Researchers discover molecule that drives aggressive breast cancer

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(Medical Xpress)—Recent studies by researchers at Thomas Jefferson University's Kimmel Cancer Center have shown a gene known to coordinate initial development of the eye (EYA1) is a powerful breast tumor promoter in mice. The gene EYA1 was also shown to be overexpressed in a genetic breast cancer subtype called luminal B.

The scientists found that excess activity of this gene —EYA1—also enhances development of breast cancer stem cells that promote resistance to cancer therapy, recurrence, and poor survival.

Because EYA1 is an enzyme, the scientists are now working to identify a natural compound that could shut down EYA1 activity, says Richard Pestell, M.D., Ph.D., Director of Kimmel Cancer Center.

"It was known that EYA1 is over-expressed in some breast cancers, but no one knew what that meant," he says. "Our studies have shown the enzyme drives luminal B breast tumor growth in animals and the enzyme activity is required for tumor growth."

In a mouse model of aggressive breast cancer, the research team targeted a single amino acid on the EYA1 phosphatase activity. They found that inactivating the phosphatase activity of EYA1 stopped aggressive human tumors from growing.

"We are excited about the potential of drug treatment, because it is much easier to develop a drug that targets a phosphatase enzyme like EYA1,

than it is to target a gene directly," he says.

Tracing how EYA1 leads to poor outcomes

The study, which was published in the May 1 issue of *Cancer Research*, examined 2,154 breast cancer samples for the presence of EYA1. The researchers then linked those findings to patient outcomes. They found a direct relationship between increased level of EYA1 and cyclin D1 to poor survival.

They then chose one form of breast cancer —luminal B—and traced the bimolecular pathway of how EYA1 with cyclin D1 increases cancer aggressiveness. Luminal B breast cancer, one of five different breast cancer subtypes, is a hormone receptor-positive form that accounts for about 20 percent of human breast cancer. It is more aggressive than luminal A tumors, a hormone receptor-positive cancer that is the most common form of breast cancer.

Their work delineated a string of genes and proteins that are affected by EYA1, and they also discovered that EYA1 pushes an increase in formation of mammospheres, which are a measure of breast cancer stem cells.

"Within every breast cancer are breast cancer stem cells, which give rise to anti-cancer therapy resistance, recurrence and metastases," Dr. Pestell says. "We demonstrated in laboratory experiments that EYA1 expression increase the number of mammospheres and other markers of breast cancer stem cells."

"As the EYA1 phosphatase activity drove breast cancer stem cell expansion, this activity may contribute to worse survival," he says.