibodies in several animal models for different types of cancer, such as colorectal, breast and skin cancer. As expected, the combination of the three antibodies significantly improved tumor tissue destruction in all cancers.

A more detailed analysis also showed that this success was based on the predicted mechanism: the addition of the two anti-angiogenic antibodies ensured the tumors had more intact blood vessels. Unexpectedly, however, the investigations also showed that the antibody combination very effectively strengthens the immune system in several ways; for example, through a better penetration of the tumor by killer cells and by promoting a tumor-hostile inflammatory reaction in the tumor microenvironment.

"Our results illustrate how important it is to understand the biology of tumors," says Kashyap. He believes that patients with 'cold' tumors—tumors that do not respond well to immunotherapy—could benefit most from this new combination. "The anti-angiogenic antibodies may make the 'cold' tumors 'hot,' so that immunotherapy functions better." In the meantime, several early clinical trials of similar therapies in humans are underway.

Cooperation strengthens results

According to Kashyap, the strength of the study lies not only in the large effects measured, but also in the fact that several different laboratories achieved the same results. The experiments were carried out at the University Hospital of Basel, EPFL and the Roche Innovation Center Zurich.

This is also confirmed by Alfred Zippelius, Professor of Translational Oncology at the University of Basel and senior author of the study: "The innovative and translational potential of this work is the result of a close and excellent collaboration between applied and basic research, between the University of Basel and EPFL, and between academia and industry."

More information: Abhishek S. Kashyap el al., "Optimized antiangiogenic reprogramming of the tumor microenvironment potentiates CD40 immunotherapy," *PNAS* (2019).

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