Determining the structure of nuclear receptor has implications for a host of diseases

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In a study published this week in *PLoS Biology*, Eric Xu and colleagues have determined the molecular structure of a nuclear receptor, which regulates the expression of specific genes within cells, that may serve as a drug target for diseases related to heart and blood vessel development, human embryonic development and female infertility. Researchers also found that the receptor, named COUP-TFII, is activated by retinoic acid, a form of Vitamin A.

"Not only does the structural information provide a basis for drug design in any diseases that COUP-TFII plays a role in, but it also can provide insight into the entire subfamily of receptors that COUP-TFII belongs to, which could have implications for additional associated diseases," said Xu, who heads the laboratory that published the findings.

The researchers determined the molecular structure of COUP-TFII through X-ray crystallography, which involved purifying the protein, growing crystals, directing X-rays at the crystals, and using the resulting information to determine the structure. Structural information can help drug developers fit therapeutics more perfectly to the receptors they bind to for maximum potency and can also aid in manipulating drugs to produce fewer side effects.

The findings could also have implications for cancer therapy. "Since COUP-TFII plays a role in embryonic blood vessel development, it might play a similar role in tumors and cancer growth," said Schoen Kruse, lead author of the study. "Formation of new blood supply in

tumors is a stepping stone in the ability of cancers to grow and metastasize within the body."

The signal-triggering molecules known as ligands, which activate nuclear receptors have been discovered for most receptors, but not for a subset of "orphan" nuclear receptors whose ligand remains unknown. The study's finding that COUP-TFII is activated by retinoic acid is significant since the receptor previously belonged to this subset of "orphan" receptors.

Citation: Kruse SW, Suino-Powell K, Zhou XE, Kretschman JE, Reynolds R, et al. (2008) Identification of COUP-TFII Orphan Nuclear Receptor as a Retinoic Acid–Activated Receptor. PLoS Biol 6(9): e227. doi:10.1371/journal.pbio.0060227
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