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Immune therapy breaks down wall around pancreatic tumors for chemo to attack

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Many facets of the immune system can be manipulated to combat cancer, including macrophages, an immune cell subset that is commonly associated with aiding tumor growth. In a new preclinical study in *Cancer Discovery,*, researchers from the Abramson Cancer Center (ACC) at the University of Pennsylvania have uncovered the poorly understood mechanics of how macrophages can be "re-educated" by an experimental immune therapy to help tear down the scaffolding that surrounds and protects pancreas cancer from chemotherapy.

The study, led by Gregory L. Beatty, MD, PhD, an assistant professor of Hematology/Oncology at the Perelman School of Medicine at the University of Pennsylvania and the ACC, defines the key steps necessary to redirect macrophages to attack the walls around the tumor, known as the microenvironment.

"We've unraveled some of the complex, bidirectional messaging between a tumor and its microenvironment. We've learned how antibodies that target a cell surface molecule called CD40 work with the immune system to tear back that wall," said Beatty. "Additionally, our findings identify a novel role for CD40 antibodies—as a 'lead-in' therapy to enhance the efficacy of chemotherapy and possibly other biological treatments for pancreatic cancer."

In 2016, the American Cancer Society reported that the five-year survival rate for pancreatic cancer patients went from 7 to 8 percent, a small, though welcomed increase that still underscores the need for

improved therapies.

A 2011 study from Penn published in *Science* previously demonstrated CD40's ability to re-educate the monocytes and macrophages in the blood and tissue to break down the tumor microenvironment in both humans and mice; however, the biology behind that mechanism and the therapeutic implications remained unclear.

In that initial study, a team of researchers also led by Beatty, were surprised to see CD40 antibodies stimulate macrophages to attack pancreatic cancer because they had historically been thought to work by activating T-cells. However, the team detected no role for T cells.

Using mouse models in the new study, the team has now identified a role for several factors, including chemokine ligand 2 (CCL2) and interferon gamma (IFN-?), that are released by the immune system after treatment with CD40 antibodies, and cooperate to redirect macrophages to attack cancer. Whereas CCL2 is required for facilitating macrophage infiltration into tumors, IFN-γ is necessary to "re-educate" tumor-infiltrating macrophages to induce the release of key metalloproteinases, which are enzymes capable of degrading the fibrotic scaffold that surrounds and protects tumors from chemotherapy. This complex cascade of events is ultimately what leads to fibrosis degradation, the researchers found.

The findings also point to the optimal time to deliver CD40 antibodies for enhancing the benefit of gemcitabine, a standard chemotherapy used in the treatment of pancreatic cancer. The team found that the fibrotic scaffold of tumors remained degraded after CD40 treatment for approximately one week, raising the possibility that chemotherapy may be more efficacious during this therapeutic window.

The timing of delivery of a CD40 agonist and chemotherapy is critical,

the authors said. Mice treated with gemcitabine two days after receiving CD40 antibodies were found to poorly tolerate chemotherapy and had significant weight loss, with 30 percent mortality. However, when chemo was administered five days after CD40, it was both well-tolerated and produced promising clinical activity marked by tumor cell death and shrinkage.

This finding demonstrates the potential of CD40 antibodies to improve the efficacy of chemotherapy - a finding that may best explain the promising clinical results seen in the 2011 report, said Beatty.

"Together, we believe that this data supports further investigation of therapeutics that redirect monocytes and macrophages, rather than depleting them. Macrophages can be very potent killers of cancer. Since keeping them out of tumors is a challenge, why not harness their recruitment? This may be the Achilles heel of pancreatic cancer," Beatty said. "Now that we better understand this biology, we are hopeful that our findings will spark further clinical interest and a path forward to test this treatment approach in patients."

More information: K. B. Long et al. IFN-gamma and CCL2 cooperate to redirect tumor-infiltrating monocytes to degrade fibrosis and enhance chemotherapy efficacy in pancreatic carcinoma, *Cancer Discovery* (2016). DOI: 10.1158/2159-8290.CD-15-1032

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