Researchers show how a targeted drug overcomes suppressive immune cells

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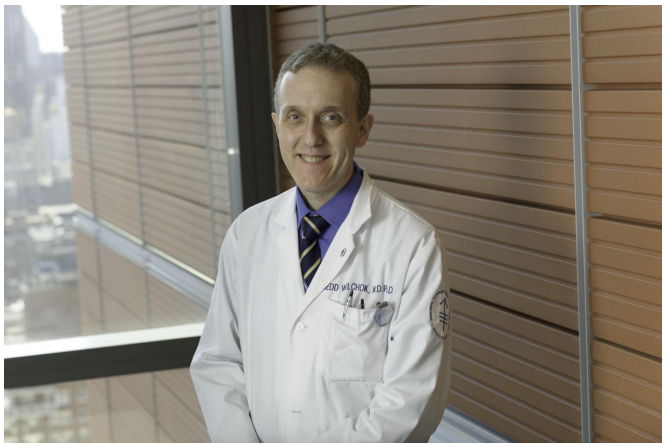

Jedd Wolchok is the Director of the Ludwig Collaborative Laboratory at Memorial Sloan Kettering Cancer Center. Credit: Ludwig Cancer Research

A Ludwig Cancer Research study shows that an experimental drug currently in clinical trials can reverse the effects of troublesome cells that prevent the body's immune system from attacking tumors. The researchers also establish that it is these suppressive cells that interfere with the efficacy of immune checkpoint inhibitors. This class of immunotherapies lifts the brakes that the body imposes on the immune system's T cells to unleash an attack on cancer cells.

"Though checkpoint inhibitors have durable effects when they work, not all patients respond to the treatment," says Taha Merghoub, an investigator at the Ludwig Memorial Sloan Kettering Collaborative Laboratory who led the study with Director Jedd Wolchok. "Part of the reason for this is that some tumors harbor tumor-associated myeloid cells, or TAMCs, that prevent T cells from attacking tumor cells."

In a study published online today in *Nature*, Merghoub and his team used mouse models of cancer to show that the effects of TAMCs can be reversed by an appropriately targeted therapy.

To show that TAMCs were indeed involved in resistance to checkpoint blockade, the researchers used a specific growth stimulant to increase their number in melanoma tumors to create a suitable model for their studies. They found that this made the tumors less susceptible to checkpoint blockade.

"We were able to make a tumor that was not rich in immune suppressing myeloid cells into one that was," says Merghoub.

Having established a link between TAMCs and checkpoint inhibitor resistance, the researchers next set out to test the hypothesis that blocking immune suppressor cell activity would improve immunotherapy response. To do this, they used an experimental drug manufactured by Infinity Pharmaceuticals called IPI-549. The drug, which is available for clinical use, blocks a molecule in the suppressor cells called PI3 kinase-gamma. Blocking this molecule changes the balance of these immune suppressor cells in favor of more immune activation.

"We effectively reprogrammed the TAMCs, turning them from bad guys into good guys," Merghoub said.

IPI-549 dramatically improved responses to immune checkpoint blockade (ICB) therapy for tumors with high concentrations of TAMCs. When checkpoint inhibitors were administered to mice with suppressed tumors, only 20% of the animals underwent complete remission. When the same drugs were administered with IPI-549, that number jumped to 80%. IPI-549 provided no benefit to tumors lacking the suppressor cells.

Merghoub and his team also showed that tumors that were initially sensitive to checkpoint inhibitors were rendered unresponsive when their TAMC

concentrations were boosted with growth stimulants.

Taken together, these results indicate that TAMCs promote resistance to checkpoint inhibitors and that IPI-549 can selectively block these cells, thereby overcoming their resistance.

Merghoub said the findings help pave the way for a precision medicine approach to immunotherapy that will allow cancer treatments to be tailored to a patient's particular tumor profile. "We can now potentially identify patients whose tumors possess immune suppressor cells and add a drug to their treatment regimen to specifically disarm them," he added.

IPI-549 is currently undergoing a Phase I trial in the United States to assess its safety when administered alone and in combination with the FDA-approved checkpoint inhibitor drug nivolumab (Opdivo).

More information: Olivier De Henau et al, Overcoming resistance to checkpoint blockade therapy by targeting PI3K? in myeloid cells, *Nature* (2016). DOI: 10.1038/nature20554

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