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Combining neurologic and blood pressure drugs reduces breast tumor development in mice

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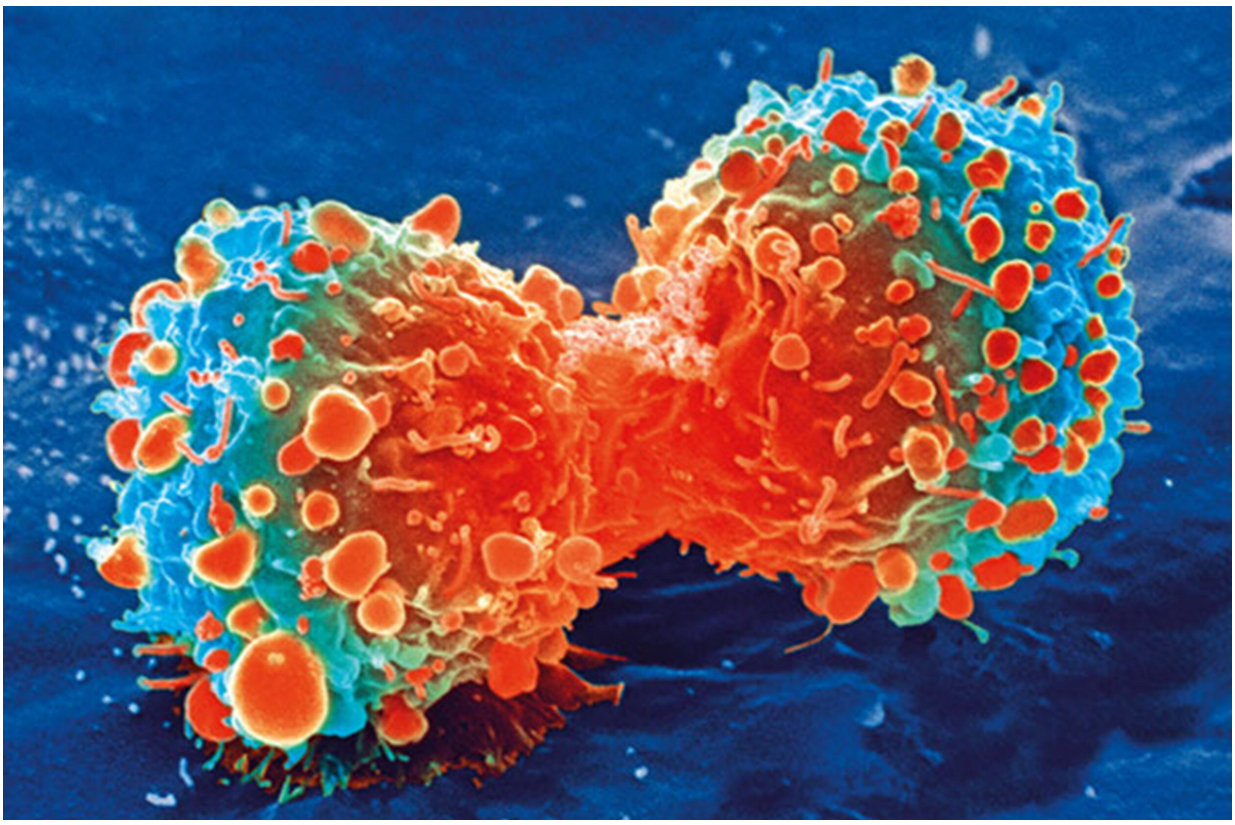

Cancer cell during cell division. Credit: National Institutes of Health

Adding a medication used to treat epilepsy, bipolar disorder and migraines to a blood pressure medicine reversed some aspects of breast

cancer in the offspring of mice at high risk of the disease because of the high fat diet fed to their mothers during pregnancy. Conversely, this treatment combination increased breast cancer development in the offspring whose mothers had not been fed a high fat diet during pregnancy. The study by Georgetown Lombardi Comprehensive Cancer Center researchers appeared December 30, 2019, in *Scientific Reports*.

The key drug in the study regimen was valproic acid which, among several targets, inhibits histone deacetylase (HDAC), an important epigenetic silencer of genes. In contrast to mutations that permanently disrupt the normal functions of genes, epigenetic modifications are reversible. Valproic acid was combined with the blood pressure medication hydralazine that inhibits another critical epigenetic regulator, DNA methyltransferase (DNMT). Early treatment studies in people have shown that these two drugs can work in tandem to disrupt tumor growth.

"We believe that our research is the first to show that we can reverse some aspects of increased breast cancer risk found in offspring of mouse mothers fed a high fat diet during pregnancy," said Leena A. Hilakivi-Clarke, Ph.D., a professor of oncology at Georgetown Lombardi. "This finding may have important implications in people because exposures in the womb to certain chemicals, or a mother's high fat diet, or being obese, can subsequently increase a daughter's breast cancer risk."

These research findings demonstrate how impactful an epigenetic methyl group addition or subtraction from DNA can be. Compounds that reduce methylation of tumor suppressor genes that are excessively methylated (hypermethylated) can be beneficial. However, these drugs can have the opposite effect if tumor suppressor genes are not hypermethylated; they may remove methyl groups from cancer-causing genes, making these genes more active and potentially leading to more aggressive cancers.

The other key aspect of this finding involves the potential impact of diet

on cancer risk. Many fruits and vegetables have compounds (such as flavones) that chemically react in the same ways as the HDAC- and DNMT-inhibiting drugs in this study. Some compounds in these foods, especially folic acid, have opposite effects. This research suggests that exposure to a high fat diet or endocrine disrupting chemicals in the womb might be reversed by the consumption of foods high in DNMT and HDAC inhibitors, while those who have not had such exposures might also gain a cancer protective benefit from consuming foods high in folic acid. The scientists note, however, that their findings, particularly as they relate to diet, need to be studied in people.

"Our next step will be to try to identify biomarkers in humans that indicate an exposure in the womb to diets or endocrine disrupting chemicals that could increase breast cancer risk later in life," said Hilakivi-Clarke. "If we can identify such biomarkers, we'll look to see if specific foods consumed by women can reverse epigenetic changes to their DNA that might lead to increased breast cancer risk."

More information: F. de Oliveira Andrade et al, Reversal of increased mammary tumorigenesis by valproic acid and hydralazine in offspring of dams fed high fat diet during pregnancy, *Scientific Reports* (2019). DOI: 10.1038/s41598-019-56854-5

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