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Disabling critical 'node' revs up attack when cancer immunotherapies fall short

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An existing drug known as a JAK inhibitor may help patients who don't respond to the so-called checkpoint inhibitor immunotherapy drugs overcome that resistance, suggests a new preclinical study published online in *Cell* today by Penn Medicine researchers. Importantly, the results demonstrate that shutting down the interferon pathway, shown here to be critical to a tumor's resistance to immunotherapy, with a JAK inhibitor may improve checkpoint inhibitor drugs and even bypass the need for combinations of these drugs, which often come with serious side effects.

Today's checkpoint inhibitor drugs target receptors such as PD1 and CTLA-4, which act as a type of "off switch" on a T cell to prevent it from attacking other cells. Inhibiting these pathways with one or a more of the drugs releases these "brakes" so the immune system can fight the disease. However, over half of patients on the drugs relapse or their cancer progresses.

"The proposed approach has some elegance to it - rather than try to figure out all inhibitory pathways that the tumor has enabled, find a critical pathway that regulates many of the inhibitory signals and cripple that instead," said senior author Andy J. Minn, MD, PhD, an assistant professor of Radiation Oncology in the Perelman School of Medicine at the University of Pennsylvania. "Interferon signaling is like a critical node in a network. Disable it and a large part of that network collapses."

Using breast cancer and melanoma mouse models, Minn, first-author

Joseph L. Benci, a graduate student in Penn's Cell and Molecular Biology Graduate Group, and their colleagues from the departments of Radiation Oncology, Abramson Family Cancer Research Institute and Penn's Parker Institute for Cancer Immunotherapy showed that prolonged interferon signaling in tumor cells increased resistance to checkpoint inhibitors through multiple inhibitory pathways, and that blocking this response resulted in improved survival and powerful tumor responses.

Authors on the paper also include Robert Vonderheide, MD, DPhil, the Hanna Wise Professor in Cancer Research, Amit Maity, MD, PhD, a professor of Radiation Oncology, and E. John Wherry, PhD, a professor of Microbiology and director of the Institute for Immunology at Penn.

Studies have shown that combining checkpoint inhibitors, ipilimumab and pembrolizumab, for instance, as well as adding radiation therapy, as described in a Penn paper from the same researchers in *Nature* in 2015, elicits promising tumor responses in patients. But many still do not respond because of additional unidentified "brakes."

Researchers modeled this unknown resistance in breast cancer and melanoma mouse models with various lab techniques, including the genetic tool CRISPR, and found that treating the mice with checkpoint inhibitors (against PD1 and/or CTLA4) with or without radiation, along with the JAK inhibitor ruxolitinib, effectively restored complete responses and long-term survival in mice with tumors that are normally highly resistant to therapy.

Inhibiting this pathway could also bypass the need for multiple checkpoint inhibitors: one checkpoint inhibitor (anti-CTLA4) and the JAK inhibitor in the breast cancer mouse model resulted in a 100 percent complete response and survival.

JAK inhibitors, U.S. Food and Drug Administration-approved drugs to treat myelofibrosis and psoriasis, target the well-studied interferon pathway, typically considered to be immunostimulatory. However, the authors found that over time interferon signaling changes how cells respond epigenetically to molecular signals in the tumor, switching from stimulatory to suppressive, similar to what happens in a chronic viral infection. Thus, blocking it switched off the tumor's resistance in mice.

"To our surprise, blocking interferon driven resistance not only antagonizes multiple inhibitory pathways that hinders combination therapies in mice," Minn said, "but it may also provide a general strategy to the challenge of designing complex combination checkpoint blockade therapies that seek to address the well-known problem of resistance."

Downgrading the number of checkpoint inhibitors for therapy has its advantages, given the severe and sometimes life-threatening toxicities that come along with combination therapies, including autoimmune complications such as colitis and fatal myocarditis.

"There is a real translational implication here," Minn said. "Because the interferon signaling pathway is targetable pharmacologically, we could perhaps mimic what we did in mice using JAK inhibitors that already exist for other purposes."

The team is looking to begin a new clinical study in lung cancer patients based on their findings in the upcoming months. The researchers also identified two potential biomarkers, MX1 and IFIT1, that may help identify tumors in patients under the influence of this interferon suppression.

Provided by Perelman School of Medicine at the University of Pennsylvania