Discovering a protein's role in gene expression

November 10 2017, by Anna Williams

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Northwestern Medicine scientists have discovered that a protein called BRWD2/PHIP binds to histone lysine 4 (H3K4) methylation—a key molecular event that influences gene expression—and demonstrated that it does so via a previously uncharacterized protein structural domain.

Beyond providing new insights into the regulation of gene expression, the findings have important implications for several diseases, as

BRWD2/PHIP is overexpressed in metastatic melanoma, and mutations in related genes are associated with neuro-developmental syndromes.

The study, published in the journal *Genes & Development*, was led by Ali Shilatifard, PhD, the Robert Francis Furchgott Professor and chair of Biochemistry and Molecular Genetics. Marc Morgan, PhD, a postdoctoral fellow, was the first author.

Human DNA is wrapped around proteins called histones. When these proteins are modified through a molecular process called histone methylation, they also play a role in determining which genes are turned on or off.

Close to two decades ago, Shilatifard discovered that methylation at a certain histone location called H3K4 is catalyzed by a family of enzymes he named COMPASS. Since then, Shilatifard's laboratory has continued to make extensive discoveries about the process of histone H3K4 methylation, how it controls gene expression, and how its misregulation might give rise to cancer and other disorders.

In the current study, the scientists demonstrated for the first time that the protein BRWD2/PHIP directly binds to COMPASS-implemented H3K4 methylation in human cancer cells, mouse embryonic stem cells and Drosophila (fruit flies).

They further discovered that BRWD2/PHIP recognizes the modification through a previously unknown domain of the protein they named the CryptoTudor domain.

"This gives a molecular function to a gene that was on people's radars because of its role in human disease," Morgan said. "We show that it's actually part of a pathway that we know a lot about, and we provide a mechanism for how it binds to a specific substrate."

The scientists demonstrated the findings through a multi-disciplinary approach that took advantage of many state-of-the-art experimental technologies, including CRISPR-Cas9 gene editing, next-generation sequencing, mass spectrometry and biophysical experiments.

The findings are particularly illuminating, Morgan notes, because there is a striking overlap between the conditions affecting individuals who have mutations in the genes encoding COMPASS and BRWD proteins, such as intellectual disabilities.

"Our thinking is that if COMPASS activity initiates H3K4 methylation, and that's what BRWD2 binds to in the chromatin, then they must be part of the same pathway," Morgan said. "Now, the next big step is to understand precisely what this protein actually does—and that's what we're doing in the lab now."

Future studies, beyond determining the function of BRWD2, will also aim to understand how its binding might help regulate the process of transcriptional control.

"We've found this family of H3K4 binding factors, and we're going to build upon that and determine what they do," said Shilatifard, also a professor of Pediatrics and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. "It's just like a puzzle—before, nothing was fitting in this piece of the puzzle, and now we have a piece that makes sense. Now we have to discover the rest of the puzzle."

More information: Marc A.J. Morgan et al. A cryptic Tudor domain links BRWD2/PHIP to COMPASS-mediated histone H3K4 methylation, *Genes & Development* (2017). DOI: 10.1101/gad.305201.117