Deciphering structure of NatA, an enzyme complex that modifies most human proteins

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A team of researchers from Philadelphia and Norway has determined the structure of an enzyme complex that modifies one end of most human proteins and is made at elevated levels in numerous forms of cancer. A study in *Nature Structural & Molecular Biology*, led by researchers at The Wistar Institute, depicts the structure and the means of action of a protein complex called NatA. Their findings, they believe, will allow them to create an inhibitor—a potential drug—that could knock out NatA in order to curb the growth of cancer cells.

"NatA appears essential for the growth of cells and their ability to divide, and we can see elevated production of this enzyme in many forms of cancer" said Ronen Marmorstein, Ph.D., senior author, Hilary Koprowski, M.D. Professor, and leader of The Wistar Institute Cancer Center's Gene Expression and Regulation program. "Obviously, this is a particularly appealing drug target and we are currently leveraging our recent understanding of how the protein works to develop small molecules that will bind to and inactivate NatA."

NatA is a member of a family of N-terminal acetyltransferase (NAT) enzymes (or enzyme complexes) that modify proteins in order to control their behavior—for example by turning proteins on, telling proteins where to move, and tagging proteins or the cell for destruction.

According to Marmorstein, NatA works with an amazing specificity for a particular sequence of amino acids—the individual building blocks of proteins—and unraveling the roots of that specificity has proven an

alluring puzzle for scientists.

The Marmorstein laboratory has proven expertise in the study of acetylation enzymes, proteins that modify other molecules in the cell with an acetyl group "tag." In the cellular world, structure dictates function, and acetylation is a universal process for controlling protein behavior and gene expression in living organisms.

"Modifying protein structures is one way that our cells control how proteins function," Marmorstein explained, "and enzymes in the NAT family modify nearly 85 percent of human proteins, and 50 percent of these are modified by NatA."

According to Marmorstein, NatA operates in a complex of two proteins, an enzymatic subunit and an auxiliary partner. When they developed the structure of NatA—by bombarding a crystallized sample of the enzyme with powerful X-rays—they found how the auxiliary partner protein is crucial for turning the enzymatic subunit on.

Binding to an auxiliary protein causes a structural change in the enzymatic subunit that properly configures the active site of the protein—the region of the protein where the chemical reaction occurs—essentially acting as a switch that activates the enzyme.

"When it binds to its auxiliary protein, the enzymatic subunit of NatA actually changes shape, reconfiguring the structure to allow it to properly grab its target protein N-terminal sequence for acetylation," Marmorstein said.

Importantly, others have found that NatA function is required for the proliferation of cancer cells. Marmorstein says, understanding the structure of NatA has allowed his team to better understand how to inactivate the protein in cancer cells. The structure has yielded targets

for small molecules that will act as inhibitors, essentially stopping the protein by gumming up its structure.

More information: Molecular basis for N-terminal acetylation by the heterodimeric NatA complex, DOI: 10.1038/nsmb.2636

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