Study challenges conventional theory of modern drug design

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Scientists from The Scripps Research Institute have uncovered new evidence that challenges the current theory about a process key to the way modern drugs are designed and how they work in the human body.

The new study was published October 10, 2010 in an advance, online edition of the journal Nature Chemical Biology.

Currently, the theory about ligands – compounds that bind to proteins and trigger a specific biological action – and how they bind to proteins runs along the lines of a one person-one vote paradigm. Ligands are considered to be the relatively static partner in the process, and easily rejected if the protein dramatically changes shape.

In contrast, working with the molecular systems that recognize the hormone estrogen, the new Scripps Research study found that as protein receptors change shape ligands can adapt to that change, binding productively to both active and inactive structures.

"To our great surprise, the ligand bound differently to the active and inactive conformations of the receptor," said Kendall Nettles, an associate professor in the Department of Cancer Biology at Scripps Florida. "This strongly suggests a novel mechanism for managing [cell] signaling activity. The implications of this are profound, both for our understanding of how ligands regulate protein activity, and as a novel approach in drug discovery."

Changing the Drug Discovery Model

In the current study, the scientists worked with a receptor (which binds substances triggering certain biological effects) for the hormone estrogen and a well known estrogen receptor antagonist (which blocks the receptor). Estrogen receptors are activated by the hormone estrogen, which is one of two primary female sex hormones (the other is progesterone). Disturbances in estrogen levels play a role in number of disorders including cancers, heart disease, and stroke in women.

When ligands bind to a specific subset of receptors, the ligands stabilize specific protein conformations, turning on (or off) molecular switches that control diverse cellular functions. For example, the binding of the breast cancer treatment tamoxifen is specific for the inactive conformation of the estrogen receptor – this locks the receptor in place, blocks the active conformation and prevents tumor growth.

"Our new findings suggest that we need to think not only about an ensemble of protein conformations, but also an ensemble of ligand binding orientations when we think about therapeutic compounds," Nettles said. "As the protein and ligand move together, each can have a unique affinity, and activity profile, which working together defines the signaling output."

Nettles is excited by the possibility the new study suggests of working with an ensemble of ligand conformations, perhaps combining one with anti-inflammatory properties – which play a role in cancer – with another that blocks tumor growth. "This would give you dual therapeutic activity, potentially doubling the effectiveness of the treatment," he said.

Nettles is also eager to find out whether the new study's findings apply to other ligand-protein pairs. "If ligand dynamics turn out to be a general feature of small molecule signaling," he said, "then our findings have the

potential to transform how we think about chemical biology."

More information: "Coupling of receptor conformation and ligand orientation determine graded activity," John Bruning et al., *Nature Chemical Biology*.

Provided by The Scripps Research Institute