Small molecules mimic natural gene regulators

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(PhysOrg.com) -- In the quest for new approaches to treating and preventing disease, one appealing route involves turning genes on or off at will, directly intervening in ailments such as cancer and diabetes, which result when genes fail to turn on and off as they should.

Scientists at the University of Michigan and the University of California at Berkeley have taken a step forward on that route by developing small molecules that mimic the behavior and function of a much larger and more complicated natural regulator of gene expression. The research, by associate professor of chemistry Anna Mapp and coworkers, is described in the current issue of the journal *ACS Chemical Biology*.

Molecules that can prompt genes to be active are called transcriptional activators because they influence transcription---the first step in the process through which instructions coded in genes are used to produce proteins. Transcriptional activators occur naturally in cells, but Mapp and other researchers have been working to develop artificial transcription factors (ATFs)---non-natural molecules programmed to perform the same function as their natural counterparts. These molecules can help scientists probe the transcription process and perhaps eventually be used to correct diseases that result from errors in gene regulation.

In previous work, Mapp and coworkers showed that an ATF they developed was able to turn on genes in living cells, but they weren't sure it was using the same mechanism that natural activators use. Both natural transcriptional activators and their artificial counterparts typically have

two essential parts: a DNA-binding domain that homes in on the specific gene to be regulated, and an activation domain that attaches itself to the cell's machinery through a key protein-to-protein interaction and spurs the gene into action. The researchers wanted to know whether their ATFs attached to the same sites in the transcriptional machinery that natural activators did.

In the current work, the team showed that their ATFs bind to a protein called CBP, which interacts with many natural activators, and that the specific site where their ATFs bind is the same site utilized by the natural activators, even though the natural activators are much larger and more complex.

Then the researchers altered their ATFs in various ways and looked to see how those changes affected both binding and ability to function as transcriptional activators. Any change that prevented an ATF from binding to CBP also prevented it from doing its job. This suggests that, for ATFs as for natural activators, interaction with CBP is key to transcriptional activity.

"Taken together, the evidence suggests that the small molecules we have developed mimic both the function and the mechanism of their natural counterparts," said Mapp, who has a joint appointment in the College of Pharmacy's Department of Medicinal Chemistry. Next the researchers want to understand in more detail exactly how the small molecules bind to that site. "Then we'll use that information to design better molecules."

More information: *ACS Chemical Biology*: pubs.acs.org/journal/acbcct

Source: University of Michigan (news : web)