Scientists uncover new DNA role in modifying gene function

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For years, scientists have thought of DNA as a passive blueprint capable only of producing specific proteins through RNA transcription. Now, research led by scientists from the Florida campus of The Scripps Research Institute has shown DNA can also act to fine-tune the activity of certain proteins known as nuclear receptors.

These new findings may make it possible to design therapies that could activate specific genes in a highly targeted manner in a number of important diseases including osteoporosis, obesity, autoimmune disease, and cancer.

The study was published April 10, 2011, in the journal *Nature Structural & Molecular Biology*.

"This study offers the first direct evidence of what we now recognize as critically important interactions," said team leader Patrick R. Griffin, PhD, chair of the Department of Molecular Therapeutics and director of the Translational Research Institute at Scripps Florida. "This new understanding could lead to the development of ways to promote highly targeted activity, which is exactly what you need in order to produce safe and effective therapies."

The new study focuses on the interactions between a protein complex comprising the vitamin D receptor and the retinoic X receptor and their ligands, vitamin D and 9-cis-retinoic acid (a metabolite of vitamin A), respectively, as well as DNA, and a coregulatory protein. Receptors are

proteins to which one or more specific kinds of signaling molecules bind.

Scientists at Eli Lilly and Company collaborated on this study to better understand how vitamin D works at its most basic level, given that vitamin D plays a major role in bone health and is thus linked to the company's research platform in osteoporosis.

"These findings will potentially enable us to design safer medicines that work via the vitamin D pathway to help the osteoporotic patient," said Jeffrey A. Dodge, PhD, senior research fellow at Lilly. "Specifically, the technology developed at Scripps to understand these receptor ligand interactions has been critical and is a great example of industry-academia collaboration to solve important scientific questions."

Dynamic Interactions

In the new study, the scientists used a technology known as hydrogen-deuterium exchange (HDX) mass spectrometry to measure the interaction of various ligands with the vitamin D receptor complex. Ligands can be small synthetic compounds, hormones, other proteins, or DNA and they bind to large molecules such as proteins and change these molecules' behavior. In this study, the ligands were vitamin D, a metabolite of vitamin A, DNA, and a coactivator protein known as SRC1 (steroid receptor coactivator 1).

"HDX mass spectrometry is a high-precision, high-sensitivity mapping technique," Griffin explained. "With it, we can find the specific regions of the protein complex that are altered upon interaction with ligand. This information can be used to infer structural changes that are the result of a specific interaction."

In their research, the scientists found that DNA can actually alter the

structure and function of the receptor complex through a wide variety of long-range structural effects. These long-range effects had been hypothesized, but this study is the first to actually detect them directly with high spatial resolution. The changes wrought by these dynamic interactions were impressive.

The study shows these binding events have substantial consequences; for example, that the DNA binding at one site alters the stability of both the ligand binding site as well as coactivator interaction surface at opposite ends of the complex and vice versa. Those alterations influence a number of key processes, from coactivator-mediated interactions with various cofactors to the modification of the DNA binding domain so that the receptor can recognize specific DNA sequences.

"There is an elaborate biochemical dialogue going on between the receptor, ligand, coregulatory proteins, and the specific DNA sequence that the nuclear receptor complex is bound to," said Griffin. "But until this study, it was not completely clear what the structural basis for this crosstalk was."

More information: "DNA Binding Alters Coactivator Interaction Surfaces of the Intact VDR/RXR Complex," by Jun Zhang et al., *Nature Structural & Molecular Biology*.

Provided by The Scripps Research Institute