MedicalXpress

Researchers reveal how pancreatic cancer cells sidestep chemotherapy

January 30 2015

Pancreatic cancer is one of the deadliest forms of the disease. The American Cancer Society's most recent estimates for 2014 show that over 46,000 people will be diagnosed with pancreatic cancer and more than 39,000 will die from it. Now, research led by Timothy J. Yen, PhD, Professor at Fox Chase Cancer Center, reveals that one reason this deadly form of cancer can be so challenging to treat is because its cells have found a way to sidestep chemotherapy. They hijack the vitamin D receptor, normally associated with bone health, and re-purposed it to repair the damage caused by chemotherapy. The findings, which will be published in the January 3 issue of the journal *Cell Cycle*, raise hopes that doctors will one day find a way to turn this process against the tumor and help chemotherapy do its job.

Most patients diagnosed with pancreatic cancer receive a drug called gemcitabine, which works by preventing cells from replicating their DNA—thus stopping tumor cells from dividing and causing them to die off. Sadly, many patients die within a few months, often because their cancer finds a way to work around treatment. But how does that happen? "Maybe there is something we don't understand about how gemcitabine works," says Dr. Yen. "More likely, cancer cells have found a way to avoid DNA-damaging drugs."

To determine how pancreatic cancers sidestep chemotherapy and the effects of gemcitabine, Dr. Yen and his colleagues removed every one of the ~24,000 genes, one by one, in pancreatic cancer cells, exposed the cells to gemcitabine, and noted which gene "knockout" caused cells to be

more sensitive to the drug.

One of those "knocked-out" genes was particularly important, namely, the gene for a protein which normally binds to vitamin D. "When we inactivated this vitamin D receptor in cancer cells and added gemcitabine, almost all of them died," says Dr. Yen.

That's when the researchers realized they had identified a key mechanism driving chemotherapeutic effectiveness against pancreatic cancer. "If we find a drug that inactivates the vitamin D receptor, it may allow gemcitabine to selectively kill pancreatic cancer cells while leaving healthy cells unharmed," says Dr. Yen. "Patients would just need to drink lots of milk or take calcium supplements to make sure their bones stay healthy."

Although the precise role of the vitamin D receptor in pancreatic cancer remains uncertain, it's clear that pancreatic cancer cells need it, says Dr. Yen. "Cancer cells are good at finding ways to survive," he explains. "We suspect that cancer cells hijacked the vitamin D receptor and reassigned it to perform other cellular functions, such as by repairing DNA damage caused by gemcitabine so the cancer can continue to divide and spread."

Although pancreatic cancer cells need the vitamin D receptor to survive, other normal cells don't, which Yen says is good news for patients because future cancer treatments can knock out the receptor without causing too much collateral damage or side effects, as long as patients take calcium supplements to keep their bones healthy.

"By knocking out the vitamin D receptor, we could inactivate that DNA repair process that is allowing drug-treated tumor cells to live. As a result, we could eliminate more cancer cells at the outset," says Dr. Yen. "The Pancreatic Cancer Action Network has launched an initiative to

double patients' survival by 2020; with this new finding, we believe it's a step in the right direction."

Provided by Fox Chase Cancer Center