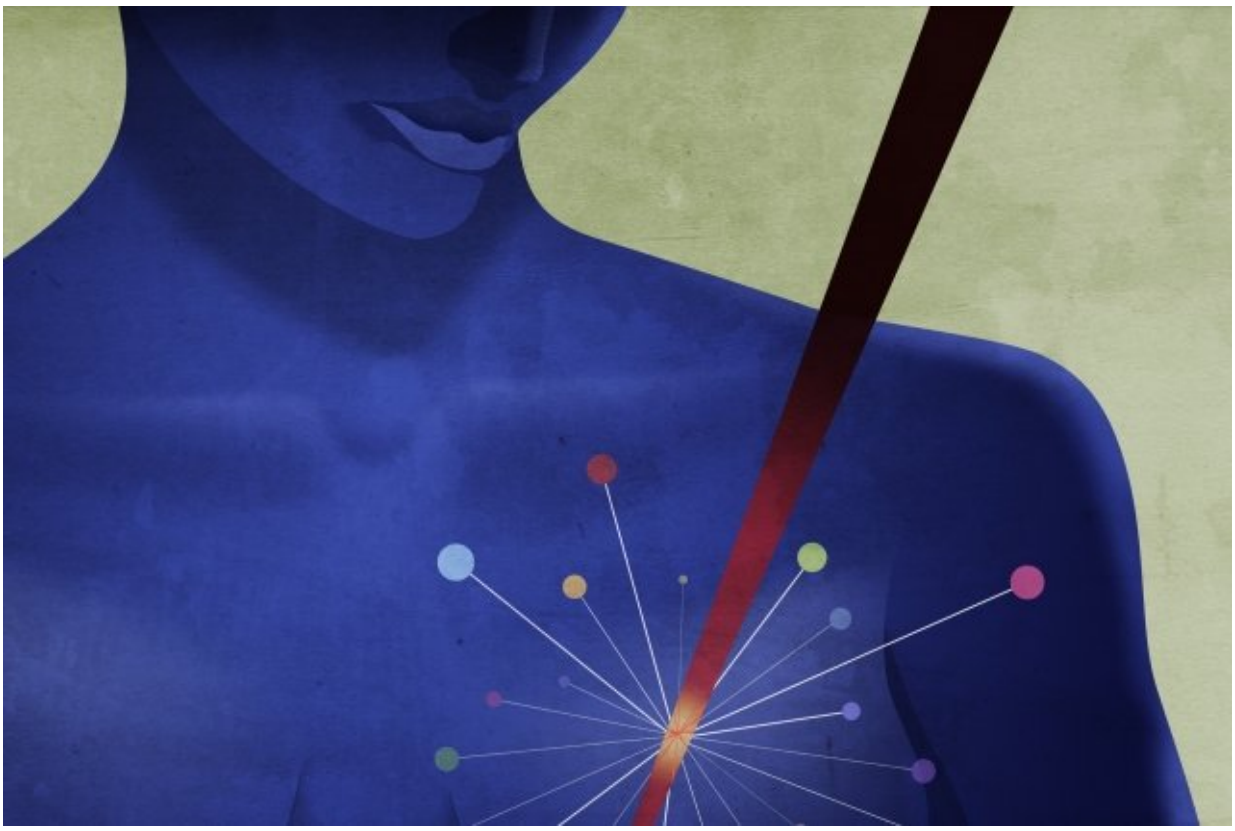
Medical Xpress

# Mouse study links early metastasis to systemic inflammation caused by wound healing

April 12 2018, by Nicole Giese Rura



Credit: Steven Lee/Whitehead Institute

According to new research conducted in mice by Whitehead Institute scientists, surgery in breast cancer patients, which while often curative,

may trigger a systemic immunosuppressive response, allowing the outgrowth of dormant cancer cells at distant sites whose ability to generate tumors had previously been kept in check by the immune system. Taking a non-steroidal anti-inflammatory drug (NSAID) around the time of surgery may thwart such early metastatic relapse without impeding post-surgical wound healing.

The team's work was published in the April 11 issue of the journal *Science Translational Medicine*.

"This represents the first causative evidence of surgery having this kind of systemic response," says Jordan Krall, the first author of the paper and a former postdoc in the lab of Whitehead founding member and MIT Professor Robert Weinberg. "Surgery is essential for treating a lot of tumors, especially breast cancer. But there are some side effects of surgery, just as there are side effects to any treatment. We're starting to understand what appears to be one of those potential side effects, and this could lead to supportive treatment alongside of surgery that could mitigate some of those effects."

Although the association between surgery and metastatic relapse has been documented, a causal line between the two has never been established, leading many to consider early metastatic relapse to be the natural disease progression in some patients. Previous studies of breast cancer patients have shown a marked peak in metastatic relapse 12-18 months following surgery. Although the underlying mechanism for such a spike has not been understood, a 2010 retrospective clinical trial conducted in Belgium provides a clue: Breast cancer patients taking an NSAID for pain following tumor resection had lower rates of this early type of metastatic relapse than patients taking opioids for post-surgical pain. Anti-inflammatory drugs also have previously been shown to directly inhibit tumor growth, but Krall and Weinberg thought that the NSAIDs' effects in these studies may be independent of the mechanism

responsible for the effects noted in the retrospective clinical trial.

To investigate the causes of early metastatic relapse after surgery, the team created a mouse model that seems to mirror the immunological detente keeping in check dormant, disseminated tumor cells in breast cancer patients. In this experimental model, the mice's T cells stall the growth of tumors that are seeded by injected cancer cells. When mice harboring dormant cancer cells underwent simulated surgeries at sites distant from the tumor cells, tumor incidence and size dramatically increased. Analysis of the blood and tumors from wounded mice showed that wound healing increases levels of cells called inflammatory monocytes, which differentiate into tumor-associated macrophages. Such macrophages, in turn, can act at distant sites to suppress the actions of T lymphocytes that previously succeeded in keeping the implanted tumors under control. Krall and Weinberg then tested the effects of the NSAID meloxicam (brand name Mobic), thinking that this anti-inflammatory drug might block the effects of immuno-suppressive effects of wound healing. In fact, when mice received the NSAID after or at the time of surgery, the drug prevented a systemic inflammatory response created by the wound healing and the meloxicam-treated mice developed significantly smaller tumors than wounded, untreated mice; often these tumors completely disappeared. Notably, meloxicam did not impede the mice's wound healing.

Still, Weinberg cautions that scientists are just beginning to understand the connections between post-surgical wound healing, inflammation, and metastasis.

"This is an important first step in exploring the potential importance of this mechanism in oncology," says Weinberg, a professor of biology at MIT and director of the MIT/Ludwig Center for Molecular Oncology.

**More information:** Jordan A. Krall et al. The systemic response to

surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy, *Science Translational Medicine* (2018). DOI: 10.1126/scitranslmed.aan3464

*This story is republished courtesy of MIT News (web.mit.edu/newsoffice/), a popular site that covers news about MIT research, innovation and teaching.*

Provided by Massachusetts Institute of Technology