Enzyme that silences DNA activity may be crucially involved in health and cancer

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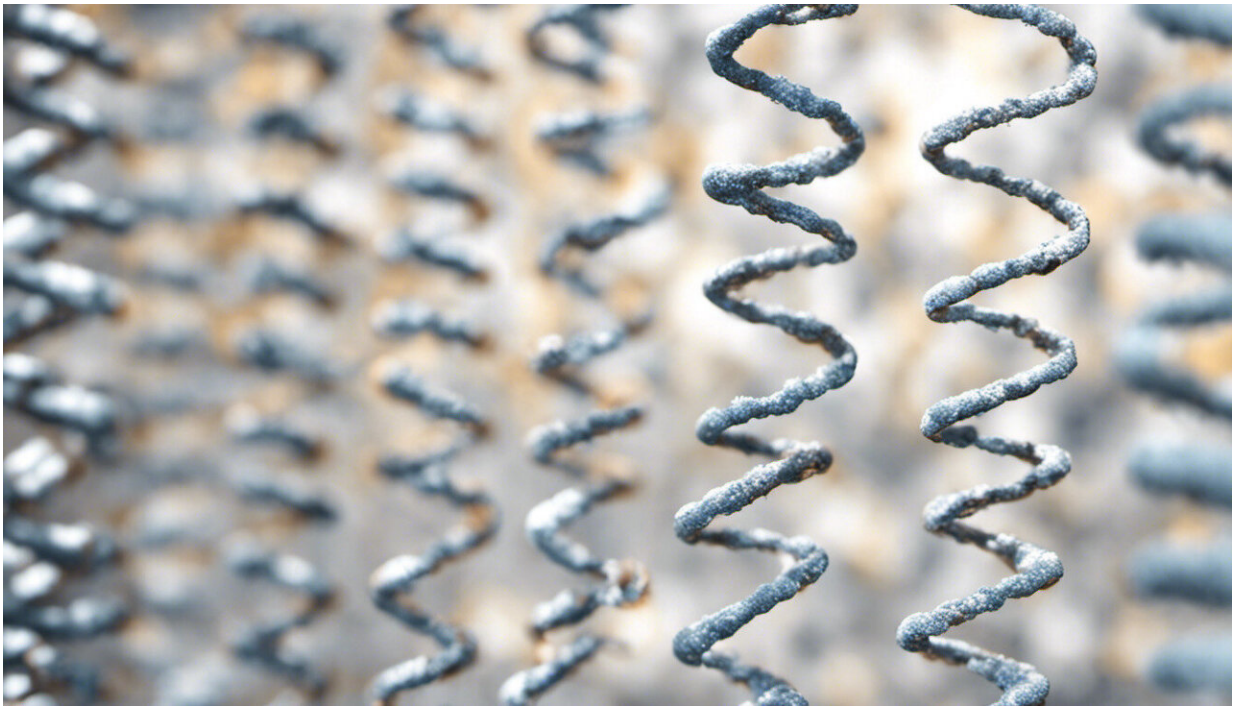

Credit: AI-generated image (disclaimer)

Cancers can develop when the complex molecular networks that control the activity of DNA are disrupted. Researchers from the A*STAR Institute of Molecular and Cell Biology in Singapore, led by Dmitry Bulavin, have studied Wip1, an enzyme central to these molecular networks that may both help to keep cells healthy but also become part

of the problem when things go wrong. The team's findings suggest that this enzyme, and its associated signaling pathways, could be a target for the development of new drugs to combat some types of cancer. They may also explain why some cancers are resistant to drug therapy.

Bulavin and co-workers uncovered the role of the Wip1 enzyme when examining the deactivation or 'silencing' of regions of DNA by DNA methylation. DNA methylation occurs when methyl (CH3) groups are added to the cytosine bases of DNA. This process is known to be vital for the normal control of gene activity as cells and organisms develop. Changes in DNA methylation patterns, however, are also involved in the development of many diseases, including cancer.

Wip1 is known to influence the activity of other molecules by removing phosphate (PO43–) groups. However, enzymes rarely act alone to regulate gene activity—they are components of complex networks of interactions. To clarify the Wip1 enzyme's role in health and disease, the team looked at its direct and indirect interactions with several other molecules already implicated in cancer, including DNA itself.

Working in mice and with human cancer cells, the researchers examined the effects of creating Wip1 deficiency, as well as stimulating the overexpression of the gene that makes Wip1. They found varied effects on more than a thousand genes, including increases and decreases in DNA silencing when the normal activities of Wip1 were disrupted. Taken together, the results suggest that the Wip1 enzyme plays an important role in controlling DNA methylation in tightly coiled—and often inactive—regions of DNA known as 'heterochromatin'. The enzyme's DNA-silencing effects are mediated through interaction with two other proteins involved in the onset of cancer, known as ATM and BRCA1.

The team's results may be particularly relevant to mutations in primary

breast cancers. "Ultimately, cancer develops and evolves as a result of mutations that contribute to these processes, but the phenomenon is very poorly understood," says Bulavin. "We show Wip1 is critical to maintaining the integrity of the genome, which provides new avenues to understanding cancer evolution and the mechanisms responsible for developing anticancer drug resistance."

More information: Filipponi, F., Muller, J., Emelyanov, A. & Bulavin, D. V. "Wip1 controls global heterochromatin silencing via ATM/BRCA1-dependent DNA methylation." *Cancer Cell* 24, 528–541 (2013). dx.doi.org/10.1016/j.ccr.2013.08.022

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