Disrupting cancer pathway could enhance new immunotherapies

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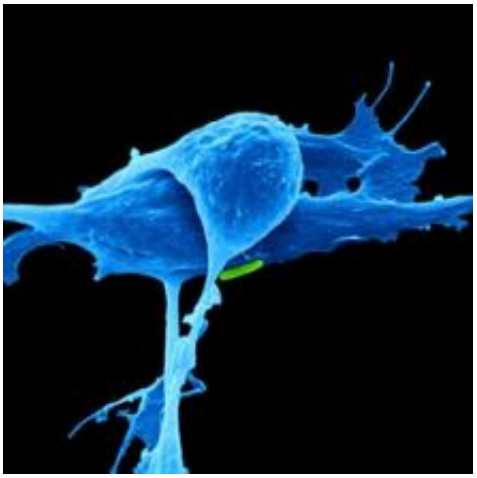

Understanding how to overrule a signaling pathway that can cause treatments to fail in metastatic melanoma patients should help physicians extend the benefits of recently approved immunity-boosting drugs known as checkpoint inhibitors to more patients.

In the May 11, 2015 issue of *Nature*, researchers from the University of Chicago show how these tumors shield themselves from T cells—the immune system's front-line anti-cancer weapon—by producing high levels of beta-catenin, an intracellular messenger. They show how beta-catenin prevents T cell invasion and undermines treatment. They also suggest ways to circumvent this roadblock.

"This is the first identified cell-intrinsic cancer-causing pathway that disrupts T cell infiltration in melanoma," said study author Thomas Gajewski, MD, PhD, professor of medicine and pathology at the University of Chicago. "This pathway enables multiple tumor types to evade immune surveillance. Developing strategies to inhibit this signaling within tumor cells could help restore T cell access and enhance the potential of immune-mediated cancer treatment."

"Working with mice," he added, "we think we have found ways to do that."

Wnt/beta-catenin signaling is a tightly regulated, multi-functional pathway involved in in many cellular processes, including cellular decisions about proliferation versus differentiation. Mutations in the beta-catenin gene, or flaws in the factors that degrade it, have long been linked to more aggressive disease in various tumor types, including colon, lung and prostate cancer, and melanoma.

The researchers used tumor tissue samples from melanoma patients to search for variations in their internal messaging. They compared tissue from 91 patients who did not have T cell invasion with tissue from 106 patients with T cell-driven inflammation.

Active beta-catenin signaling stood out as the primary difference between the two groups. Forty-nine percent of the tumors that blocked T cell infiltration had high levels of beta-catenin signaling, including increased expression of six genes that are targets of beta-catenin. Only four percent of tumors that were invaded by T cells had similar signaling patterns.

Next, moving from human tumors to a mouse model, they unraveled how activated beta-catenin prevents inflammation and blocks T cell penetration.

This presented a technical challenge. Transplanting small cancers into healthy mice immediately triggers inflammation. So the team created "autochthonous" tumors by introducing cancer-causing genetic alterations into cells from those mice.

Using this model, they confirmed that beta-catenin-expressing cancers did prevent T cells from entering the tumor microenvironment. They also discovered that the protected tumor sites lacked one component of the immune system.

Dendritic cells are scavengers that search for foreign invaders —usually pathogens, but also cancerous cells. They patrol border areas such as the skin, lungs and digestive tract. When where they find harmful microbes or cellular damage, they transport these danger signals to the lymph nodes and present them to T cells.

"We noticed that tumors with elevated beta-catenin lacked a subset of dendritic cells known as CD103+," said co-author Stefani Spranger, PhD, post-doctoral fellow in the University of Chicago's Department of Pathology. "Tumor cells without beta-catenin produce an immune-signaling molecule known as CCL4, which attracts CD103+ dendritic cells. But CCL4 expression is suppressed by tumor cells with high beta-catenin levels."

Next, the researchers use two checkpoint inhibitors—the monoclonal antibodies anti-CTLA4 and anti-PD-L1, the most potent immunotherapy currently available— to treat the mice with cancers. They found that tumors that lacked beta-catenin responded to treatment. Tumors with beta-catenin did not.

"This ability to resist immunotherapy could only be overcome by injection of CD103+ dendritic cells directly into the tumor," Spranger said. "With that intervention, T cells were able to invade and accumulate

in the tumor."

This strongly suggests, the authors note, that "the major immunologic defect in the context of melanomas expressing tumor-intrinsic beta-catenin-signaling is defective recruitment of CD103+ dendritic cells."

"Understanding the molecular mechanisms behind the presence or absence of a spontaneous anti-tumor T cell response should help us predict which patients will respond to the new immunotherapies," Gajewski said.

"It also suggests we could develop ways to help patients who don't initially respond to immune-mediated treatment, such as direct injection of their own CD103+ dendritic cells. Or we could use a short course of focused radiation therapy, which causes inflammation of tumor tissue and increased immune vigilance. There is also growing interest in developing drugs that could block beta-catenin."

"Although our study focused on melanoma," he added, "the Wnt/beta-catenin signaling pathway seems to play a role in many tumor types."

In recent studies, about one-third of patients treated with immune therapies such as anti-CTLA4 or anti-PD1 respond, but the results vary widely.

"We hope this work will help increase the percentage of patients who respond to immunotherapy," Spranger added.

More information: Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity, Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity, nature.com/articles/doi:10.1038/nature14404