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Partnering cells turn off immune attack on pancreatic tumors

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Two cell types work together to protect pancreatic tumors from destruction by the immune system. But, blocking this partnership may restore the system's ability to attack these same tumor cells.

These are the findings of a study in mice led by researchers from NYU Langone Medical Center and its Perlmutter Cancer Center, and published online July 18 in *Cell Reports*.

The study results revolve around the immune system, which is designed to attack invaders like viruses. Immune cells also recognize cancer cells as abnormal, but such cells have the ability to turn off immune responses.

Pancreatic cancer cells, for instance, give off signaling molecules that attract regulatory T cells (Tregs), which lessen immune responses and create a "tolerance" to cancer's presence. The mechanisms behind this have not been clear.

The current study found that Tregs have their effect by keeping a second cell type, dendritic cells, from activating a third cell type, CD8+ T cells, which would otherwise kill cancer cells.

"Our results argue that blocking the partnership between Tregs and dendritic cells might be needed to achieve effective immunotherapy for pancreatic cancer," says lead author Dafna Bar-Sagi, PhD, vice dean for science and chief scientific officer at NYU Langone. "Upcoming studies

in our lab will be looking to confirm that this relationship can become the foundation of new treatment strategies."

The study focused on pancreatic ductal adenocarcinoma (PDA), a lethal form of cancer known to come with an influx of immune cells into tumors. Past studies have linked this early Treg build-up in tumors with reduced survival.

As part of the normal immune response, T cells partner with dendritic cells to "decide" which protein pieces of viruses or cancer cells will be used to grab the immune system's attention. Upon encountering a cancer cell protein, a dendritic cell "swallows it," breaks it up, and displays the pieces on its surface for notice by T cells in the nearest lymph node.

The research team suggests that this normal contact between the two cell types is exploited by cancer cells, in which contact-based, mutually reinforcing cross-talk between them turns off the immune response. The same results suggest the Tregs and killer T cells may in fact compete for dendritic cells near tumors, say the authors.

When antibodies and other methods were used to dramatically deplete the supply of Tregs in mice, the researchers saw a dramatic jump in the numbers of activated dendritic cells and CD8+ T cells in pancreatic tumor tissue, as well as a slowing of tumor growth.

Of note, the current study is part of a recent surge in NYU Langone findings on pancreatic cancer, including studies on how first-responder cells turn off the immune response, the role of the drug nab-paclitaxel in tumor biology, cancer cells' unique fuel sources, and how immune cell infighting drives the disease. Along these lines, Perlmutter Cancer Center recently announced the creation of a multidisciplinary center of excellence to develop innovative approaches to diagnose, treat, and prevent pancreatic cancer.

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