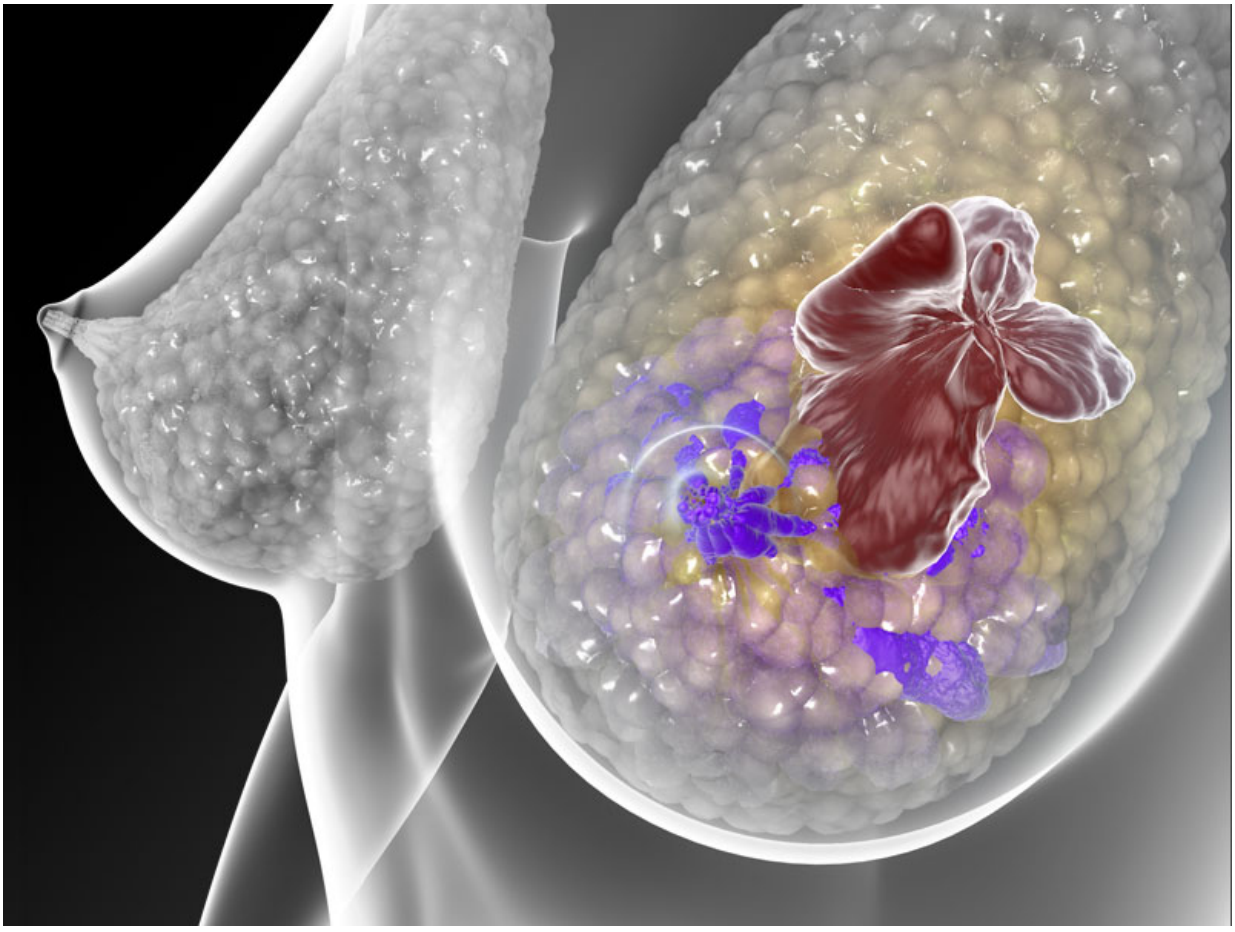
Antibody-drug compounds and immunotherapy to treat breast cancer

November 25 2015



A type of breast cancer called HER2-positive breast cancer, which overexpresses the cancerdriving HER2 receptor, often gains resistance to HER2-targeted therapy. Combining chemotherapy with immunotherapy may overcome resistance in this aggressive form of breast cancer, according to a new study. Credit: C. Bickel / Science Translational Medicine

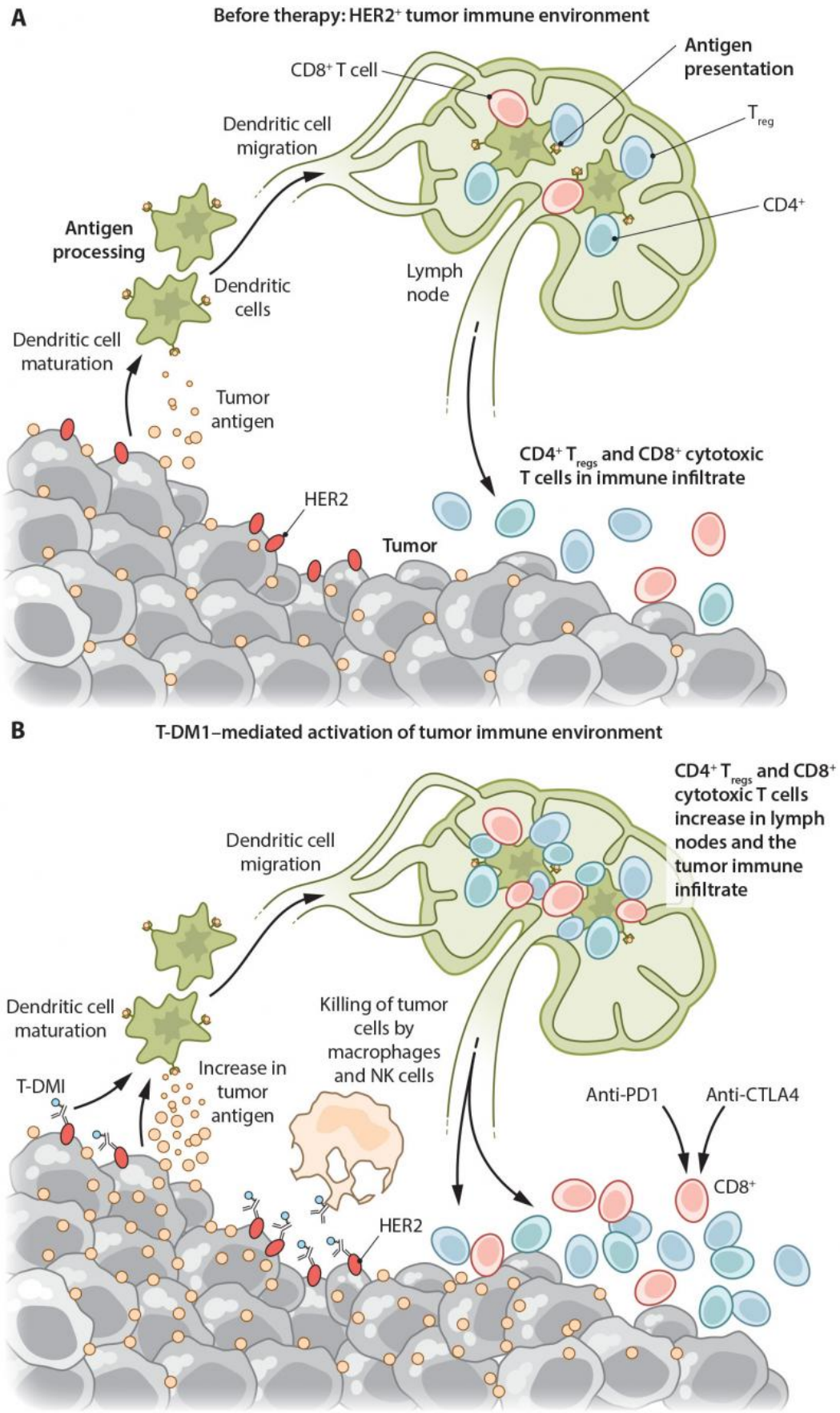
To more efficiently treat breast cancer, scientists have been researching molecules that selectively bind to cancer cells and deliver a substance that can kill the tumor cells, for several years. Researchers from the University and University Hospital Basel have now for the first time successfully combined such an antibody-drug conjugate with a therapy that stimulates the immune system to attack tumor cells. This opens the door to new therapeutic options in the treatment of breast cancer, report the researchers in the scientific journal *Science Translational Medicine*.

In nearly every fifth breast cancer patient, an above-average number of HER2 receptors are located on the surface of the tumor cells. These receptors are molecules that send growth factor signals into the cell. The overabundance of receptors causes the cancer cells to divide rapidly and the tumor grows faster than average.

For some years now, a new class of drugs called antibody-drug conjugates (ADCs) have been used, which work in two ways: they consist of an antibody that binds selectively to the tumor cell receptor and interrupts the signal to propagate; they also act as a transport vehicle for a chemical substance that enters the cancer cells with the antibody and triggers their death. The researchers demonstrate that the use of specific cytotoxic substances can also have a beneficial effect on the body's immune system.

Combination with immunotherapy

Researchers, led by Prof. Alfred Zippelius at the Department of Biomedicine, from the University and University Hospital Basel have now gone one step further: in a pre-clinical study performed in mouse breast cancer models, they combined the ADC 'trastuzumab emtansine' with an additional immunotherapy that activates the immune system into attacking tumors more efficiently.


A
Before therapy: HER2+ tumor immune environment
CD8+ T cell
Antigen presentation
Dendritic cell migration
Treg
CD4+
Antigen processing
Dendritic cells
Lymph node
Dendritic cell maturation
Tumor antigen
CD4+ Tregs and CD8+ cytotoxic T cells in immune infiltrate
HER2
Tumor
B
T-DM1–mediated activation of tumor immune environment
CD4+ Tregs and CD8+ cytotoxic T cells increase in lymph nodes and the tumor immune infiltrate
Dendritic cell migration
Dendritic cell maturation
Killing of tumor cells by macrophages and NK cells
T-DMI
Increase in tumor antigen
Anti-PD1
Anti-CTLA4
CD8+
HER2

The tumor immune infiltrate is shown before (A) and after (B) treatment with T-DM1, which results in increased tumor cell killing and antigen release as well as dendritic cell maturation. These enhancements result in increased infiltration of CD4+ and CD8+ T cells into the tumor microenviroment. The infiltrating cytotoxic CD8+ T cells, whose function may be suppressed by the immune checkpoint molecules CTLA-4 and PD-1, can be stimulated through treatment with anti–CTLA-4 and anti–PD-1. Credit: C. Bickel / Science Translational Medicine

They focused on what is known as immunoregulatory checkpoints. These are receptors on immune cells, which control for example effector T-cells by dampening their activation if damage to healthy cells is imminent. By administering a complementary antibody, they blocked the function of two such immune checkpoints, whereby different types of endogenous T-cells were activated.

On its own, this immune response had no immediate effect in the fight against the utilized breast tumors, but in combination with the ADC it proved itself effective in attacking cancer cells in mice, resulting in the complete cure of the majority of mice receiving the combination therapy. The researchers were also able to further demonstrate that regulatory T-cells play a host protective role in this therapeutic setting. Their removal resulted in excessive inflammation and tissue damage.

"Our results clearly demonstrate that antibody-drug conjugates are suitable for use in a combination therapy, opening new perspectives for the treatment of breast cancer," says lead author Dr. Philipp Müller on the significance of the study.

More information: "Trastuzumab emtansine (T-DM1) renders

HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade," *Science Translational Medicine* dx.doi.org/10.1126/scitranslmed.aac4925