Traitorous immune cells promote sudden ovarian cancer progression

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Aggressive ovarian tumors begin as malignant cells kept in check by the immune system until, suddenly and unpredictably, they explode into metastatic cancer. New findings from scientists at The Wistar Institute demonstrate that ovarian tumors don't necessarily break "free" of the immune system, rather dendritic cells of the immune system seem to actively support the tumor's escape. The researchers show that it might be possible to restore the immune system by targeting a patient's own dendritic cells.

"Our model shows where the cancer is kept in check for relatively long periods, but once they become noticeable, tumors grow exponentially," said José R. Conejo-Garcia, M.D., Ph.D., an associate professor at Wistar and leader of the Tumor Microenvironment and Metastasis Program of Wistar's Cancer Center. "More importantly, we show that by depleting these dendritic cells of the immune system, we can reverse the effect, once again allowing our immune system to recognize the ovarian tumors."

Their findings, presented in the March issue of the *Journal of Experimental Medicine*, available online now, represent the first successful attempt to model the tumor microenvironment of human ovarian cancer in a mouse model of the disease. In essence, the model replicates the inflammatory surroundings that ovarian tumors experience in humans. The more accurate model provides a better tool for researchers to understand, prevent, and treat tumors.

"Our system uses oncogene-driven tumors that are spontaneously antigenic, thus avoiding the use of artificial foreign antigens that do not accurately replicate what drives anti-tumor immune responses in humans," Conejo-Garcia said.

Ovarian cancer remains one of the most deadly forms of cancer in women. According to the National Cancer Institute, 21,990 women will be diagnosed with ovarian cancer, and 15,460 women will die of the disease this year Because early-stage ovarian cancer does not often exhibit noticeable symptoms, many women are not diagnosed until the cancer is at a later stage, when it is most difficult to treat.

"While we have seen an increase in survival rates for most cancers over the last 40 years, ovarian cancer survival has only improved slightly since the 1970's," Conejo-Garcia said. "We created our ovarian cancer model to get a better understanding of how these tumors acquire such aggressive characteristics and evade the immune system."

According to Conejo-Garcia, their model demonstrates how a localized ovarian tumor flares into an aggressive metastatic disease.

"You can see where, if one ovary is cancerous, it is almost unrecognizable until an instantaneous moment, when it explodes into exponential growth," Conejo-Garcia said. "The key to this moment, our evidence suggests, is in the phenotypic changes taking place in the dendritic cells that are part of the tumor microenvironment."

In healthy tissue, dendritic cells function as sort of alarm system to alert the adaptive part of the immune system to potential threats. They work as antigen-presenting cells, offering foreign or disease-causing molecules (called antigen) to the white blood cells that can then respond to an infection or, in this case, tumorous growths. Amid the ovarian cancer microenvironment, dendritic cells also induce the immune system to

attack tumor cells and inhibit their growth.

Until, that is, dendritic cells seem to switch sides.

"We see a change in the dendritic cells themselves, which allows tumors to progress to terminal disease in a very short time," Conejo-Garcia said. "Interestingly, the tumors themselves are still immunogenic—they could still otherwise elicit an immune response—it is just that the dendritic cells are actively suppressing the involvement of other anti-tumor immune cells; primarily T cells."

Conejo-Garcia and his colleagues believe that their findings offer a twist on the emerging theory of "cancer immunoeditting." The immunoeditting hypothesis suggests that the immune system actively "edits" tumor cells to eliminate antigens that are recognized by immune cells, keeping the cancer at bay before it becomes symptomatic. All symptomatic tumors, therefore, represent a failure of the immune system, where tumors lose their immunogenicity—their ability to trigger and be recognized by our immune system.

The researchers found that that depleting dendritic cells early on accelerating tumor expansion, while removing dendritic cells later on actually delayed the tumor's progression. According to Conejo-Garcia, their findings suggest it is a change in the immune system itself, specifically the dendritic cells, and not primarily any loss of immunogenicity on the part of the tumor.

"It is almost as if anti-tumor T cells become exhausted, they can no longer keep up the effort," Conejo-Garcia said. "Still, our findings suggest that the enduring activity of these T cells would allow us to control metastatic ovarian cancer by targeting the dendritic cells that actively prevent their anti-tumor functions."

In fact, Conejo-Garcia and his colleagues have already developed a strategy to reprogram traitorous dendritic cells. In a an upcoming edition of the journal Cancer Research, available online now, the researchers demonstrate how synthetic RNA molecules can be used to win back the allegiance of dendritic cells and restore their ability to stimulate tumor suppression.

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