Scientists identify first synthetic activator of two critical proteins

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Scientists from the Florida campus of The Scripps Research Institute have identified a novel synthetic activator of a pair of proteins that belong to a protein family playing key roles in human metabolism and immune function. The discovery could provide new and potentially more effective therapeutic approaches to diseases ranging from diabetes to osteoporosis.

The study was published in the November issue (Volume 5, Issue 11) of the journal *ACS Chemical Biology*.

"This new compound is particularly important because it works in vivo, and it is selective for certain receptors," said Tom Burris, a professor in the Department of Molecular Therapeutics at Scripps Florida who led the study. "These two properties give it significant potential as a possible therapeutic compound."

The new discovery represents the very first synthetic ligand (binding partner) that functions as an agonist (activator) of retinoid-related orphan (ROR) nuclear receptor. Nuclear receptors are protein molecules that mediate hormone activity inside the cell; they have been implicated in the progress of a number of cancers, and have also become drug development targets for diseases including type 2 diabetes, atherosclerosis, and metabolic syndrome.

Although scientists don't know the full therapeutic significance of the new synthetic ligand, its potential usefulness is clear, Burris noted.

"For example, loss of RORα in animal models renders them resistant to weight gain," he said, "while RORγ has been shown to be involved in development of cells that are implicated in autoimmune diseases – and loss of RORγ results in animals that are resistant to these types of disease."

RORα has also been shown to be required for normal bone development; animal models lacking this receptor develop osteoporosis, strongly suggesting that RORα agonists may have potential as a treatment of this disease. Osteoporosis affects as many as 44 million Americans, according to the National Institutes of Health. Burris and his colleagues also discovered a pathway stimulating liver secretion of FGF21—which has been shown to treat diabetic animals—via activation of ROR. Diabetes is estimated to affect 23.6 million Americans, according to the National Institutes of Health.

Second Major Discovery

This new agonist is the second that Burris and his Scripps Florida colleagues have identified.

In 2009, Burris and Patrick R. Griffin, chair of the Department of Molecular Therapeutics and director of the Translational Research Institute at Scripps Florida, identified a high affinity synthetic inverse agonist of this same pair of nuclear receptors. An inverse agonist, which binds to the same site as an agonist, induces the opposite action of an agonist of that receptor.

For this new study, Burris said they used that first discovery, a compound known as T1317, as a molecular scaffold to synthesize an array of compounds and assess their activity against a number of receptors, including RORα and RORγ.

The one compound that stood out was SR1078, which displayed a unique pharmacological profile that indicated it had a high potential for use as a chemical probe for assessing ROR receptor function in general.

"Unexpectedly, we found that SR1078 functioned as a ROR agonist," Burris said. "When we treated cells with SR1078 we got a significant increase in RORα transcription. Similarly, with RORγ, SR1078 treatment resulted in a stimulation of RORγ dependent transcription activity. Basically, it produced more of these receptor proteins, significantly so."

More information: The first author of the study, "Identification of SR1078, a Synthetic Agonist for the Orphan Nuclear Receptors RORα and RORγ," is Yongjun Wang of Scripps Research. Others authors include Naresh Kumar, Philippe Nuhant, Michael D. Cameron, Monica A. Istrate, William R. Roush, and Patrick R. Griffin, also of Scripps Research. For more information on the study, see pubs.acs.org/doi/abs/10.1021/cb1002575

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