Protein related to aging holds breast cancer clues

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The most common type of breast cancer in older women -- estrogen and progesterone receptor (ER/PR) positive breast cancer -- has been linked to a protein that fends off aging-related cellular damage.

A new study led by Vanderbilt-Ingram Cancer Center researcher David Gius, M.D., Ph.D., now shows how a deficiency in this aging-associated protein may set the stage for these tumors to develop.

The findings, published in *Molecular Cell*, provide information that could assist in the screening, prevention and treatment of these common age-related cancers.

While the young are certainly not spared cancer's wrath, cancer is primarily a disease of aging, with the majority of cases occurring in people over 50.

However, the biological processes that underlie this association are not clear.

"The connection between aging and cancer is one of the most established phenomena in cancer research," said Gius, associate professor of Cancer Biology, Pediatrics and Radiation Oncology. "The problem to address this clinically significant question is that this field lacks in vivo models to study this."

In the late-1990s, proteins called "sirtuins" were linked to extended

lifespan observed in several species maintained on a calorically restricted diet. These nutrient-sensing sirtuin proteins seemed to defend against aging-related cellular damage.

Sirtuins are present in all living organisms, with humans having seven different sirtuin proteins.

"When (the sirtuins) were discovered, it seemed obvious to conclude that there might be a mechanistic connection between the genes that determine length of survival and cancer," Gius said.

Previously, while at the National Cancer Institute, Gius and colleagues created mice lacking some of these sirtuins. They reported last January in Cancer Cell that when they knocked out Sirt3 — a sirtuin localized in the mitochondria, the cellular "power plants" — the mice developed ER/PR positive breast tumors, the most common type of breast cancer in postmenopausal women.

These tumors also exhibited increased levels of damaging free radicals and "reactive oxygen species" (ROS) — including superoxide, the primary metabolite of oxygen in the mitochondria — which provided an important clue as to how Sirt3 deficiency might permit these tumors to develop.

"The mechanism, at least in part, for why these mice develop receptor positive breast cancer is altered mitochondrial ROS, including superoxide," Gius said.

But how deficiency in a longevity gene led to increased ROS was not clear.

Since superoxide is generally removed from the cell with the help of a detoxifying enzyme called manganese superoxide dismutase (MnSOD),

Gius hypothesized that the Sirt3 deficiency may abnormally regulate MnSOD.

In the current study, the researchers show that Sirt3 knockout mice have decreased MnSOD activity despite having normal levels of the protein.

Gius and colleagues determined that the MnSOD in Sirt3 knockout mice was abnormally modified (with a chemical "acetyl" group) at a specific amino acid (lysine 122).

This aberrant modification of MnSOD reduced the enzyme's ability to detoxify superoxide and appeared to explain the increase in ROS in Sirt3 knockout mouse tumors.

"These results suggest that aberrant regulation of MnSOD plays a role in receptor positive breast cancer," said Gius.

Gius and colleagues also developed an antibody that can assess the acetylation status of MnSOD, which he says can potentially be used "to screen breast tissue samples to determine what women are at risk for (receptor positive) cancer or for recurrence because of this dysregulation of MnSOD."

Additionally, agents that target the acetylation of this amino acid on MnSOD may be useful as chemopreventive therapies in women at risk of these cancers and of recurrence, he noted.

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