Misregulation of DNA building blocks associated with the development of colon cancer

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Professor Andrei Chabes is one of the researchers at Umeå University in Sweden behind the new findings. Credit: Mattias Pettersson, Umeå University

When cells divide, the proper balance between the four DNA building

blocks is required in order for the DNA to be copied without the introduction of potentially harmful mutations. Researchers at Umeå University in Sweden have now shown a connection between levels of DNA building blocks - dNTPs - and colon cancer. This discovery has been published in the *Proceedings of the National Academy of Sciences*.

"Together with other researchers, we have previously shown that small changes in the levels of DNA building blocks increase the mutation rates in yeast cells," says Professor Andrei Chabes, one of the researchers at Umeå University behind the new findings. "This is what got us interested in studying the proteins involved in the regulation of dNTP in cancerous cells. Our objective was to identify mutations that affect dNTP levels and thus increase the mutation rate in cancer cells."

The Umeå-based research team found that the protein SAMHD1, which is involved in the break-down of dNTP, is often mutated in colon cancer cells. Further studies in mice, yeast, and cultures of human cells showed that these cancer-specific mutations eliminated the SAMHD1 function and that this led to an elevation and imbalance in dNTP levels and hence an increased mutation rate.

"What's so remarkable about our observation is that even if only one of the two SAMHD1 gene copies is lost, it affects dNTP levels with an increased mutation rate as a result. Together with a deficiency in the protein MLH1, which is involved in the correction of mutations and is often mutated in colon cancers, we can see a huge increase in the number of emerging mutations," explains Professor Andrei Chabes.

The new results have been published in the highly acclaimed journal *Proceedings of the National Academy of Sciences*. The researchers have reason to believe that the results will lead to other similar discoveries - both in other cancers and in other proteins involved in dNTP synthesis.

"SAMHD1 is only one of several dozen proteins involved in the regulation of dNTPs. In theory, a change in function in any of these proteins can affect dNTP levels. We are merely showing the principle. It now remains to be seen how changes in dNTP levels affect the development of colon cancer and if changes in dNTP levels occur in other cancers," says Professor Andrei Chabes.

More information: Matilda Rentoft et al. Heterozygous colon cancer-associated mutations of have functional significance , *Proceedings of the National Academy of Sciences* (). DOI: 10.1073/pnas.1519128113

Provided by Umea University