Scientists discover a novel strategy to unmask cancer cells in high-risk neuroblastoma

Penn State College of Medicine USA

High-risk neuroblastoma is one of the most aggressive forms of solid tumors affecting children, originating in the nervous system. While a newer class of targeted immunotherapy drugs has improved survival rates, according to the American Cancer Society, cancer can hide from the immune system, causing patients to relapse or develop resistance to treatment. Now, a team of researchers from Penn State College of Medicine discovered a novel strategy to unmask cancer cells, improving the effectiveness of immunotherapy in cell experiments and in mouse models.

In a study published in the journal *Autophagy*, the researchers found that blocking a single protein, PIK3C3/VPS34, raised levels of GD2, a target molecule for neuroblastoma immunotherapy, on the surface of tumor cells. Monoclonal antibodies, which are lab-made proteins engineered to recognize and bond to a specific target, attach to GD2 on the surface of tumor cells, marking them for destruction by the patient's own immune cells. By raising the levels of GD2, the tumor cells in the study became easier to detect and more vulnerable to anti-GD2 immunotherapy. It also made the environment around the tumor more hostile to cancer growth.

The findings showed that PIK3C3/VPS34, or VPS34 for short, plays a key role in whether neuroblastoma tumors survive and respond to immunotherapy, said corresponding author Hong-Gang Wang, Lois High Berstler Professor of Pediatrics and professor of cell and biological systems at Penn State College of Medicine. He added there is a potential path to boost the effectiveness of anti-GD2 immunotherapies, such as the monoclonal antibodies dinutuximab and naxitamab, with a drug targeting VPS34, but more research is needed.

"The reality is we're trying to understand how to target neuroblastoma cells through multiple pathways to get more therapeutic benefit," Wang said. "VPS34 inhibition can enhance anti-GD2 immunotherapy, and it also independently makes the neuroblastoma tumor cells more detectable and vulnerable."

Neuroblastoma cells with more surface GD2

He explained that neuroblastoma cells with more surface GD2 - a fatty molecule with a small sugar chain on the end - are generally more "visible" to the antibodies and give them more to latch on to.

Scientists first discovered VPS34 - an enzyme, which is a specific kind of protein that helps facilitate cellular reactions - decades ago in yeast cells, identifying how it sorts and transports proteins to and from the cell membrane. VPS34 later became widely known for a second function called autophagy, a process by which cells break down and recycle their

own nutrients and other materials to survive stress, making it a key target for cancer researchers studying how cancer persists in the human body.

The team's hypothesis was rooted in this second purpose, Wang said. Prior research from the group and others had linked autophagy to both tumor cell survival and immune response. Tumors grow fast, and cells farther from its blood supply face more stress and lean harder on autophagy for nutrients to survive. Autophagy also lets tumor cells break down substances that might trigger an immune response. However, further investigation was needed to see if manipulating autophagy could improve anti-GD2 immunotherapy's effectiveness against neuroblastoma, according to first author Jiawen Zhang, biomedical sciences doctoral student at Penn State College of Medicine.

We had previously found that when we block autophagy, no matter the stage, it inhibited tumor growth, regardless if there was an immune response or not. But it had better efficacy in the models with working immune systems, which suggested it is probably also triggering the immune system to attack the tumors."

Jiawen Zhang, biomedical sciences doctoral student, Penn State College of Medicine

In this study, the team found a strong link between inhibiting VPS34 and increased effectiveness of anti-GD2 immunotherapy, but said the mechanisms surprised them. When they blocked VPS34 in cell experiments in the lab, where cancer cells have more oxygen and nutrients to survive and do not rely as heavily on autophagy, tumor cells died anyway, independent of any immunotherapy treatment.

Blocking VPS34 also sharply increased the amount of GD2 on the surface of the tumor cells, measured by flow cytometry, a laboratory technique that analyzes the levels of specific molecules by tagging them with fluorescent markers. Individual cells were passed through a laser, which identified the "brighter" ones that carried more GD2. Blocking VPS34 raised the total amount of GD2 in the cell, but surface GD2 rose more, disproportionately shifting the balance toward the outside of the cell.

"The most exciting finding for us in this study was that VPS34 inhibition increased GD2 presentation, which would make the tumor more visible to the antibody," Wang said.

In control experiments, the researchers blocked a separate protein, ATG14, that partners with VPS34 for autophagy, leaving VPS34 function untouched. The effect on GD2 was dramatically reduced, pointing to the possible importance of VPS34's initially discovered role - endolysosomal trafficking, or how the cell sorts and routes material to different destinations of the cell, including the cell membrane, according to Wang.

In a mouse model, they found that tumors grew poorly when the researchers targeted ATG14 and other genes for autophagy. The two functions of VPS34 - autophagy and endolysosomal trafficking - likely work in tandem to help the cancer cells survive, he added.

Pairing VPS34 inhibition antibodies in mice and cells

When they paired VPS34 inhibition with monoclonal antibodies in mice and cells, the combination outperformed either one alone. According to Zhang, the resulting "brighter" cancer cells with elevated levels of GD2 became easier targets, not only for the antibodies but for the natural killer or NK cells that bind to the antibodies. These NK cells then release perforin, a protein that creates holes in cancer cells' membrane, and granzymes, enzymes that go through those holes and trigger cell death. In both cell experiments and in mice, tumor growth was significantly suppressed, and in mice, survival improved.

"Combining the two therapies gave us better results," Zhang said.

According to Wang, high levels of GD2 are found in melanoma and osteosarcoma, too, but anti-GD2 immunotherapy is currently only clinically approved as standard patient care for neuroblastoma.

"This could potentially be tested in other tumor types that express high GD2 on their surface, too," he said.

Wang added VPS34 inhibitors are still mostly restricted to pre-clinical studies, with off-target effects often complicating studies in live subjects. He said he hopes that this work encourages the research community to look at VPS34 as a potentially important target and speed up drug discovery and testing efforts to complement anti-GD2 immunotherapy.

"Right now, what's missing is a clinical-grade VPS34 drug," he said. "We're providing the pre-clinical evidence and rationale that, once better VPS34 inhibitors are developed, combining them with anti-GD2 could be an important neuroblastoma treatment strategy."

Other Penn State College of Medicine authors include Longgui Chen, research technologist; Todd D. Schell, professor of cell and biological systems; Giselle Saulnier Sholler, Four Diamonds Endowed Chair for Pediatric Oncology Research and professor of pediatrics; Vladimir Spiegelman, THON Chair for Pediatric Cancer Research and professor of pediatrics; and Yoshinori Takahashi, associate professor of pediatrics and of cell and biological systems. Xiaoming Liu, who conducted this research as a biomedical sciences doctoral student at Penn State and has since graduated, also contributed.

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