Scientists solve structure of important protein for tumor growth

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In a collaborative study between Sanford Burnham Prebys Medical Discovery Institute (SBP) and the Argonne National Laboratory, scientists have used a highly specialized X-ray crystallography technique to solve the protein structure of hypoxia-inducible factors (HIFs), important regulators of a tumor's response to low oxygen (hyopoxia). The findings, published today in the journal *Nature*, open the door to search for new drugs to treat tumors by cutting off their supply of oxygen and nutrients.

"For the first time, we have solved the structures of both HIF1-alpha and HIF2-alpha complexed with the ARNT subunit, a configuration required for HIF functionality," said Fraydoon Rastinejad, Ph.D., professor in the Metabolic Disease Program at SBP. "Visualizing these multi-domain structures helps us understand their drug binding capabilities and takes us further toward the goal of developing drugs that inhibit the tumor promoting effects of HIFs."

HIF proteins regulate genes that play a role in the progression of a broad range of tumors, and modulating their activity is recognized as a promising approach in cancer therapeutics. There have been intense efforts in the pharmaceutical sector to find drugs that inhibit HIF pathways, but have only led to drug candidates that bind to another class of proteins called PHDs. PHD proteins regulate HIF activities, and there are a number of PHD inhibitors currently in clinical trials for anemia, chronic kidney disease, stroke, as well as cancer.

"This study advances efforts to find new drugs that bind to HIF directly, rather than PHDs. We identified five different pockets in the architecture of the HIF complexes, all of which may be used for targeting small-molecule inhibitors. These drugs could conceivably inhibit HIF functions by reducing their stability, their ability to interact with other protein partners, and by altering mechanisms critical for their function," added Rastinejad.

Drugs that inhibit HIFs may be very useful for treating solid tumors because these cancers outgrow their blood supply and become starved for oxygen, stimulating HIFs to turn on genes that regulate many cancer cell survival pathways, including angiogenesis, erythropoiesis, increased expression of genes associated with anaerobic metabolism, and metastasis. The coordination of all these programs helps to promote tumor growth and drug resistance, ultimately leading to decreased patient survival.

"Our next step is to analyze a large number of patient samples with mutations in HIF proteins. We'd like to see where on the protein architectures these mutations occur, and how they manifest into HIF functional aberrations," said Rastinejad. "Such mutations will offer a powerful glimpse into the structure-function activities of HIFs, and help us figure out how they turn genes on and off."

"The insights we make into the structure, function, and regulation of HIFs may also progress the development of treatments for a range of disease states beyond cancer, including heart disease, fatty liver, diabetes, and inflammatory diseases."

More information: Structural integration in hypoxia-inducible factors, *Nature*, DOI: 10.1038/nature14883

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