Chemo may get boost from cholesterol-related drug

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Johns Hopkins investigators are testing a way to use drugs that target a cholesterol pathway to enhance the cancer-killing potential of standard chemotherapy drugs. Their tests, in mouse models of pancreatic cancer, may yield new and more effective combinations of current and possibly new anti-cancer drugs.

Besides their deadly consequences, pancreatic cancer and heart disease share a connection with genetic pathways that control cholesterol and a cell signaling system known as the Hedgehog pathway. (The name refers to the shape of its mutated protein in fruit flies, one that resembles the spiky-haired animal.)

Over-activity in the Hedgehog pathway has long been known to trigger many types of cancer and is the focus of five new drugs currently in development. Each of the drugs targets the same cell-surface protein that forms the business end of the Hedgehog pathway, according to the investigators, but tumors find a way to mutate the protein and make cancer cells resistant to these new therapies.

Looking for another way to target the Hedgehog pathway, investigator William Matsui, M.D., Ph.D., professor at the Johns Hopkins Kimmel Cancer Center, teamed up with UCLA biologist Farhad Parhami, Ph.D, who had studied connections between components of cholesterol and Hedgehog pathways.

Parhami found that derivatives of cholesterol, called oxysterols, regulate

the Hedgehog pathway via so-called "liver x receptors," which bind to cholesterol and guide redistribution of cholesterol throughout the body. In doing so, liver x receptors block the Hedgehog pathway.

"Activating liver x receptor could be an alternate target for blocking the Hedgehog pathway," says Matsui, who notes that activating a target to create an anti-tumor effect is an unusual strategy in therapy. Most drugs currently in development aim to block pathways not activate them, he says.

For the Hopkins study, mice bearing implanted human pancreatic tumors received treatments of a drug called TO901317 that activates liver x receptors along with a chemotherapy drug called gemcitabine. If given alone, the liver-x receptor drug did not affect tumor growth, but in combination with gemcitabine, the tumors shrank, and investigators found a five-fold reduction in expression of Hedgehog pathway components.

Matsui says that pancreatic tumors are crowded with scar tissue, and chemotherapy drugs encounter difficulty finding cancer cells amid the scar tissue. Blocking the Hedgehog pathway by activating liver x receptors may help pancreatic cancer drugs penetrate the tumor and attack cancer cells.

Matsui and Parhami, in collaboration with UCLA chemists Michael Jung and Frank Stappenbeck, are currently developing novel, more effective and safer liver X receptor activators for use in targeting pancreatic cancer and other Hedgehog pathway-mediated tumors.

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