Protein found to shield pancreatic cancer cells from self-destruction

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An overexpressed protein protects human pancreatic cancer cells from being forced to devour themselves, removing one of the body's natural defenses against out-of-control cell growth, researchers at The University of Texas M. D. Anderson Cancer Center report in the March issue of *Molecular Cancer Research*.

The protein tissue transglutaminase, known by the abbreviation TG2, previously has been found by researchers at M. D. Anderson and elsewhere to be overexpressed in a variety of drug-resistant cancer cells and in cancer that has spread from its original organ (metastasized).

"In general, you rarely see overexpression of TG2 in a normal cell," says Kapil Mehta, Ph.D., professor in the M. D. Anderson Department of Experimental Therapeutics, who began 10 years ago studying TG2 as an inflammatory protein.

Mehta and colleagues in the past year have connected TG2 overexpression to drug-resistant and metastatic breast cancer, pancreatic cancer and melanoma.

Expression of TG2 is tightly regulated in a healthy cell, Mehta says, and is temporarily increased in response to certain hormones or stress factors. "However, constitutive expression of this protein in a cancer cell helps confer protection from stress-induced cell death," Mehta says. "We are developing TG2 as a pharmaceutical target and are now working with a mouse model to that end."

The mechanisms by which TG2 might promote drug-resistance and metastasis have remained elusive, the researchers note. In this paper, the M. D. Anderson team shows in lab experiments that inhibiting the protein in pancreatic cancer cells leads to a form of programmed cell suicide called autophagy, or self-digestion.

TG2 was inhibited in two separate ways. First, the researchers blocked another protein known to activate TG2. Secondly, they also directly targeted TG2 with a tiny molecule known as small interfering RNA tailored to shut down expression of the protein.

In both cases, the result was a drastic reduction of TG2 expression (up to 94 percent) and telltale signs of autophagy in the cancer cells, which became riddled with cavities called vacuoles.

When autophagy occurs, a double membrane forms around a cell organ, or organelle. This autophagosome then merges with a digestive organelle called a lysosome and everything inside is consumed, leaving the vacuole and a residue of digested material. If enough of this happens, the cell dies.

Gabriel Lopez-Berestein, M.D., professor of experimental therapeutics and study co-author, notes that the research also shows that the self-consuming cell death prevented by TG2 is independent of a prominent molecular pathway also known to regulate autophagy called the mammalian target of rapamycin.

"Targeting TG2, or its activating protein PKC, or both, presents a novel and potentially effective approach to treating patients with pancreatic cancer," Lopez-Berestein said. Research in the mouse model remains in the early stages, the researchers caution.

The researchers also show that the TG2 pathway also is separate from

another, better known, form of programmed cell death called apoptosis.

Apoptosis, like autophagy, is a normal biological defense mechanism that systematically destroys defective cells by forcing them to kill themselves. In apoptosis, the cells die via damage to their nucleus and DNA, with other cellular organelles preserved. Autophagy kills by degrading those other organelles while sparing the nucleus.

Mehta's lab reported in a Cancer Research paper last September that TG2 overexpression also activates a protein called nuclear factor-kB known to play a role in regulating cell growth, metastasis and apoptosis. This pathway, Mehta explained, could make TG2 an attractive target for other forms of cancer as well.

Source: University of Texas M. D. Anderson Cancer Center