Immunosuppressive Myeloid Cells Mask Pancreas Cancer from Immune Detection

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VA Morris

Pancreas cancer is the fourth most common cause of cancer-related deaths in the United States, with only 6 percent of patients surviving five years after diagnosis. Pancreatic ductal adenocarcinoma (PDA) is the most common form of the cancer. In PDA, the tumor cells are surrounded by a biological barrier that consists of inflammatory immune cells and constricted blood vessels embedded in a dense shell of proteins. This barrier makes pancreas cancer highly resistant to most standard cancer treatments, necessitating development of alternative therapies. A new study published in the journal *Gut* reveals that PDA cells secrete factors to recruit specific immunosuppressive cells into this barrier that shut down cytotoxic killer T cells that are attracted to the tumor. Lead author and postdoctoral fellow Dr. Ingunn Stromnes, co-mentored by Drs. Sunil Hingorani and Phil Greenberg in the Clinical Research Division, reversed this effect by depleting a subset of myeloid-derived suppressor cells (MDSC) to restore the immune response to the tumor in a mouse model. These results highlight the potential for future immunotherapy treatments for this deadly cancer.

Researchers from the Hingorani laboratory previously utilized a genetically engineered mouse model of PDA, which recapitulates cardinal features of human disease, to examine the accumulation of immune cell subsets during disease progression (Clark e*t al*., 2007). These studies revealed that immunosuppressive cells accumulate early on, and may mask the tumor epithelial cells from immune detection. In this study, Stromnes *et al*. further characterized the immunosuppressive cells and identified both monocytic and granulocytic MDSC (Mo-MDSC and Gr-MDSC) present in the tumors. The researchers isolated both Mo-MDSC and Gr-MDSC from tumor-bearing mice and incubated them with T cells *in vitro*. Both subsets strongly suppressed T cell proliferation and activation, suggesting a role for these cells in preventing immune detection in the pancreatic tumors.

The researchers then demonstrated that PDA cells secrete factors to recruit MDSC into the tumor and promote their survival. By characterizing which chemokines and growth factors are released by PDA cells and then blocking their function, the researchers found that both granulocyte monocyte

colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) enhanced survival of the Gr-MDSC when cultured *in vitro*. While neither factor appreciably promoted the proliferation of Gr-MDSC *in vitro*, GM-CSF was detected in the pancreatic tumors *in vivo*.

Stromnes *et al*. then examined the clinical potential of specifically depleting Gr-MDSC. The researchers focused on Gr-MDSC since their numbers dramatically increase from the pre-invasive to the invasive form of PDA. The researchers injected mice bearing metastatic PDA with a specific antibody that recognized Gr-MDSC and targeted them for destruction. The tumors in these mice did not shrink in size, but instead grew with an influx of immune cells. The researchers observed a specific accumulation of activated CD8 T cells in the tumors. These activated CD8 T cells targeted tumor epithelial cells for cell death and remodeled the architecture and integrity of the surrounding tumor stroma.

"The finding that depletion of a single population of immunosuppressive cells spontaneously uncovered an endogenous immune response against pancreas cancer is surprising. It provides strong rationale to focus on ways to target this specific population in pancreas cancer patients and will likely figure prominently in strategies to enhance anti-tumor responses," states Dr. Stromnes. "These results are also influencing our design and implementation of adoptive T cell therapy for pancreas cancer patients, in which we will be infusing T cells that have the capacity to recognize and kill the tumor cells but that must be able to retain function in the tumor microenvironment." Since MDSCs are also found in other cancers, Dr. Stromnes hopes their study will spark new ways to interfere with these cells in other cancer patients for enhancing immunotherapy.

Stromnes, IM, Brockenbrough, JS, Izeradjene, K, Carlson, MA, Cuevas, C, Simmons, RM, Greenberg, PD, Hingorani, SR. (2014). Targeted depletion of an MDSC subset unmasks pancreatic ductal adenocarcinoma to adaptive immunity. *Gut*. Epub ahead of print, doi: 10.1136/gutjnl-2013-306271.

See also: Clark CE, Hingorani SR, Mick R, Combs C, Tuveson DA, Vonderheide RH. (2007). Dynamics of the immune reaction to pancreatic cancer from inception to invasion. *Cancer Res* 67:9518-9527.

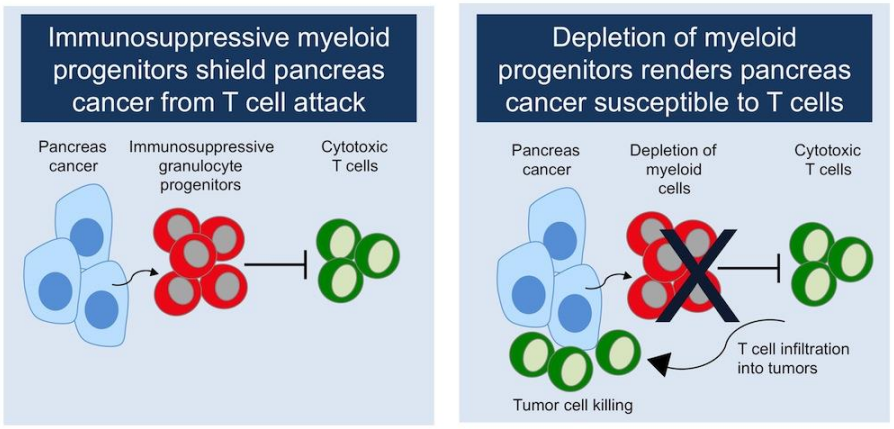

Image provided by Dr. Ingunn Stromnes

Pancreas cancer at least in part avoids destruction by the immune system by recruiting a specific population of immunosuppressive cells that shut down cytotoxic killer T cells that are attracted to the tumor. The depletion of this immunosuppressive cell population spontaneously unveiled pancreas cancer to the immune system, resulting in increased T cell infiltration into tumors and enhanced activity.