Successful anti-PD-1 therapy requires interaction between CD8+ T cells and dendritic cells

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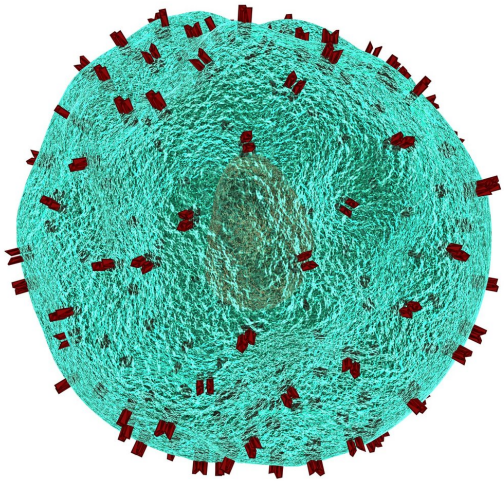

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A team led by a Massachusetts General Hospital (MGH) investigator has found that successful cancer immunotherapy targeting the PD-1 molecule requires interaction between cytotoxic CD8+ T cells, which have been considered the primary therapeutic target, and dendritic cells, critical activators of T cell response. The report that will be appearing in the journal *Immunity* and has been published online suggests potential ways of improving the efficacy and broadening the application of anti-PD-1 therapies.

"Although anti-PD-1 checkpoint immunotherapy has proven incredibly useful against some cancers, we still know relatively few specifics on how the treatment works," says Mikael Pittet, Ph.D., of the MGH Center for Systems Biology (CSB), senior author of the *Immunity* paper. "Here we show that a more complex interaction between cytotoxic T cells and intratumor dendritic cells is needed to release the brakes on T cell immunity that normally prevent the immune system from responding to cancers."

The PD-1 molecule is expressed on CD8+ T cells to prevent them from attacking "self" tissues but also protects tumors from the immune response. Monoclonal antibodies that block the PD-1 pathway have been effective in activating CD8+ T cells against several types of cancer, but many factors can limit the effectiveness of the treatment. Pittet and his team hypothesized that the cytokine interleukin 12 (IL-12), known to be important in immune control of cancer, might contribute to anti-PD-1 therapy. But since T cells do not typically produce much IL-12, the investigators took a broader look at the effects of anti-PD-1 therapy on the immune microenvironment within a tumor.

"We used intravital imaging in live mice to investigate how immune cells within tumors respond functionally to anti-PD-1 immunotherapy," says co-lead author Christopher Garris, Ph.D., of the MGH CSB. "Using this approach, we found that anti-PD-1 drugs induced CD8+ T cells to produce interferon-gamma (INF-?), which is one of the most important cytokines for an anti-cancer immune response. What was less expected is that neighboring dendritic cells also started to produce copious amounts of IL-12 in response to anti-PD-1 treatment." The researchers further found that IFN-? produced by the T cells induces dendritic cells to produce IL-12, which acts as a potent and necessary activating signal that enables CD8+ T cells to attack the tumor.

Further characterization of the tumor immune microenvironment using single-cell sequencing

technologies revealed that IL-12-producing dendritic cells had turned on the non-canonical NFkB signaling pathway. This pathway has been implicated in the activation of CD8+ T cells by dendritic cells in contexts other than cancer, suggesting that such activation could be an important functional feature of dendritic cells. Indeed, the authors found that inhibiting this pathway diminished the efficacy of anti-PD-1 therapy and that combining anti-PD-1 treatment with non-canonical NFkB pathway activators produced dramatic anti-tumor responses in mouse models of cancer, including a melanoma model that usually resists anti-PD-1. Not only did the combined treatment control tumor growth in these models more completely than treatment with a single drug, it also prevented tumors from being re-established, suggesting that the therapy generated persistent anti-cancer immune memory.

"Activation of the non-canonical NFkB pathway increased both the number of dendritic cells and their production of IL-12, further increasing the antitumor activity of CD8+ T cells," says Pittet, who is an associate professor of Radiology at Harvard Medical School. "Anti-PD-1 drugs are well known to release the brakes on T cells. Our study indicates that agents promoting intratumoral IL-12 production can further accelerate the anti-tumor reaction. Now we need to learn more about dendritic cells in cancer and whether drugs that properly activate these cells will offer clinical benefits against a broader range of tumors, aiding more cancer patients."

More information: Christopher S. Garris et al, Successful Anti-PD-1 Cancer Immunotherapy Requires T Cell-Dendritic Cell Crosstalk Involving the Cytokines IFN-? and IL-12, *Immunity* (2018). DOI: 10.1016/j.immuni.2018.09.024