Understanding cellular transcription responses to oxygen deprivation

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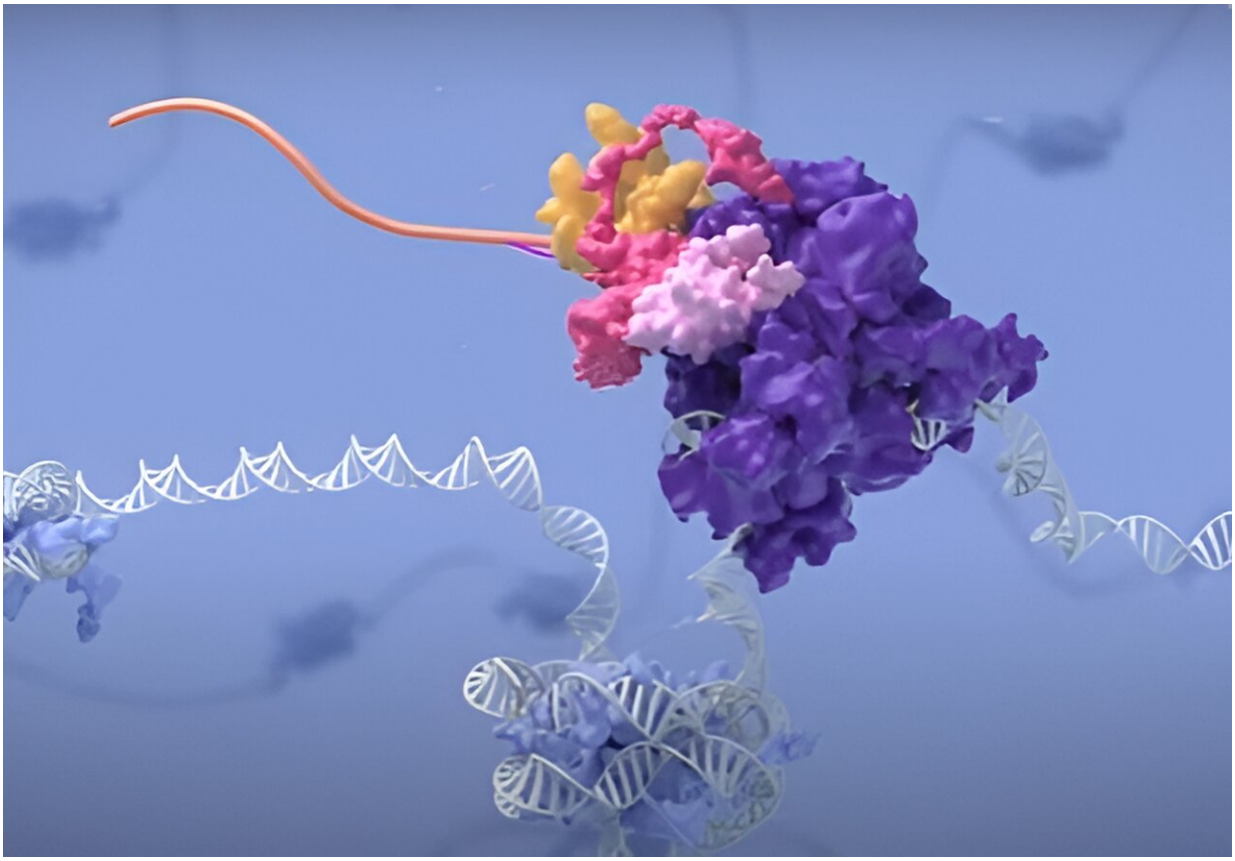

Credit: Credit: Brianna Monroe

A multiprotein complex is essential for regulating cellular responses to oxygen deprivation, a key feature of cancer, according to a Northwestern Medicine study published in the *Proceedings of the National Academy of*

Sciences.

Hypoxia, when cells are deprived of oxygen, is a key feature of cancer and other diseases including arthritis. While it's well-known that oxygen deprivation changes how cells express DNA, the molecular mechanisms involved have not been well understood, said Ali Shilatifard, Ph.D., the chair and Robert Francis Furchgott Professor of Biochemistry and Molecular Genetics, who was senior author of the study.

"Our previous groundbreaking work demonstrated that translocations associated with human leukemia are associated with a gene that regulates the rate of transcription elongation in mammalian cells," said Shilatifard, who is also the director of the Simpson Querrey Institute for Epigenetics. "Further study has solidified that transcription elongation control is a key regulatory step and this perturbation causes cancer and other diseases including aging."

In the study, Shilatifard, also leader of the Cancer Epigenetics and Nuclear Dynamics Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, and the other investigators sought to understand how cells transcriptionally respond to oxygen deprivation.

First, the scientists purified RNAPII, a multiprotein complex which plays a role in transcribing DNA, from colorectal cancer cells cultured under hypoxia. They then performed mass spectrometric-based proteomic analysis and found increased expression of the BRD4-containing CDK9 complex, a multi-protein complex known to regulate transcription elongation.

By targeting the BRD4-containing CDK9 complex in cultured cells, the scientists discovered that cell responses to oxygen deprivation were also reduced.

The findings identify BRD4-containing CDK9 complex as a key player in how cells respond to oxygen deprivation and offer potential therapeutic targets for treating cancer and other diseases such as arthritis.

"With this study, we found a new potential therapeutic target that can be used to turn hypoxia on or off through BRD4," said Marta Iwanaszko, Ph.D., research assistant professor of Biochemistry and Molecular Genetics and a co-author of the study.

"This is very important since targeting hypoxia so far was not that successful. This gives us another way to target this very important transcriptional program that is found in many diseases and is very prevalent in especially solid tumors."

Building off this discovery, members of the Shilatifard laboratory will work to identify other factors that regulate certain survival-promoting pathways and how those pathways function under cancer-related stressors, said Shimaa Soliman, Ph.D., a postdoctoral scholar and the first author of the study in the Shilatifard laboratory.

"I think we are on our way to discovering novel epigenetic factors and coactivators that can regulate a specific subset of hypoxia response genes," Soliman said.

"We are very much interested in identifying pathways that are working independently of the pathway in this research to further understand how certain genes can be turned on upon hypoxia."

More information: Shimaa Hassan AbdelAziz Soliman et al, Transcriptional elongation control of hypoxic response, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2321502121

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