Major family of gene-regulating proteins has drug-sized pocket

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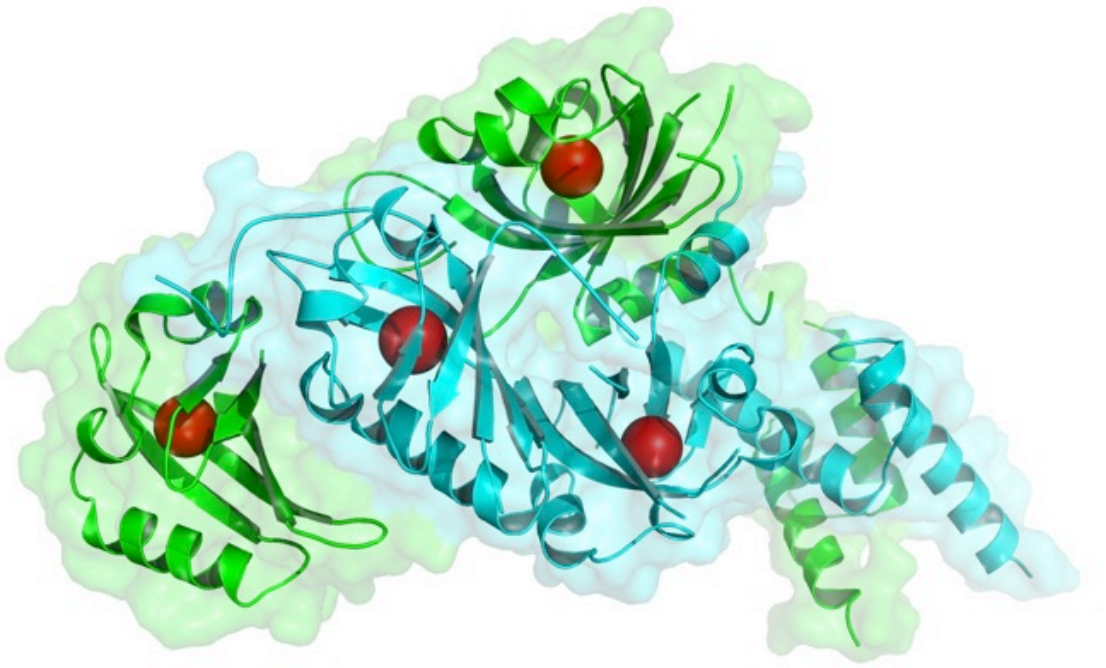

The relative positions of the four pockets (red circles) within the structure of NPAS1-ARNT. Credit: Dalei Wu, Sanford Burnham Prebys Medical Discovery Institute

An entire class of proteins called transcription factors, which regulate the activity of certain genes by interacting with specific sequences of DNA, has largely been ignored by the pharmaceutical industry because it's difficult to design and screen drugs against them. But a new study from scientists at Sanford Burnham Prebys Medical Discovery Institute suggests that a key group of transcription factors are in fact 'druggable,' including several that could be targeted to treat cancer, metabolic disease, or autoimmune conditions.

"We found that at least seven bHLH-PAS proteins have pockets where drugs would fit and remain tightly bound," said Fraydoon Rastinejad, Ph.D., professor in the Integrative Metabolism Program and senior author of the study. "That strongly suggests that all members of the family have similar, but chemically distinct, crevices that could bind drugs. Since these proteins serve as 'master regulators' for controlling whole gene programs, drugs against these targets could have broader effects than traditional ones that block single enzymes."

In the new study, published in *eLIFE*, Rastinejad and his lab first determined the structures of NPAS 1 and NPAS 3 proteins, each in complex with their partner, ARNT, using X-ray crystallography. All three proteins belong to the bHLH-PAS family of transcription factors. NPAS1 and NPAS3 control genes involved in brain and spinal cord development.

Rastinejad's team then compared the new structures to those of four other bHLH-PAS proteins, including two they previously solved, hypoxia-inducible factors (HIFs) 1α and 2α. In all seven proteins, they observed two similarly sized and architecturally positioned cavities in which small molecules could fit. Since three more bHLH-PAS transcription factors were known to interact with small molecules, it's safe to assume that these pockets are a common feature of the whole bHLH-PAS family.

Although variations in the NPAS1 and NPAS3 genes have been linked to brain disorders including autism, they aren't obvious drug targets because their function is most important in early life. However, modulating the activity of other bHLH-PAS proteins has been proposed to treat several diseases. For example, using drugs to block HIFs, which help cells survive when little oxygen is available, could stop the growth of certain cancers. Altering the function of the clock circadian regulator (CLOCK) and brain and muscle ARNT-like protein 1 (BMAL1), which keep cellular functions synchronized with day-night rhythms, could treat metabolic problems. And the aryl hydrocarbon receptor (AHR), which controls T cell differentiation, is a potential target for drugs to alleviate autoimmune disease.

"The fact that bHLH-PAS proteins have ligand-binding pockets insides their architectures suggests they're regulated by small molecules that are naturally found in the body," added Rastinejad. "That means we have a lot left to discover about these transcription factors. We anticipate that this research will spur many investigations to find their native activators and inhibitors and determine how they affect each protein's activity."

More information: Dalei Wu et al, NPAS1-ARNT and NPAS3-ARNT crystal structures implicate the bHLH-PAS family as multi-ligand binding transcription factors, *eLife* (2016). DOI: 10.7554/eLife.18790

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