

Immune system changes may drive aggressiveness of recurrent tumors

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Nearly half of the 700,000 cancer patients who undergo surgical removal of a primary tumor each year suffer a recurrence of their disease at some point, and many of those patients will eventually die from their disease. The traditional view of recurrent tumors is that they are resistant to therapy because they've acquired additional genetic mutations that make them more aggressive and impervious to drugs. Now, however, researchers at the Perelman School of Medicine at the University of Pennsylvania show in an animal model that the enhanced aggressiveness of recurrent tumors may be due to changes in the body's immune response. The findings are published this week in the *Proceedings of the National Academy of Sciences*.

"Typically when a patient has a [tumor recurrence](#), their oncologist treats them, much like they treated them for the primary tumor – with drugs aimed at the [tumor cells](#) themselves. But we've found that it might be better to attack the tumor cells and knock down the bad immune cells that are protecting the tumor," says senior study author Sunil Singhal, MD, assistant professor of Surgery and director, Thoracic Surgery Research Laboratory at the Perelman School of Medicine.

To assess the impact of anti-cancer vaccines on primary and recurrent tumors, the researchers immunized mice that had a primary or a recurrent tumor in their flank. Although both groups of animals developed an immune response to the vaccine, only the primary-tumor animals showed [tumor shrinkage](#) in response to the vaccine. The recurrent tumors appeared unaffected by the vaccine response.

Moreover, this pattern held for several different vaccines.

Despite the prevailing models of tumor recurrence—which emphasize [genetic changes](#) in the tumor cells themselves—Singhal and colleagues could not find substantial genetic or behavior differences in the recurrent versus primary tumors that might account for the pattern of response.

By contrast, when the team looked at the types of immune cells in and around the tumor, Singhal's team saw a big difference. The recurrent-tumor mice had a large increase in the number of regulatory T cells, compared with primary-tumor animals. That could be important, says Singhal, because T regulatory cells are responsible for holding other [immune cells](#) in check and blocking immune responses.

Additionally, macrophages that protect the tumor cells from immune system also increased in number and activity in the recurrent-tumor animals.

Remarkably, when the researchers treated recurrent-tumor animals with drugs that block macrophage activity, tumor growth slowed significantly. However, the same drugs had no effect on primary-tumor animals.

Singhal says it is not clear exactly what triggers the immune system changes, but whatever it is appears to happen at the time of surgery. His group has already started looking for alterations in signaling molecules.

In the meantime, though, he notes that there are newly approved drugs and experimental agents that block regulatory T cells. Given his team's new results, he thinks testing these agents in patients with recurrent disease – in combination with drugs that attack the tumor cells themselves – could be an important advance for patients.

"We could impact the outcomes of as many as 250,000 patients a year, if

this strategy works," he said.

Provided by University of Pennsylvania School of Medicine

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