Molecule thought cancer foe actually helps thyroid tumors grow

June 20 2012

A molecule widely believed to fight many forms of cancer actually helps deadly thyroid tumors grow, and cancer therapies now being tested in humans might boost the activity of this newly revealed bad guy, researchers at Mayo Clinic in Florida say. Their findings are published online this month in the *Journal of Cell Science*.

The study found that in anaplastic thyroid cancer, the Forkhead transcription factor, FOXO3a, is not the helpful tumor suppressor everyone thought it was, but, instead, is a lethal promoter of tumor growth. When FOXO3a was silenced in laboratory models of human anaplastic thyroid cancer, the cells grew slowly, but when it was added, they grew much faster.

"This result is exactly the opposite of what we expected," says senior author John A. Copland, Ph.D., a Mayo cancer biologist. "We were more than surprised. We were concerned."

FOXO3a is known as a suppressor of tumor growth because it responds to all forms of cell stress, including that produced in cancer, by turning on genes inside the nucleus that trigger the cell's death. Cancer, in turn, is known to shut down FOXO3a by sending it out of the nucleus and into the cell's cytoplasm, where it is degraded. The molecule that ships FOXO3a out of the nucleus is Akt, which tries to keep cancer cells alive.

The research team used an Akt blocker — similar to the ones now being used in human cancer clinical trials — expecting to increase nuclear

FOXO3a and suppress cancer growth in anaplastic thyroid cancer. They were trying to find a treatment for one of the deadliest known cancers, which accounts for just 2 percent of thyroid cancer cases in the U.S. but is responsible for about 40 percent of thyroid cancer deaths.

"The issue we are grappling with is that there are no effective treatments for this cancer. These tumors are so aggressive because there are so many genetic abnormalities," says study co-author Robert Smallridge, M.D., a Mayo endocrinologist who treats thyroid cancer patients. "We are studying what drives this cancer and how it can be treated."

The study showed that FOXO3a remained in the nucleus, with the use of an Akt inhibitor, and that instead of helping to kill cancer cells, FOXO3a was accelerating their growth. This raises concern about the use of Akt inhibitors since one of the mechanisms is to cause FOXO3a to remain active in the nucleus.

"We discovered a biological switch that turns FOXO3a from a good guy into a bad actor, but we don't know what that is yet, or in which cancers that might happen," says lead researcher Laura Marlow, a Mayo biologist.

"Cancer researchers, including those testing Akt inhibitors, should know that FOXO3a has pro-cancer activity as well as anti-cancer properties," Dr. Copland says. "Concern should be raised that an Akt inhibitor will enhance retention of FOXO3a in the nucleus, causing FOXO3a to remain active.

But there was some hopeful news regarding a potential therapy for the cancer. The researchers found that FOXO3a turns on a certain gene, cyclin A1, which promotes growth in the cancer cells. A different member of the cyclin family — cyclin A2 — is a well-known oncogene, but, before this study, no one had shown that cyclin A1 does the same

thing as cyclin A2, says Peter Storz, Ph.D., a Mayo cancer biologist and co-author.

"It is not expressed much in human tissues and we found it highly expressed in anaplastic thyroid cancer," Dr. Smallridge says. "And that suggests that targeting cyclin A1 may be a possible strategy in treating anaplastic thyroid cancer."

Provided by Mayo Clinic