

Novel drug combo activates natural killer cell immunity to destroy cancer cells

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Most skin cancer drugs that activate the immune system work by triggering immune cells, called T cells, to attack tumors, but when T cells are activated for too long, they can wear out and cease to function. A new study led by Penn State College of Medicine scientists finds that another type of immune cell—natural killer cells—can be harnessed to pick up the slack when T cells no longer work and may also reinvigorate T cells to attack melanoma tumors. The team has identified a unique combination drug strategy to activate this natural killer cell-mediated immunity in mice. The individual agents are clinically used but not in combination, and the combination still must be demonstrated to be effective in humans.

"Long-term effective treatments are difficult to achieve in [melanoma patients](#) due to a variety of factors, one of which includes T-cell exhaustion. This occurs over time as [cancer patients](#) are treated with drugs to enhance T-cell mediated immunity," said Gavin Robertson, professor of pharmacology, pathology, dermatology and surgery, Penn State College of Medicine. "If T-cell-mediated immunity is no longer working, switching to an approach that activates natural killer cell-mediated immunity could be a major advancement."

Robertson explained that natural killer cells can be lacking in [solid tumors](#), likely due to limitations of signals attracting them into tumors, activation once in the [tumor](#), and the general immunosuppressive microenvironment that occurs in tumors. He said that therapies that can increase natural killer cell infiltration and/or activation in tumors are urgently needed.

Known as "the guardian of the genome," p53 is a class of proteins tasked with suppressing tumor development. However, melanoma cells counter this attack by producing Murine Double Minute (MDM) proteins, which hamper the activity of p53 and prevent the pathway from being active.

"Emerging evidence suggests that restoration of p53 signaling within tumor cells can lead to natural killer cell infiltration and activation in the tumor," said Robertson, a Penn State Cancer Institute researcher. "Yet, studies have found that drugs targeting MDM proteins in order to restore p53's tumor-suppression activities tend to be toxic."

Instead, he said, targeting a different set of proteins—AKT and WEE1—may be a potentially non-toxic and novel approach to increase p53 activity. Like MDM proteins, explained Robertson, both AKT and WEE1 are overexpressed in 80% of melanomas and play a unique role with the MDM proteins to prevent the p53 pathways from being active. What they found is that targeting both AKT and WEE1 uniquely reverses the effects of the MDM proteins, reactivating the p53 pathways in a way that does not occur when using MDM inhibitors. Thus, the effect is better p53 pathway activation without the [toxic effects](#) seen with MDM inhibitors.

In their study, which published on June 3 in the journal *Cancer Immunology Research*, Robertson and his colleagues tested the abilities of two AstraZeneca cancer drugs—cavimasertib (AZD5363), which is known to inhibit AKT, and adavosertib (MK1775), which is known to inhibit WEE1—to solicit a natural killer cell immune response.

They conducted their first experiment with cultured mouse melanoma cells. The team incubated the cells, along with different concentrations of the two drugs, for 24 hours. Afterward, they added natural killer cells and later assessed the number of healthy melanoma cells that remained.

"We found that simultaneous inhibition of both AKT and WEE1 with capivasertib and adavosertib synergistically reduced melanoma cell proliferation and increased melanoma cell death mediated by the natural killer cells," said Robertson. By contrast, he added, inhibiting the proteins individually was not effective at causing the natural killer cell response.

The team conducted a similar study in live mice with [melanoma](#) tumors and found that the drug combination reduced tumor volumes by approximately 80% compared to mice in the control group. In addition, the researchers found that the drug combination was not toxic to the animals.

Importantly, not only did the scientists identify drugs that are effective against melanomas, but they also determined the specific mechanisms of the drugs' actions. The team found that the drugs inhibited AKT and WEE1, which in turn resulted in restoration of p53 pathway activity and increased the abilities of natural killer cells to infiltrate tumors. This occurred because the drugs changed the surfaces of tumor cells, and the [tumor cells](#) produced factors that attracted natural killer cells into the tumors and activated them once there.

"When we used these drugs to draw natural killer cells into the tumors, the [natural killer cells](#) also pulled in T-cells, whose activity could then be triggered with an additional agent, called an immune checkpoint inhibitor," said Robertson. "Using this approach, we were able to completely eliminate tumors in mice."

He noted, "Before now, natural killer cell-mediated immunity triggered with drugs had not been investigated for the management of cancer. We are the first to identify an efficient, non-toxic approach to activate this type of immunity with drugs, which could significantly impact cancer treatment."

More information: Saketh S. Dinavahi et al, Targeting WEE1/AKT Restores p53-Dependent Natural Killer–Cell Activation to Induce Immune Checkpoint Blockade Responses in "Cold" Melanoma, *Cancer Immunology Research* (2022). [DOI: 10.1158/2326-6066.CIR-21-0587](https://doi.org/10.1158/2326-6066.CIR-21-0587)

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