SOUTHWESTERN NEWS

Media Contact: Amanda Siegfried
214-648-3404
amanda.siegfried@utsouthwestern.edu

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Researchers outline possible drug targets for treating metabolic syndrome

DALLAS – Aug. 10, 2005 – Ongoing studies by researchers at UT Southwestern Medical Center and other institutions have uncovered the biochemical basis of many of the factors contributing to what is known as the metabolic syndrome, suggesting potential new drug targets for treating the condition.

The metabolic syndrome, which affects more than 47 million Americans, is a constellation of disorders of the body's metabolism – such as abdominal obesity, hypertension and insulin resistance – that increase one's risk of heart disease, dangerous plaque buildup in artery walls and non-insulin-dependent diabetes.

In a review article in the Aug. 11 issue of *The New England Journal of Medicine,* UT Southwestern's Dr. David Mangelsdorf, professor of pharmacology and biochemistry, and Dr. Andrew Shulman, a Medical Scientist Training Program fellow, examine how one category of proteins found in the cell's nucleus, called retinoid X receptor heterodimers, are promising novel drug targets for treating the metabolic syndrome.

"Our research has taught us that these receptors are potentially legitimate therapeutic targets that show great promise," Dr. Mangelsdorf said. "But we also have learned that, as with any drug development, it is going to be a challenge to come up with the right drug or drugs to do the job."

The metabolic syndrome, sometimes referred to as syndrome X, is characterized by multiple risk factors, with the underlying causes being obesity, physical inactivity and genetic factors. The characteristic disorders present in the metabolic syndrome include: excessive fat tissue in and around the abdomen; high blood pressure; insulin resistance or glucose intolerance; blood fat disorders, mainly high triglycerides and low high-density lipoproteins, or "good" cholesterol; and abnormalities in blood clotting.

Any one of these disorders by itself is a risk for certain diseases, but in combination they can dramatically boost one's chances for developing life-threatening illnesses, said Dr. Mangelsdorf, a Howard Hughes Medical Institute investigator.

"One person may have a more severe case of type 2 diabetes, for example, or another person may not have hypertension, yet they may all have the syndrome," he said. "There's not one factor that overrides everything else. Lipid, or fat, metabolism is an important component, however, and in fact, lipid metabolism may drive the syndrome. The question is, why?"

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The answer may lie in research conducted by Dr. Mangelsdorf and others that identified the protein retinoid X receptor, or RXR, which play`s a key role in lipid metabolism. This protein can bind to several other so-called nuclear receptors to form distinct molecular complexes called heterodimers. Each complex then can go on to control certain genes involved in regulating lipid and cholesterol metabolism.

"When RXR is paired with a nuclear receptor called PPAR-gamma, for example, it activates one set of genes," Dr. Mangelsdorf said. "When RXR is paired with another receptor called LXR, it acts on a different set of genes. All of the genes, however, are involved with lipid metabolism."

Drugs that target RXR and its binding partners are already in clinical use or trials for the treatment of cancer, dermatological disorders, endocrine disorders and some aspects of the metabolic syndrome. In their review article, Drs. Mangelsdorf and Shulman outline promising research findings on how drugs that target RXR complexes may be used in the management of the metabolic syndrome.

One of the challenges to developing therapies targeting these receptors is that activating or blocking a given receptor can have both positive and negative effects on the body. The trick, Dr. Mangelsdorf said, is to develop drugs that selectively act on a particular receptor to activate only the good effects while dialing out the bad effects.

For example, activating the LXR receptor, which binds with RXR to modulate cholesterol levels, also has the effect of increasing fat synthesis, which is undesirable, Dr. Mangelsdorf said.

Some drugs that selectively modulate nuclear receptors have already proved successful as cancer drugs. For instance, tamoxifen citrate acts on estrogen receptors to selectively block the activity of estrogen in breast tissue while acting like estrogen in other tissues, where it slows bone loss and lowers blood cholesterol.

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