Protein's flexibility helps its response to diverse pollutants

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How some industrial pollutants or abnormal levels of cellular metabolites contribute to diverse human diseases is now more clearly understood, based on a new study from the University of Wisconsin Carbone Cancer Center (UWCCC) and the McArdle Laboratory for Cancer Research.

The study, published online April 10 in the journal *Proceedings of the National Academy of Sciences*, solved the structure of the aryl hydrocarbon receptor, or AHR. Initially discovered for its cellular role in responding to the pollutant TCDD, a byproduct of fossil fuel or industrial waste burning, decades of research has identified numerous other chemicals to which AHR responds. It also responds to normal products of cell growth. AHR contributes to healthy development but it is also linked to cancer, immune and cardiovascular diseases.

"The difficulty with studying AHR is that it can respond to all these different chemical signals that might cause different biological consequences," says Yongna Xing, a UW–Madison associate professor of oncology at McArdle Lab and UWCCC. "This is why structural biology is absolutely crucial."

AHR is inactive in cells until it interacts with one of its chemical signals. Then, AHR changes its shape, exposing a part of the receptor protein that directs it to enter the nucleus where all the cell's DNA resides. Once in the nucleus, AHR partners with another protein, ARNT, and together they increase the expression of genes which correspond to the chemical signal that the AHR receptor protein "received."

Xing said researchers have been studying AHR for nearly five decades, but no clear explanation exists for how one protein can interact with so many different small molecule signals and then activate so many different genes. In contrast, AHR is very closely related to another protein, HIF1a, which also uses ARNT as a partner in the nucleus. Unlike AHR, however, HIF1a is responsive to merely a few chemical signals.

"Researchers in the field have proposed several hypotheses for how AHR might respond to different chemicals and cause different consequences, including how it targets different DNA sequences to express different genes," Xing says. "In the AHR structure, we showed it has a high flexibility, especially compared to HIF1a or other members in the same family, and that flexibility provides a basis for versatile mechanisms for responding to diverse chemicals."

In the structure, Xing and colleagues, including UW–Madison oncology professor Christopher Bradfield, show how AHR and ARNT interact with each other and with target DNA. The research team was able to examine the level of protein flexibility from the structure, where they found that AHR is higher than HIF1a. Just as a flexible person is better able to contort themselves than an inflexible person, AHR is able to adopt more changes in the protein structure upon chemical activation than HIF1a.

"This structure suggests that when the different chemicals bind to AHR, each one can induce just enough different structural changes in AHR so that it may regulate different populations of genes," Xing says. "At least, that's the potential mechanism provided by this structure."

With a three-dimensional map now in hand, any researcher interested in AHR can test how each chemical signal changes AHR's structure and function. Xing also expects that the AHR structure will allow researchers

to develop drugs that can block those chemicals associated with disease onset.

"AHR is a naturally-evolved machinery for our bodies to respond to many different environmental and cellular chemical cues and then cause different biological consequences, different readouts," Xing says. "Our goal is to gain enough knowledge on the structure-activity relationship of AHR and hijack this machinery to better control the harmful effects caused by AHR-responsive chemicals."

More information: Seung-Hyeon Seok et al. Structural hierarchy controlling dimerization and target DNA recognition in the AHR transcriptional complex, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1617035114

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