How immune cells facilitate the spread of breast cancer

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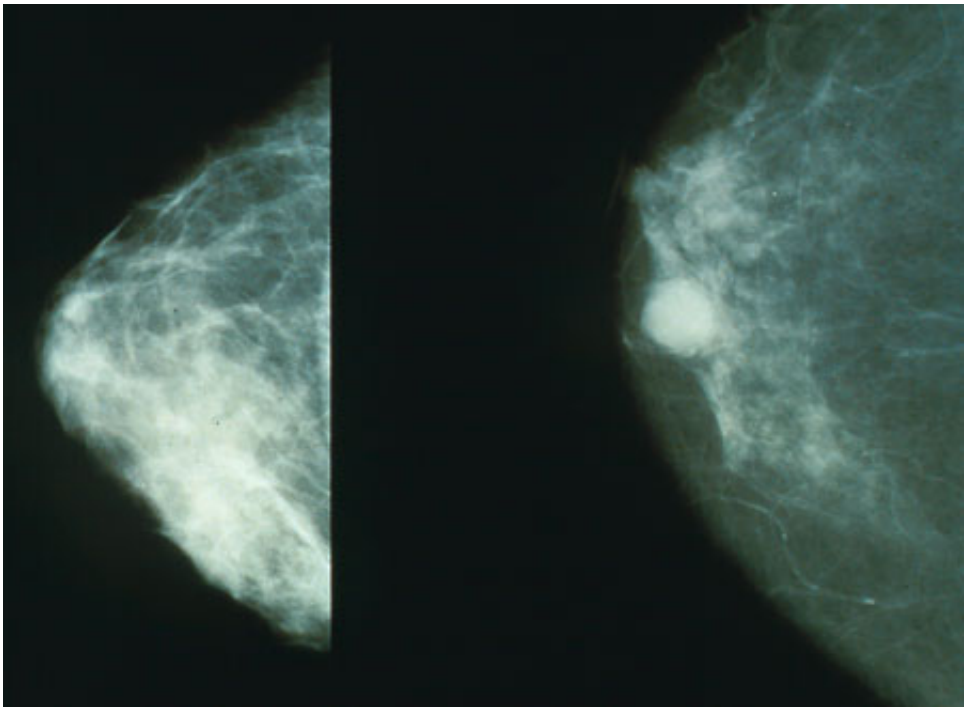

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

The body's immune system fights disease, infections and even cancer, acting like foot soldiers to protect against invaders and dissenters. But it turns out the immune system has traitors amongst their ranks. Dr. Karin de Visser and her team at the Netherlands Cancer Institute discovered that certain immune cells are persuaded by breast tumors to facilitate the spread of cancer cells. Their findings are published advanced online on

March 30 in the journal *Nature*.

In Western countries about one in eight women will develop breast cancer. Of the women who die of this disease, 90 percent die because the cancer has spread to other parts of their body and formed metastases. For this reason, cancer researchers are trying to understand how the process of metastasis occurs. A few years ago, it was reported that breast cancer patients with a high number of immune cells called neutrophils in their blood are at increased risk of developing metastases. Immune cells are supposed to protect our body. So why are high neutrophil levels linked to worse outcome in women with breast cancer?

Dr. Karin de Visser, group leader at the Netherlands Cancer Institute, and her team discovered that certain types of breast tumors cause a domino effect of reactions within the immune system. The tumor sends out signaling molecules that through a number of steps cause the immune system to produce lots of neutrophils. This normally happens as part of an inflammatory reaction, but the neutrophils that are activated by the tumor behave differently. It turns out they are able to block the actions of other immune cells, called T cells. T cells are the cells that can (sometimes) recognize and kill cancer cells.

De Visser and her team went on to discover that a signaling protein called interleukin 17 (or IL17) is important for this process. "We saw in our experiments that IL17 is crucial for the increased production of neutrophils", says De Visser. "And not only that, it turns out that this is also the molecule that changes the behavior of the neutrophils, causing them to become T cell inhibitory."

The first author of the paper in *Nature*, postdoctoral researcher Seth Coffelt, showed the importance of the IL17-neutrophil pathway by inhibiting this pathway in a mouse model that mimics human breast cancer metastasis. When neutrophils were inhibited, the animals

developed much less metastases than animals from the control group, in which the IL17-neutrophil route was not inhibited. "What's notable is that blocking the IL17-neutrophil route prevented the development of metastases, but did not affect the primary tumor," De Visser comments. "So this could be a promising strategy to prevent the tumor from spreading."

Since neutrophils are important to protect us from infections, drugs that inhibit neutrophils would make patients susceptible to all kinds of infections. Inhibition of IL17 might be a safer strategy. In fact, drugs that do so already exist. Anti-IL17 drugs are currently being tested in clinical trials as a treatment for inflammatory diseases, like psoriasis and rheumatism. Last month, the first anti-IL17 based therapy for psoriasis patients was approved by the U.S. Federal Drug Administration (FDA). "It would be very interesting to investigate whether these already existing drugs are beneficial for breast cancer patients. It may be possible to turn these traitors of the immune system back towards the good side and prevent their ability to promote breast cancer metastasis," De Visser says.

More information: IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis, DOI: 10.1038/nature14282

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