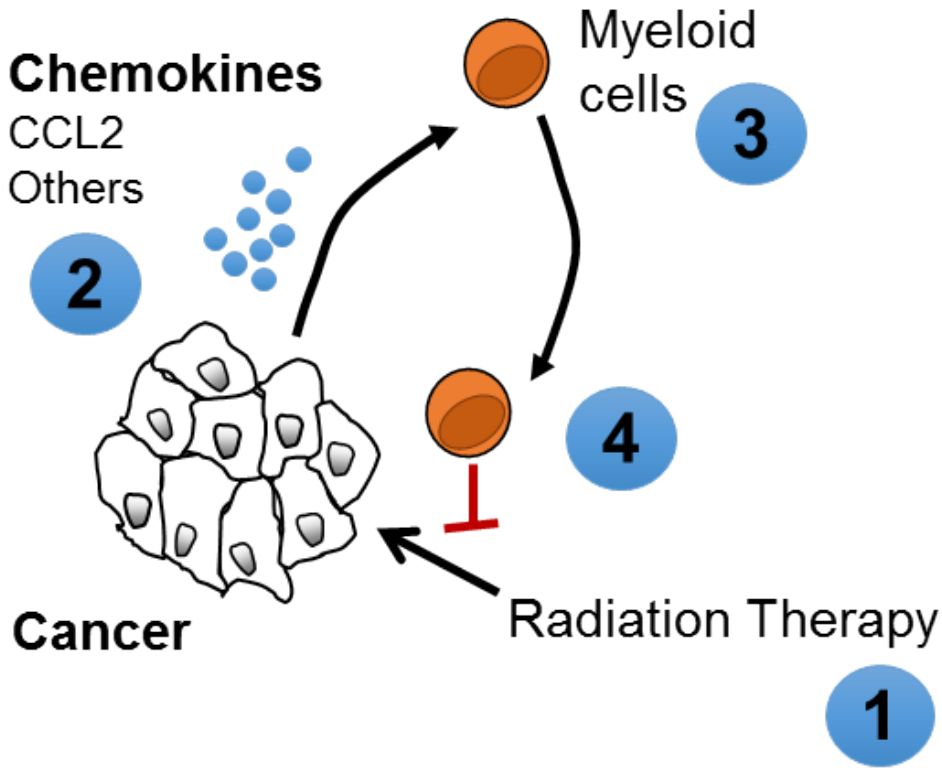
Penn researchers help unravel mysteries of pancreatic cancer's resistance to standard therapies

January 24 2017



Conceptual model. Pancreatic cancer responds to radiation therapy **(step 1)** by releasing chemokines **(step 2)** which recruit myeloid cells to the tumor microenvironment **(step 3)** where they then support tumor regrowth and inhibit the efficacy of radiation **(step 4)**.

This shows how pancreatic cancer responds to radiation therapy. Credit: Penn Medicine

Pancreatic cancer has long been one of the hardest to treat. Now, in a new study, researchers at the Perelman School of Medicine at the

University of Pennsylvania have illuminated one of this cancer's major resistance mechanisms: a form of inflammation that is triggered by the tumor in response to treatment and helps keep tumor cells alive.

Blocking this inflammation after radiation therapy brought a significant improvement in survival in a mouse model of the disease.

"This is a step forward in understanding pancreatic cancer's resistance to standard therapies," said principal investigator Gregory Beatty, MD, PhD, an assistant professor of Hematology/Oncology at Penn and a member of Penn's Abramson Cancer Center. The study was published in the January issue of *Clinical Cancer Research*.

That strong resistance to treatment has kept pancreatic cancer near the top of the list of the deadliest cancers. Only about eight percent of patients diagnosed with the usual type of pancreatic cancer—pancreatic ductal adenocarcinoma—survive another five years. Annually, about 40,000 people in the United States, and more than 300,000 around the world die of this form of cancer.

Studies in recent years by Beatty's laboratory and others have pointed to one potential source of this treatment resistance: Pancreatic tumors tend to surround themselves with a protective "microenvironment."

"We know that if you take these tumor cells out of a patient and put them in a petri dish, they can be killed by chemotherapy," Beatty said. "But in the body, within the microenvironment they create, they somehow manage to resist elimination even by our most cytotoxic therapies."

This tumor-protecting microenvironment includes inflammatory white blood cells called monocytes and macrophages. In pancreatic cancer, their activity boosts tumor growth and spread, and may also help

suppress T cells and other immune elements that would otherwise attack the tumor.

An early-stage clinical study by another institution, published in the Lancet Oncology in May 2016, combined chemotherapy with an experimental drug that blocks CCR2, a receptor on monocytes and macrophages whose activation stimulates these cells to infiltrate tumors. Though the study was small, the results were promising: blocking CCR2 led to a much better tumor response compared to chemo alone.

For their new study, Beatty and colleagues tested a similar inflammation-blocking strategy, this time in combination with radiation therapy. Radiation is often used to treat pancreatic tumors that haven't spread but can't be removed with surgery.

The first author of the study is Anusha Kalbasi MD, at the time a radiation oncology resident at Penn Medicine. Kalbasi is now a clinical instructor at University of California, Los Angeles School of Medicine. In mice with pancreatic tumors, Kalbasi and other members of the team found relatively high levels of inflammatory compounds including CCL2, the signaling molecule that activates CCR2 on monocytes and macrophages to make these cells migrate to tumors. After a large dose of radiation therapy, comparable to what human patients receive, CCL2 levels rose even higher—in fact, several times higher—and the scientists found that it was being secreted by the tumor cells themselves.

"They're dying in response to the radiation, and that's causing them to release these chemical signals that call in help, which then allows them to regrow," Beatty said.

The tumors' recruitment of these inflammatory cells thus enabled them to resist what would otherwise have been a deadly dose of radiation, so that their growth slowed only modestly compared to control mice that

had received no radiation. By contrast, when the team treated the mice with radiation plus a CCL2-blocking antibody, the tumors' recruitment of monocytes and macrophages was sharply reduced, and the tumor growth was slowed more dramatically. "Not only did the combination of radiation and CCL2-blockade slow tumor growth, it prolonged survival in mice as well," said Kalbasi. The boost in survival time allowed the mice to live roughly 25 percent longer than those treated with radiation alone.

To the Penn scientists, the findings indicate that blocking the CCL2-CCR2 inflammatory pathway in pancreatic cancer is worth investigating as an add-on to radiation therapy, not just to chemotherapy. Along those lines, the researchers now plan to investigate the relationship between tumor-associated inflammatory cells and the response to radiation therapy in human pancreatic cancer patients.

"We might find that patients who respond more to radiation therapy are those whose tumors produce less CCL2 and thus have less recruitment of tumor-protecting monocytes and macrophages," Beatty said. "If so, it would be useful to identify such patients in the clinical setting because they might benefit from radiation in the absence of a CCR2 or CCL2 inhibitor."

He cautioned, however, that even the radiation-plus-CCL2-blocking strategy explored in the new study "doesn't cure the mice—there's still more to be done."

In particular, although radiation treatment regimens for some other cancers have been found to unleash an anti-tumor response by the patient's own T-cells, the team found no such effect in their pancreatic cancer model. Thus, there are probably other resistance mechanisms that block the antitumor immune response in pancreatic cancer—mechanisms that, when they are better understood, could be

targeted with future drugs to allow anti-tumor immunity to work against this deadly form of cancer.

"We're still trying to figure out why these anti-tumor T-cells don't go into pancreatic tumors like they do for other malignancies," Beatty said.

More information: Anusha Kalbasi et al. Tumor-Derived CCL2 Mediates Resistance to Radiotherapy in Pancreatic Ductal Adenocarcinoma, *Clinical Cancer Research* (2017). DOI: 10.1158/1078-0432.CCR-16-0870

Provided by Perelman School of Medicine at the University of Pennsylvania