Elusive cancer-related protein captured in flight

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Nuclear magnetic resonance is one of the methods the researchers used to study the proteins at atomic resolution. Credit: Charlotte Perhammar/Linköping University

Scientists have for the first time seen how the MYC protein, which plays a central role in cancer, binds to a key protein and controls important functions in the cell. The study, published in *Nature Structural and Molecular Biology*, is a collaboration between scientists at Linköping University, Sweden, and the Princess Margaret Cancer Center in Toronto, Canada. The new discovery may in the long term help in the development of new cancer drugs that disrupt the function of MYC in tumor cells.

The MYC protein regulates many important functions in healthy cells. But MYC is often extremely overactive in aggressive tumors, where its function can be likened to that of an accelerator pedal that has got stuck. The mechanisms by which MYC functions in the cell are largely unknown. The scientists who carried out the present study, therefore, wanted to find out how the transcription factor MYC interacts with another protein, the TATA-binding protein (TBP). TBP acts as a starting button for the expression of many genes in the cell.

MYC, however, has proved to be elusive for structural biologists. It is what is known as a "disordered" protein, which constantly shifts between different structures in a very dynamic manner. MYC can bind to over 300 different proteins in the cell. The key to MYC being able to interact with so many other proteins so rapidly is probably its adaptability and its ability to change structure in a flash.

Around 70 percent of proteins implicated in cancer development are disordered proteins. If we can disturb the function of these proteins in tumor cells, we may have the basis of new treatments for cancer. But first, we must understand in detail how they function. One of the challenges facing researchers is that they must find conditions in which the MYC protein is sufficiently stable for them to examine the protein structure at atomic level. They have now managed to capture an instantaneous image of MYC bound to TBP, and been able to study the protein complex using methods such as crystallography and nuclear magnetic resonance (NMR).

"We already suspected that there was a binding site on the seat of the saddle-shaped TBP protein. But the first thing we found by crystallography was how MYC binds the concave side of the TBP 'saddle,' which we weren't expecting," says Maria Sunnerhagen, professor in the Department of Physics, Chemistry and Biology at Linköping University and leader of the study.

The next step was to see whether the structure they had found played a role in the protein's biological function. The scientists created mutations of MYC in which different features of the binding site had been removed. They then investigated how the function of the protein, and how cell growth and survival, were affected.

"We have shown that both binding sites influence MYC activity and affect cell growth and proliferation. Breaking the interaction between MYC and TBP dramatically decreases the ability of the cells to survive," says Maria Sunnerhagen.

The scientists have not been able to directly image the dynamic binding site that has the greater biological function at atomic resolution yet. For this reason, they combined data from different methods and carried out advanced calculations in a supercomputer to model the interaction

between the two proteins. They used AI to home in on the structure that agrees best with the observed data and in this way identified a previously unknown binding site. The researchers believe that MYC helps to increase gene expression by making it easier to place TBP at the correct location on the DNA.

More information: "Multiple direct interactions of TBP with the MYC oncoprotein", Yong Wei, Diana Resetca, Zhe Li, Isak Johansson-Åkhe, Alexandra Ahlner, Sara Helander, Amelie Wallenhammar, Vivian Morad, Brian Raught, Björn Wallner, Tetsuro Kokubo, Yufeng Tong, Linda Z. Penn and Maria Sunnerhagen, (2019), *Nature Structural and Molecular Biology*, published online 4 November 2019, DOI: 10.1038/s41594-019-0321-z

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