Exosomes May Help Tumors Evade Immune System

Though researchers knew that exosomes play important roles in cancer and in the immune system, only now are they learning the specifics.

September 28, 2018 By National Cancer Institute

A new study has identified what may be an important and previously unknown route by which tumors evade the immune system: They secrete small membrane-encased sacs, called exosomes, that are studded with a protein that dials down the immune response.

The study, led by researchers at the University of Pennsylvania, found that in lab models of the skin cancer melanoma and in humans with the disease, tumor cells release exosomes coated with proteins called PD-L1. These proteins are part of a family of immune checkpoint proteins that bind to partner molecules on immune cells, effectively deactivating them.

The researchers likened the PD-L1-studded exosomes to a fleet of drones engaged in preemptive strikes, moving throughout the body to thwart an antitumor attack before immune cells—namely those known as cytotoxic T cells—ever have a chance to reach the tumor.

Findings from the study, published August 8 in Nature, also raise the possibility that measuring levels of PD-L1 on exosomes in patient blood samples could help to guide treatment decisions, said study co-leader Xiaowei Xu, MD, PhD.

Although the study's findings are provocative, it's still too early to know to what extent exosomes carrying PD-L1 influence the immune response against tumors in people with melanoma, said Suzanne Topalian, MD, associate director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins University.

"There are still many, many questions" to address before reaching that conclusion, said Topalian, who was not involved in the study. And the study also raises other questions, she added.

Among them, she said: "What other types of immune-modulating molecules might be on the surface of these exosomes?"

Following the Evidence Trail

For many years, scientists thought exosomes served strictly as molecular garbage trucks,

transporting waste out of cells. But it's become clear that extracellular vesicles like exosomes influence a variety of biological processes, said Jennifer Jones, MD, PhD, of NCI's Center for Cancer Research.

Researchers have known for some time that "exosomes have important roles in cancer and in the immune system," Jones said. "But it has been difficult to know which exosomes do what."

The volume of each exosome is one million times smaller than the volume of a typical cell, she continued, and "most of the tools of modern biomedical research are not suitable for precise and functional analyses of the cargo within individual exosomes."

Based on some earlier studies that found PD-L1 in blood samples and different types of vesicles released by cancer and other cells, the Penn team used a broad approach to look more closely at PD-L1 in these cellular outcasts to see if they influence the immune system's interaction with tumors.

On the Surface of Tumor Cells and Exosomes

Melanoma is known for eliciting a particularly strong immune response, and several immune checkpoint inhibitors have been approved by the Food and Drug Administration to treat melanoma. So the researchers began by evaluating different melanoma cell lines.

Right away they were surprised by what they found, Xu said.

Exosomes released from melanoma cells did contain PD-L1, they confirmed. Moreover, the exosomes from metastatic melanoma cells contained far more PD-L1 than cells from an initial, or primary, melanoma tumor.

The surprise came when they used electron microscopy to get a detailed view of the exosomes. The PD-L1 proteins were not inside the exosomes. Rather, the proteins were carried on their surface, with the binding portion of the protein protruding outside the surface—just as it does on tumor cells.

"That got us really excited, because if that's the case, that means the exosomal PD-L1 can directly interact with T cells," said Xu.

Further experiments confirmed that possibility. The team showed that the exosomes could bind to cytotoxic T cells—the immune cells most involved in directly killing cancer cells—and prevent them from proliferating and killing cancer cells.

When they moved their work to mouse models of melanoma, the research team also found exosomes studded with PD-L1 on their surface. Using a mouse model of melanoma that more closely mimics human cancer, injecting the mice with exosomes with PD-L1 on their surface made the tumors grow faster and reduced the accumulation of T cells and other immune cells in and around tumors.

A Treatment Biomarker?

The research team next looked at blood samples collected from people who had been treated for melanoma, and again they saw exosomes coated with PD-L1. They also found extracellular vesicles, most commonly exosomes, carrying PD-L1 in blood samples collected from people who had been treated for breast and lung cancers.

Their work raised an interesting possibility: that levels of PD-L1 on exosomes could be used to potentially identify patients who are most likely to respond to checkpoint inhibitors or to track their response to these drugs, Xu said.

For example, they analyzed blood samples from people who had been treated for melanoma with the checkpoint inhibitor pembrolizumab (Keytruda), which blocks PD-1, the immune cell binding partner of PD-L1. Patients whose tumors responded best to the drug had much lower exosomal PD-L1 levels before treatment than those who did not respond. And patients with the highest pretreatment levels of exosomal PD-L1 had worse outcomes than those with lower levels.

Exosomal PD-L1 levels measured after treatment began, however, told a different story. Patients who had large increases anywhere from 3–6 weeks after beginning treatment were much more likely to have reductions in the size of their tumors than those who had smaller increases.

Although the findings appear to be contradictory, they make biological sense, Xu said.

“It means there are two different processes going on,” he explained.

Before treatment, the exosomal PD-L1 levels likely reflect the size of the tumor or extent of the disease. Meaning, if the circulating PD-L1 is high, there’s a lot of tumor, which is associated with a poor prognosis.

After treatment with pembrolizumab, he said, “the rapid increase of exosomal PD-L1 [in treatment responders] means that the T cells are being activated, so they secrete more cytokines like IFN-gamma,” he said. Cytokines are signaling molecules that can stimulate the immune system.

In melanoma cell lines, in fact, the researchers showed that treating the cells with IFN-gamma increased exosomal PD-L1. And in their analysis of patient samples, they found that exosomal PD-L1 levels tended to rise and fall with IFN-gamma levels.

More Work to Do

The Penn team has “identified one important exosome population among a tremendously diverse repertoire of exosome populations that influence biological processes,“ Jones said. ”New tools and new approaches are needed to study these very small packages in more precise detail.”

Topalian stressed that further studies are needed, including those that involve a much larger number of samples from patients with melanoma—and more cancer types—and those that closely compare PD-L1 in tumor biopsies and tumor-released exosomes.

For example, work by Topalian's lab and others has shown that only about 40% of human melanomas contain tumor cells expressing substantial levels of PD-L1 on their surface. Future studies, she said, should look to see if there is a correlation between the amount of PD-L1 in tumors and on exosomes from the same patient.

Also, the idea that there is a large amount of exosomal PD-L1 in the circulation of people with melanoma would imply that it's having "a global effect on suppressing immunity" in those patients, she said. "And there's no evidence that most patients with stage IV melanoma are globally immune suppressed."

This post was originally published on September 7, 2018, by the National Cancer Institute. It is republished with permission.

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