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Study finds novel mechanism of action for NK cells in checkpoint inhibitor for cancer

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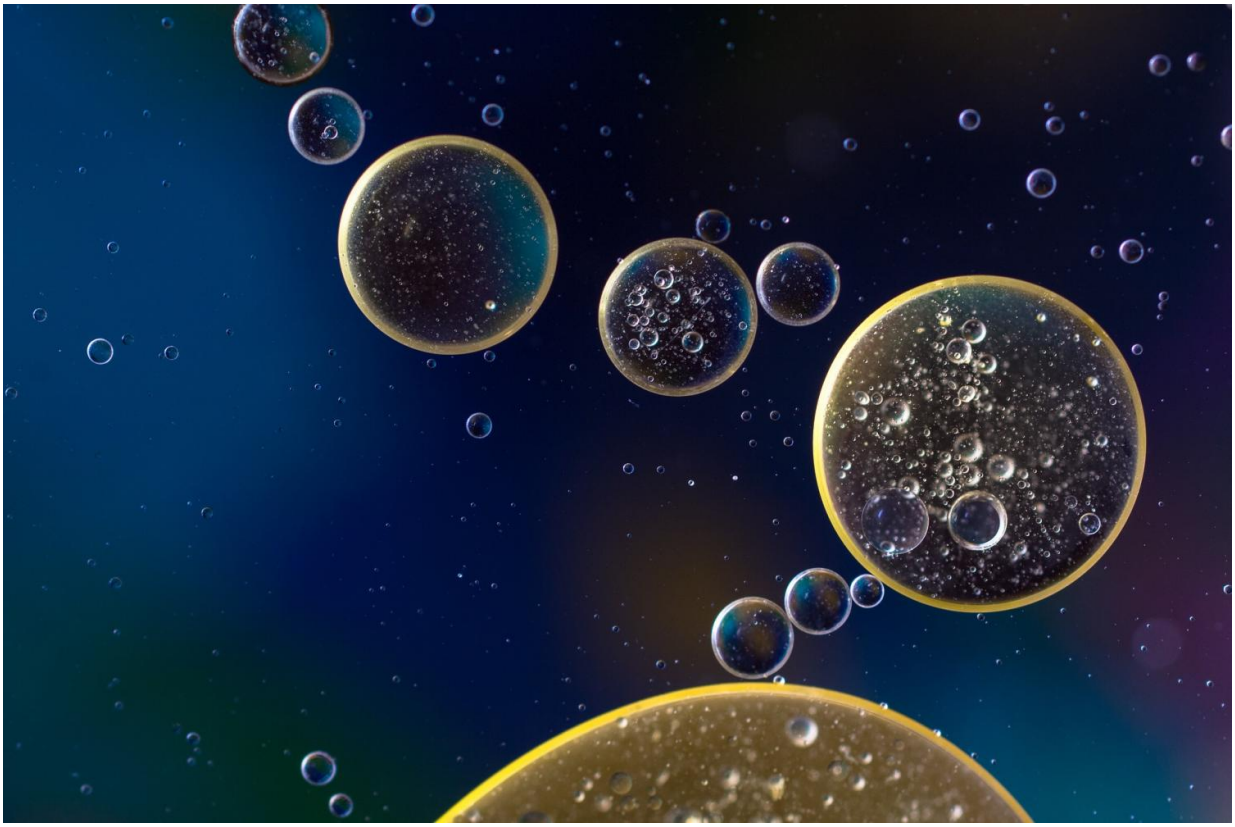

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PD-L1 checkpoint inhibitors are a powerful and growing form of immunotherapy used to treat melanoma, kidney cancer, head and neck cancers, Hodgkin's lymphoma and other cancers. The PD-L1 protein is

expressed on tumor cells and aids the cancer by signaling to immune cells, such as T cells, to stop working against tumors.

Checkpoint inhibitors, also called anti-PD-L1 monoclonal antibodies, block the PD-L1 protein to help the immune system and, specifically, T cells, do what they're designed to do, eradicate cancer. However, in some instances, anti-PD-L1 antibodies show anti-tumor activity in patients whose tumors do not express PD-L1.

Now, for the first time, City of Hope scientists have discovered that natural killer (NK) cells provide one reason why anti-PD-L1 antibodies might work when tumor cells do not express PD-L1. The study, published today in *Cancer Discovery*, found that NK cells can also express PD-L1 in some cancer patients. PD-L1 expression on the NK cells identifies them as charged or highly activated and can demonstrate anti-tumor activity.

Further, when bound by the anti-PD-L1 antibody, the NK cells can kill the tumor cell better regardless of PD-L1 expression on the tumor cells.

If an NK cell expressing PD-L1 is treated with a PD-L1 antibody, the interaction activates PD-L1+ NK cells to control the growth of tumors by killing those tumors and by the secretion of cytokines. This demonstrates a novel mechanism of action that provides a significant role for the NK cell and the anti-PD-L1 antibody in anti-tumor activity especially in instances where the tumor cell does not express PD-L1.

"We have provided a scientific explanation as to how checkpoint inhibitor therapy can work when there's no checkpoint expressed on a patient's cancer cells," said Jianhua Yu, Ph.D., one of the study's senior authors, City of Hope professor in the Department of Hematology & Hematopoietic Cell Transplantation, and a Scholar of The Leukemia & Lymphoma Society. "Using checkpoint inhibitors for NK cells with PD-

L1 expression can lead to stronger anti-cancer activity, providing us with another powerful therapy against even more cancers."

Michael Caligiuri, M.D., the study's other senior author, president of City of Hope National Medical Center and Deana and Steve Campbell Physician-in-Chief Distinguished Chair, M.D., noted that NK cells comprise a group of innate immune cells that can attack cancer and viral infections. But there's been no research on how PD-L1 and NK cells interact against cancer.

"Natural killer cells are the body's first line of defense against cancer and viral infections," Caligiuri said. "When NK cells detect tumor or viral cells in the body, they have the potential to kill them immediately. But in those with cancer, tumors have developed mechanisms to circumvent NK cells and T cells. We believe PD-L1 expression on NK cells identifies tumors that could be susceptible to destruction by NK cells, thereby providing a new immunotherapeutic avenue to explore."

The scientists studied PD-L1+ and PD-L1- NK cells in both humans and mice with PD-L1- tumors. PD-L1+ NK cells, upon encountering and being activated by NK-susceptible tumor cells, secreted more cytokines and cytolytic granules, which both increased the immune cells' effectiveness. PD-L1+ NK cells, which can also be generated in the laboratory by culturing with some tumor cells or with cytokines, killed more tumor cells in vitro than NK cells that were PD-L1- or than NK cells that do not see tumor cells or cytokines. These results were able to be repeated in an in vivo mouse model containing human NK cells.

Researchers also found that NK cells from a majority of 79 AML patients examined had expressed moderate to high levels of PD-L1, and those who entered a complete remission from their leukemia had a higher percentage of PD-L1+ NK cells at the time of remission when compared to diagnosis. In contrast, patients who failed to enter a

complete response had no change in the percentage of PD-L1+ NK cells at remission when compared to diagnosis.

Because the percentage of PD-L1+ NK cells following chemotherapy correlated with a positive clinical response—in contrast to those AML patients whose NK cells did not express PD-L1—the study's authors believe a next step could be a clinical trial for particular AML patients displaying an increase in PD-L1+ NK cells at the time of remission. The trial would include anti-PD-L1 monoclonal antibodies with or without NK cell-activating cytokines, thereby exploiting a novel pathway that is independent of T cells and PD-1, the other target for checkpoint inhibitor therapy.

City of Hope is also planning similar clinical trials for patients with other cancers such as lung cancer.

More information: Wenjuan Dong et al, The mechanism of anti-PD-L1 antibody efficacy against PD-L1 negative tumors identifies NK cells expressing PD-L1 as a cytolytic effector, *Cancer Discovery* (2019). DOI: 10.1158/2159-8290.CD-18-1259

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