Researchers discover trigger for muscle-wasting condition

12 June 2019

Courtney Houchen, M.D. Credit: OU Medicine

Among all major cancers, pancreatic cancer has the highest rate of death—93 percent of patients die within five years of diagnosis.

Treating the disease is difficult not only because the tumors spread quickly, but because of a muscle-wasting condition called cachexia that affects at least 80 percent of people with pancreatic cancer. However, a team of researchers from the OU College of Medicine has published a groundbreaking research study that reveals how cachexia is triggered, setting the stage for further studies on how to prevent it. The research was recently featured in the journal *Gastroenterology*, the leading publication in GI tract disease.

"Pancreatic cancer is a very tough disease, and novel therapies like treating cachexia are the only way we're going to make progress because the traditional approach of trying to destroy the tumor isn't enough," said Courtney Houchen, M.D., a senior author on the study.

Although cachexia can occur in several types of cancers, it is especially prevalent in pancreatic cancer. Patients with cachexia experience a dramatic loss of muscle mass, usually accompanied by loss of appetite, weight loss and fatigue. Because cachexia takes such a toll on patients with pancreatic cancer, many cannot withstand surgery and they respond poorly to chemotherapy and radiation.

OU College of Medicine researchers set out to learn more about why cachexia occurs, in order to give patients the best chance at fighting pancreatic cancer. The team focused on a protein called ZIP4, which they already knew is excessive in pancreatic cancer. In the new study, researchers discovered that ZIP4 is at the center of a communication that occurs between pancreatic cancer cells and muscle cells. During that communication, ZIP4 prompts the cancer cells to release two specific types of molecules and even sparks the opening of a pathway for their journey to the muscles. ZIP4 also does the equivalent of hailing a cab for the molecules—called an exosome—which ferries them to the muscle cells, where they prompt cachexia to begin.

"We think this discovery is significant because of its potential to be translated into a therapy for patients. If we can find a way to inhibit ZIP4, we hope to intervene much earlier with cachexia and help more patients become able to undergo surgery, when they previously would have been too weak. That also means they would respond better to chemotherapy and radiation, which would also increase the survival rate," said Min Li, Ph.D., another lead author on the study, who holds the Virginia Kerley Cade Endowed Chair in Cancer Treatment.

The OU College of Medicine research team, which includes both scientists and medical doctors from the Department of Medicine, leverages that collaboration for a quicker conversion of a

laboratory finding into a patient treatment. Their next steps are to further study ZIP4 and to search for a way to hinder its role in triggering cachexia.

"The way we have traditionally looked at cancer is that if you can just kill the cancer cells, then people will get better. But that's not realistic—we have to address complications like cachexia to help people survive," Houchen said. "Now we have the opportunity to look at potential targets for overcoming cachexia, which may then improve the treatment of pancreatic cancer and its devastating consequences."

More information: Daofu Feng et al, 454 – Pd-L1 Expression Regulates Tumor Cell Apoptosis Via Upregulation of Bh3-Only Proteins in Human Colon Cancer Cells, *Gastroenterology* (2019). DOI: 10.1016/S0016-5085(19)37027-1

Provided by University of Oklahoma