Gene blamed for immunological disorders shown to protect against breast cancer development

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Researchers at Georgetown University Medical Center (GUMC) are voicing alarm that drugs to treat a wide variety of allergies, asthma and autoimmune diseases now in human clinical trials may errantly spur development of breast tumors.

As the researchers report in the October 15 issue of PLoS ONE, the gene SYK and its protein product, Syk*, are crucial for prevention of breast cancer in the mice and human breast cells they studied. The research is the most definitive yet to demonstrate the beneficial function of Syk as a tumor suppressor, but Syk is better known for its negative role in ramping up activity of the immune system, leading to a cornucopia of immunological disorders.

The concern the authors have is that agents for these conditions - which are now being tested in humans - might spur breast cancer development because they are designed to inhibit the activity of Syk. "Our study shows that in normal breast cells, Syk is needed to control growth and thus prevent breast cancer. So if people use a drug that stops Syk activity, they could be at risk for developing this cancer, particularly at a young age during breast development" says the study's senior author, Susette Mueller, PhD, professor of oncology at the Lombardi Comprehensive Cancer Center at GUMC.

"Years of research has led us to believe that Syk is important in breast

cancer, but we still need to find out why and when some women lose Syk function," she says. "In the meantime, we can only voice concern that inhibiting the protein may have unfortunate consequences."

She adds that Syk is a complex gene product, and that researchers elsewhere have also shown that it can promote development of other types of cancer, such as head and neck and certain forms of leukemia. "As we are discovering more and more, proteins can have different functions in the human body, depending on the context in which they are used. Syk is a perfect example of this phenomenon," Mueller says.

Mueller and her collaborators have been studying Syk for about a decade, and have the largest body of work detailing how it functions in the breast. They first showed that Syk protein is present in normal breast cells and its absence correlated with invasion and metastasis in tumor cells and later found that as breast tumors progressed, more and more Syk protein was lost. Now, it is recognized that the amount of Syk present in a tumor is an indicator of risk of metastasis.

In this study, first author You Me Sung, PhD, a postdoctoral researcher in Mueller's lab, conducted mice studies in which one of two Syk alleles were genetically deleted. (Because Syk is believed to be important in embryonic development as well, deleting both will not sustain life.) The research team demonstrated that loss of the single allele led to "profoundly" increased proliferation and invasion of normal breast cells in the mouse mammary gland during puberty, resulting in development of breast cancer in adulthood. They then studied normal human breast cells in laboratory culture, and showed that knocking out Syk protein dramatically increased cell growth as well, and produced changes that would allow cells to invade through tissue-like barriers.

"Our findings in living mouse and in human breast cells mirrored each other," Mueller says. "All the data on Syk suggest it is very important in

controlling growth as breast tissue develops indicating a potent role as tumor suppressor for breast cancer."

The researchers are now studying patients who have lost Syk function in order to pinpoint the reason why the gene no longer produces its protein. Ultimately, the goal is to identify the molecules that Syk negatively regulates in order to target them for breast cancer therapy.

Source: Georgetown University