Breast cancer tumor suppressor gene silenced by low O2

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Low oxygen can silence the BRCA1 tumor suppressor gene and contribute to the progression of cancer, according to a paper in the August 2011 issue of the journal *Molecular and Cellular Biology*. Silencing this particular gene is one of the steps on the malignant pathway to breast cancer. The research may ultimately lead to ways of reactivating this and other tumor suppressor genes, in order to thwart cancer, says corresponding author Peter Glazer of Yale University, New Haven.

This study grew out of Glazer's laboratory's previous findings that low oxygen stress to cells can cause changes in expression of many human genes, sometimes boosting, and sometimes reducing expression. "We had found a few years ago that hypoxia reduces expression of BRCA1, and so I had the idea to ask whether it could drive silencing of the gene," says Glazer.

Hypoxia is common in human tumors, partly because newly emerging tumors lack blood vessels. "They become hypoxic because they don't get enough blood," says Glazer. As they enlarge, they begin to grow blood vessels, in a process known as angiogenesis. But "that process is never perfect, so tumors have a very variable and incomplete blood supply," says Glazer. "That makes them more genetically unstable, and helps drive them towards more malignant properties," he adds, citing earlier work by his laboratory.

The silencing could be a first step towards cancer, but Glazer thinks it

more likely is a later step, since without the tumor, the hypoxia that drives gene silencing is less likely to occur, says Glazer.

Understanding the mechanism of reduced expression would open the way to research that could lead to strategies for interfering with the gene silencing. What we know so far: the mechanism for the silencing involves the histones, proteins that wrap around the chromosomes when they are silent, but which unwrap around genes that are being expressed. Glazer showed that the silencing of BRCA1 is accompanied by a change in the histones, called methylation, which is frequently seen when gene expression is reduced.

“We then found that one particular enzyme, called lysine demethylase [LSD1] is manipulating the methylations,” says Glazer. Finding a way to block that enzyme could lead to reactivating BRCA1, he says, noting that this might be done by finding a small molecule that inhibits that enzyme’s activity. Such a drug might reactivate other tumor suppressors as well, he says.

Glazer thinks that cell stress in general caused by hormones or environmental toxins may lead to silencing BRCA1, and he plans to investigate that hypothesis.

More information: Y. Lu, et al., 2011. Hypoxia-induced epigenetic regulation and silencing of the BRCA1 promotor. *Mol. Cell. Biol.* 31:3339-3350

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