Tumors disrupt the immune system throughout the body

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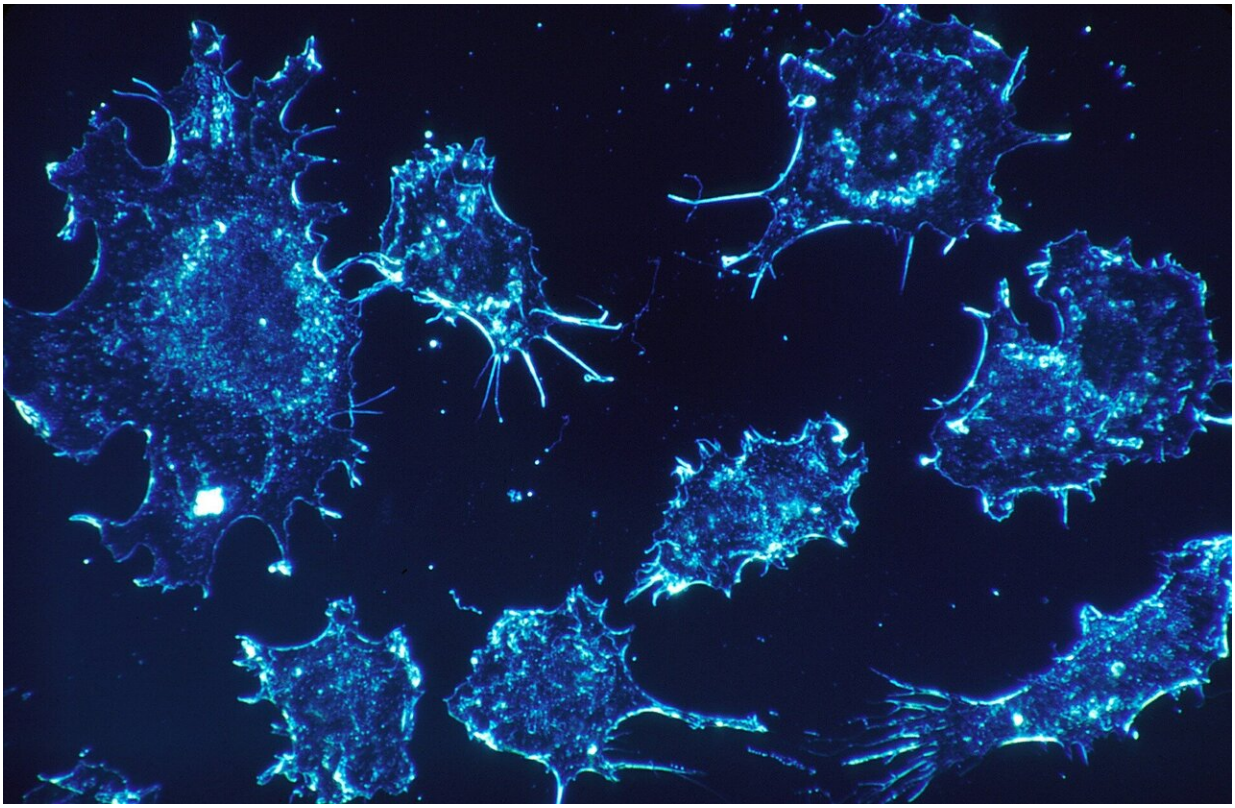

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Cancer treatment has advanced with the advent of immunotherapies that, in some cancers, can overcome tumors' ability to evade the immune system by suppressing local immune responses. But a new study in mice by UC San Francisco researchers has found that, depending on a cancer's

tissue of origin, tumors cause widespread and variable disruption of the immune system throughout the body, not just at the primary tumor site.

Greater success for immunotherapy regimens will rely on taking these different patterns of immune system disruption into account, they said, and findings from the new study, published online in *Nature Medicine* on May 25, 2020, are already being investigated in the clinic.

"Different cancers do different things to change the systemic immune system, and immunotherapies that help the patient's immune system attack cancer may work best when they trigger lasting immune responses throughout the body," said the study's principal investigator, Matthew Spitzer, Ph.D., an assistant professor of otolaryngology and member of the UCSF Helen Diller Family Comprehensive Cancer Center.

Spitzer's lab team, including the study's lead authors, Breanna Allen and Kamir Hiam, both UCSF graduate students, determined the abundance and activity of different types of peripheral immune cells—sampled from blood, bone marrow, spleen and lymph nodes near untreated tumors—in mice with different types of cancer, including brain, colon, pancreatic, skin (melanoma) and breast cancer. They used mass cytometry, a recently refined technique which relies on unique metallic molecular markers and mass spectrometry to quickly quantify and identify dozens of cell types in various states of activation.

Spitzer earlier discovered that proliferation of new immune cells originating far from a tumor was required for immunotherapy treatment to be effective. In the new study, his lab team has determined that not only does an untreated cancer change the way the immune response unfolds both locally and at a distance from the tumor, but also that this disruption of the immune system evolves over time. Remarkably, however, the immune system perturbations tracked by the researchers were reversed when the tumors were surgically removed.

Three distinct types of breast cancer examined in the study caused similar patterns of disruption in peripheral immune sites, while tumors originating in other tissues caused distinctly different changes in the relative abundance and activity of different immune cell types. These differences are likely a reflection of both anatomy and physiology, according to Allen.

"Different tissues have different needs and risks when interacting with the immune system," she said. "A site like the breast, which has a lot of fat and a lot of drainage, is going to have a different level of access and interaction with immune system in comparison to another tissue. Even in the brain, typically viewed as a protected compartment that excludes most immune cells, we found that localized tumors had effects on the immune system, even in the periphery of the body, although the response we saw was distinct from what we observed with the breast cancers."

To assess whether cancers have similar effects on the human immune system, the researchers also analyzed publicly available data on immune markers in the blood of human breast cancer patients and compared them to data from healthy individuals. They found that cancer patients showed indicators of an altered immune system that were consistent with data from the new mouse study, suggesting the findings may have direct applications to improving human immunotherapies.

Weakened Immune Defenses to Infection

While different tumor types in the study had different effects on the immune system, a common feature identified by the researchers was diminishment of the immune system's capacity to mount a new immune response, an important consideration for fighting infection as well as cancer.

People with cancer are known to have weaker responses to both

infection and vaccination, but it has been unclear to what extent this may be due to immunosuppressive effects of treatment rather than the cancer itself. The new UCSF study bolsters the evidence that cancer, before any treatment, can weaken the immune system's response to infection: the researchers found that mice with cancer had weakened immune responses to both viral and bacterial infection.

Cancer immunotherapy is most effective in patients whose immune systems are already mounting an immune response; the treatment needs to be able to stimulate preexisting immune system cells, especially "killer" T cells, in order to boost their ability to effectively attack tumor cells. However, the new research suggests that many tumors may render these treatments less effective by systemically reducing the number of immune cells available to be stimulated. "Our results demonstrate an unappreciated impairment of new cellular immune responses in the context of cancer," Spitzer said.

Tumor growth in the study was linked to reduced activation of immune cells known as antigen-presenting cells, a step that must occur in order for new T cells to become activated. Antigen-presenting cells grab onto a foreign target molecule, or antigen, and display it to other cells of the immune system, including T cells. The cells that detect the antigen target are thereby primed to expand their ranks and to attack any tumor or infectious pathogen that displays the same antigen.

"Our study suggests that the antigen presenting cells may be significantly functionally altered in cancer patients, and that this alteration compromises immune responses," Hiam said.

The researchers determined that poor functioning of antigen-presenting cells in mice with cancer was responsible for the weakened response to infection. They were able to boost antigen-presenting cell activation and the immune response to infection by treating the mice with so-called "co-

stimulatory molecules," which normally are made by the immune system.

"Going forward we see a time when cancer patients would receive a different formulation of the flu vaccine, for example, that a healthy person would not require, one that would activate antigen-presenting cells to produce a good immune response," Spitzer said.

"Our hope for the future is that results from this study will allow us to treat more patients with more effective immunotherapies that don't just target T-cells, but which also consider the context in which those T cells are residing, and the other types of cells they need to communicate with in order to become properly activated and to reject a tumor," Spitzer said. Spitzer is collaborating with oncologists on clinical trials to explore treatments to re-activate antigen-presenting cells, including a phase II trial to treat pancreatic cancer.

More information: Breanna M. Allen et al, Systemic dysfunction and plasticity of the immune macroenvironment in cancer models, *Nature Medicine* (2020). DOI: 10.1038/s41591-020-0892-6

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