UT SOUTHWESTERN MEDICAL CENTER NEWS

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First 'encyclopedia' of nuclear receptors reveals organisms' focus on sex, food

DALLAS – Aug. 25, 2006 – Organisms thrive on sex and food, and so do their cells' receptors.

In creating the first "encyclopedia" of an entire superfamily of nuclear receptors – proteins that turn genes on and off throughout the body – UT Southwestern Medical Center researchers found that certain receptors form networks and interact to regulate disease states and physiology in two main areas, reproduction and nutrient metabolism.

Receptor networks also have key roles in metabolism's biological clock, researchers found.

The findings, published today in two studies in the journal *Cell*, chart the anatomy and timing of nuclear receptor expression throughout the body in hopes that researchers can uncover global receptor functions to improve prediction, diagnosis and treatment of diseases, from hypertension to diabetes.

"This 'systems biology' approach to look at the whole superfamily, not just individuals, is a new way to understand how nuclear receptors regulate physiology," said Dr. David Mangelsdorf, chairman of pharmacology and senior author of one study. "Remarkably, receptors break into two big clusters centered on reproduction and metabolism. So it really is all about sex and food.

"The power of this analysis is highlighting such receptor associations that may predict functions heretofore unknown. This really is pointing to new directions in biology."

Much already is known about individual nuclear receptors, which are proteins found in cell nuclei in reproductive, digestive and liver, immune, and many other tissue systems. Such receptors act as sensors for hormones and dietary molecules, binding to them to trigger gene expression.

Individual nuclear receptors are among the most successful targets for drugs currently available or being developed to treat a number of conditions, including reproductive disorders, cancer, diabetes, cardiovascular disease and high cholesterol. But how receptors work together to impact physiology has been largely unknown.

To find out, researchers from UT Southwestern and the Salk Institute in California collaborated on two studies to document the gene-expressing activity of the superfamily of 49 nuclear receptors, anatomically and in circadian rhythms – better known as the biological clock.

(MORE)

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In the anatomical study, researchers used mice to profile the location and activity of the superfamily of nuclear receptors. They found that receptors, by virtue of similar patterns of expression in certain tissues, separate into two main clusters to regulate reproduction and nutrient metabolism. Dr. Mangelsdorf said groups of receptors likely interact to control many processes, such as the use of diet-derived lipids as fuel for the body.

"You see that certain receptors have similar patterns in certain tissues. The common themes suggest that those receptors together regulate a similar regulatory circuit," said Dr. Mangelsdorf, an investigator in UT Southwestern's Howard Hughes Medical Institute and holder of the Doris and Bryan Wildenthal Distinguished Chair in Medical Science.

In the circadian study, researchers used mice to see how daily circadian rhythms influence the activity of the nuclear receptor superfamily in key metabolic tissues.

They found that the activity of more than half of receptors follow rhythmic cycles, so coordinated changes in receptor activity helps explain the cyclic behavior of metabolism. This also suggests that the superfamily acts as a mega-network to influence metabolism, rather than in a series of independent signaling pathways.

"Understanding timing patterns of receptors might help explain aspects of the out-of-rhythm states linked to many metabolic diseases," Dr. Mangelsdorf said.

Researchers detailed all receptor expression in the superfamily on a single poster, also published in today's *Cell*. Dr. Mangelsdorf said the poster will be a tool for researchers engaged in advanced investigation of the biological role of each receptor individually and as a superfamily. The paper and poster also are available online as part of the Nuclear Receptor Signaling Atlas (www.NURSA.org), a consortium of scientists working in the field of nuclear receptor science.

Other UT Southwestern researchers involved in the studies were graduate students Angie Bookout and Yangsik Jeong. The Salk Institute was involved in both studies, and the Texas A&M Health Science Center and the University of Virginia were involved in one.

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