How Pancreatic Cancer Cells Escape Immunotherapy

Damon Runyon-Rachleff Innovator Rushika M. Perera, PhD, and colleagues may have found an answer.

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Doctors have grappled with the longstanding question: why are pancreatic cancers so resistant to immunotherapies that use the body's own immune defenses to fight cancer? Now, Damon Runyon-Rachleff Innovator Rushika M. Perera, PhD, at the University of California, San Francisco, and colleagues at New York University Grossman School of Medicine may have found an answer. The researchers discovered that pancreatic cancer cells can appropriate an internal waste removal process to dispose of tags (MHC-1) on their surfaces which trigger the immune system to destroy tumors.

T cells in the immune system ignore cells with MHC-I displaying "self" tags specific to each person's cells, but recognize and attack cells with foreign tags, like those on cells infected with viruses and, in some cases, on cells that have become cancerous.

The new study found that pancreatic cancer cells pull abnormal MHC-I from their cell surfaces into compartments called vesicles where the tags are degraded by autophagy. By removing the MHC-I tags, autophagy enables cancer cells to hide from the immune system and avoid being targeted by immunotherapies. This new found role in immune evasion suggests that targeting the autophagy pathway could make pancreatic and other cancers more susceptible to treatment.

Experiments in mice with pancreatic cancer showed that blocking autophagy, either with genetic approaches or with the anti-malaria drug chloroquine, caused an increase in the abnormal MHC-I molecules on the surfaces of the tumor cells. Further mouse studies showed that chloroquine combined with checkpoint inhibitors significantly increased tumor responses over treatment with immunotherapy alone. The researchers plan to follow up with studies that translate these findings to patients.

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