Study reveals new mechanism for estrogen suppression of liver lipid synthesis

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By discovering the new mechanism by which estrogen suppresses lipid synthesis in the liver, UC Irvine endocrinologists have revealed a potential new approach toward treating certain liver diseases.

With this finding, Dr. Ellis Levin and colleagues believe they are changing long-held views in the field. Study results appear in the May 21 issue of the journal *Science Signaling*.

"The dogma in the steroid receptor field for 50 years has been that only receptors located in the nucleus respond to steroid hormones by regulating genes that produce the developmental, functional and pathological effects of steroid hormones," said Levin, Professor of Medicine, biological chemistry and pharmacology, and Chief of endocrinology, diabetes and metabolism at UC Irvine and the VA Long Beach Healthcare System.

"In our study, we show that an estrogenic receptor compound acting at the cell membrane-based estrogen receptor alpha in the liver of transgenic and wild type mice suppresses all lipid synthesis. This includes cholesterol, triglycerides and fatty acids."

Levin said this occurs through AMP kinase signaling, which inhibits the processing of the key transcription factor for many lipid-synthesis pathways genes. This causes the transcription factor to be retained in cytoplasm and prevents lipid synthesis gene expression.

"This action occurs without any participation of the nuclear receptor pool," he added. "Thus, the membrane ER-alpha can regulate genes that produce a metabolic phenotype entirely unrelated to the nuclear receptor contributing."

Estrogen plays a role in liver functions, and may be a deterrent to liver cancer, as men get this type of cancer at a rate of four-to-six times more than women and animals models of this cancer show clear suppression by estrogen. The hormone also helps suppress the development of fatty liver, which can lead to liver damage and failure, and inflammatory liver disease that result from chronic hepatitis. Levin said that he and his colleagues are now testing compounds that target the membrane estrogen receptor in transgenic mice to see the impact for such diseases.

"We're re-thinking the whole idea of hormone replacement of estrogen by exploring ways to boost estrogen receptor action selectively in a positive way," he said. "This could include targeting one form of the receptor, or receptors at one location in cells but not all estrogen receptors."

Last month, Levin was honored with the 2013 Solomon A. Berson Distinguished Researcher Award and Lectureship from the American Physiological Society, Endocrinology Division. The award is in recognition of Levin's work on estrogen receptors outside the nucleus that mediates important functions of this steroid in breast cancer and the cardiovascular system, and is applicable to many other steroid receptors, including progesterone and androgen receptors in breast and prostate cancer, respectively.

Provided by University of California, Irvine

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