New combination therapy could deliver powerful punch to breast cancer

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These are Drs. Kapil Bhalla (right) and Rekha Rao, assistant research scientist and first-author on the autophagy study presented this week. Credit: Medical College of Georgia

A powerful new breast cancer treatment could result from packaging one of the newer drugs that inhibits cancer's hallmark wild growth with another that blocks a primordial survival technique in which the cancer cell eats part of itself, researchers say.

While they are powerful killers of some breast cancer cells, new drugs called histone deacetylase inhibitors, or HDAC inhibitors, also increase self-digestion, or autophagy, in surviving, mega-stressed cells, Medical College of Georgia Cancer Center researchers reported during the Molecular Targets and Cancer Therapeutics International Conference

this week in Boston. The conference is sponsored by the American Association for Cancer Research, the National Cancer Institute and the European Organisation for Research and Treatment of Cancer.

"To meet the energy demands of growth and survival, cancer cells start eating up their own organelles, so that surviving cells become dependent on this autophagy," says Dr. Kapil Bhalla, director of the MCG Cancer Center.

"By also using autophagy inhibitors, we pull the rug out from under them. The only way out is death," he says.

Researchers showed the potent HDAC inhibitor panobinostat's impact on autophagy in human breast cancer cells in culture as well as those growing in the mammary fat pads of mice. When they added the anti-malaria drug chloroquine, which inhibits autophagy, breast cancer kill rates increased dramatically.

"As breast cancer is growing, it's developing these mechanisms of resistance to death," says Dr. Bhalla, Cecil F. Whitaker, Jr., M.D./Georgia Research Alliance Eminent Scholar in Cancer and Georgia Cancer Coalition Distinguished Cancer Scholar. "What we are saying is there is a new way to affect a resistant population."

Fundamentals of survival and growth put a lot of stress on cancer cells. Their drive for both comes from the activation of oncogenes and loss of tumor suppressor genes that leaves cells looking desperately for ways to support their marching orders. Much like the extreme measures plane crash victims may take while stranded on a frozen mountaintop, autophagy becomes a survival strategy for the most stressed out cancer cells.

Stress kicks in as cancer cells quickly outgrow available blood supplies

and nutrients, which stimulates new blood vessel formation and consumption of unprecedented amounts of fuel. Alterations in gene copy numbers create an imbalance in gene products or proteins adding to the stress of cancer cells, which are starting to make improperly folded - and functioning - proteins.

Protein degradation gets revved up and cells also start making more heat shock proteins which are supposed to help properly fold proteins and protect against cell death, a stress cause and effect Dr. Bhalla showed nearly a decade ago. He suspected then the connection he just found: promoting autophagy is one way heat shock proteins carry out their protective mission.

This is where HDAC inhibitors come into play: they promote acetylation or a modification in the key heat shock protein, hsp70, which further promotes autophagy. "Basically HDAC inhibitors promote acetylated hsp70 which promotes autophagy on which a stressed-out cancer cell depends," Dr. Bhalla says.

He notes that chloroquine, a known anti-malarial and inhibitor of autophagy, already is being paired with chemotherapy and radiation is some cancer clinical trials. But because of its significant side effects, new, more tolerable autophagy inhibitors need to be developed which can be combined with currently available anticancer agents, such as panobinostat, to attain superior therapeutic effect against breast cancer, Dr. Bhalla says.

Source: Medical College of Georgia

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