Molecule's structure reveals new therapeutic opportunities for rare diabetes

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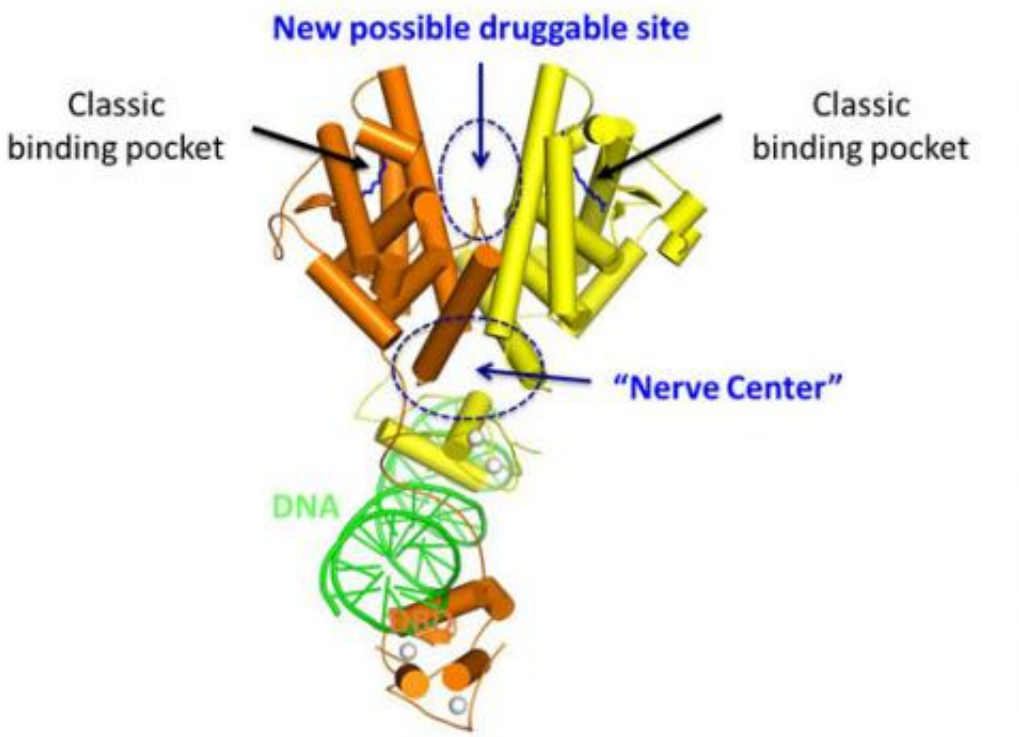

This is the newly discovered 3D structure of HNF-4alpha;, a protein mutated in a rare, inherited form of diabetes. The structure revealed new pockets that could be targeted with therapeutic drugs aimed at alleviating the disease. Credit: Sanford-Burnham Medical Research Institute

Researchers at Sanford-Burnham Medical Research Institute have determined the complete three-dimensional structure of a protein called

HNF-4α. HNF-4α controls gene expression in the liver and pancreas, switching genes on or off as needed. People with mature onset diabetes of the young (MODY1), a rare form of the disease, have inherited mutations in the HNF-4α protein. This first-ever look at HNF-4α's full structure, published March 13 in *Nature*, uncovers new information about how it functions. The study also reveals new pockets in the protein that could be targeted with therapeutic drugs aimed at alleviating MODY1.

"Previous structural studies of HNF-4α and related nuclear receptors only revealed smaller, isolated fragments of these proteins," said Fraydoon Rastinejad, Ph.D., professor in Sanford-Burnham's Diabetes and Obesity Research Center, located at the Institute's Lake Nona campus in Orlando, Fla., and senior author of the study. "Because those studies looked only at separate pieces of HNF-4α, many people suspected there was no coordination between different regions of the protein. But we showed those assumptions are incorrect. HNF-4α's domains are highly organized in a way that has implications for our understanding of MODY1 and the development of treatments for the disease."

Implications for MODY1

Rastinejad's study helps explain why inherited genetic mutations that alter HNF-4α protein structure can be so damaging. The mutations that lead to MODY1 usually occur within a very small, specific region of the HNF-4α protein that's separate from the DNA-binding region. Rastinejad and his team found that, despite their distant location, the mutations telegraph a signal to the DNA-binding region, causing HNF-4α to malfunction and thus MODY1 to develop.

The team also discovered new pockets in the HNF-4α protein that could be targeted with therapeutic drugs. Like other nuclear receptors,

HNF-4α has a pocket that binds natural signaling molecules or could be targeted with synthetic drugs. But this new study revealed several other pockets in other regions of the protein. And because they also found cross-communication among different regions on the protein, the team believes that a drug binding a distant pocket could still influence DNA binding.

"We're now working with our colleagues in Sanford-Burnham's Conrad Prebys Center for Chemical Genomics to screen a large chemical library—a collection of around 300,000 compounds—to find molecules that bind to these newly discovered HNF-4α sites," Rastinejad said. "We're looking for molecules that restore DNA binding in MODY1 patients. This way, even if we can't fix the mutation, we can still send a molecule to rescue the receptor's ability to tightly bind DNA."

More about HNF-4α

HNF-4α is a special type of protein called a nuclear receptor. It sits on the DNA in a cell, controlling thousands of genes by switching them on or off in response to outside signals. Nuclear receptors make good drug targets because one region is bound to DNA, while a pocket sits open on another part of the protein, just waiting to hold a signaling molecule. Therapeutic drugs can also be made to fit these pockets, switching the nuclear receptor on or off to alter gene expression.

Until this latest study, many researchers believed that most nuclear receptors are organized like beads on a string. Each bead (protein domain) has a function, but the string itself is just loose. Rastinejad and his team showed that the opposite is true. HNF-4α's domains are organized and coordinated—a domain that receives a signal can actually transmit it to a distant site on the protein. According to Rastinejad, the domains are interconnected, talking to one another.

HNF-4α is found mostly in liver and pancreatic cells, where it turns on genes needed by those organs and keeps other, unnecessary genes off. HNF-4α helps control carbohydrate metabolism, glucose regulation, insulin production, and many other important processes. In other words, HNF-4α is what makes a liver a liver and a pancreas a pancreas.

Provided by Sanford-Burnham Medical Research Institute