Finding Molecular Targets of an HIV Drug used in Cancer Therapy

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Use of chemical systems biology may represent the future of drug discovery

Researchers at the University of California, San Diego and Hunter College of the City University of New York (CUNY) have identified potential human molecular targets of the anti-HIV drug Nelfinavir, which may explain why the drug is also effective as a cancer therapy. Their study will be published in the online edition of *PLoS Computational Biology* on April 28.

Nelfinivir is a protease inhibitor that prevents replication of the HIV virus, but it has also been found to have a positive effect on a number of solid tumor types, and is currently in clinical trial as a cancer therapy. However, the mechanism of how the drug worked in humans was not clear.

The researchers discovered that Nelfinavir may interact with multiple human protein kinases – enzymes that modify other proteins and regulate the majority of cellular pathways. Protein kinases comprise approximately 2 percent of the human genome, and are important anti-cancer drug targets.

Surprisingly, the interactions between Nelfinavir and kinases are much weaker than those from more specific, rationally designed drugs, said Philip Bourne, PhD, professor of pharmacology at UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences. Bourne and colleagues suggest that it is the collective effect of these weak interactions that leads to the clinical efficacy of Nelfinavir.

The research team – Li Xie, PhD, from UC San Diego, Thomas Evangelidis, a former graduate student in Bourne's lab, now at the University of Manchester, and research scientist Lei Xie, PhD, now an associate professor at Hunter College, CUNY – combined a wide array of computational techniques to investigate the molecular mechanisms underlying Nelfinavir's observed anti-cancer effect.

While drug molecules are designed to bind to targeted proteins in order to achieve a therapeutic effect, small drug molecules can attach to off-target proteins with similar binding sites. The result may be unwanted side effects or, as in the case of Nelfinavir, a secondary and positive effect.

In the traditional strategy for drug discovery, scientists use high-throughput screening to find a suitable drug target. However, utilizing the RCSB Protein Data Bank – a worldwide repository of tens of thousands of three-dimensional protein structures – the UCSD researchers computationally compared binding sites in order to identify which proteins might be unintended targets.

Taking a single drug molecule, they looked at all proteins encoded by the human proteome to which that molecule could possibly bind.

"Computer analysis allows us to search for other binding sites that match a particular drug-binding site – like looking for other locks that can be opened by the same key," said Lei Xie.

While this novel computational pipeline is promising in fishing for drug targets from a significant portion of the human genome, Lei Xie cautioned that "it is especially challenging to validate weak drug-target interactions both computationally and experimentally." He added that modeling such drug actions requires that scientists find relevant proteins and then examine them in the context of a biological network, while at the same time simulating their cumulative effects.

"This is indeed challenging, but uncovering which protein receptors Nelfinavir binds to may help us design better anti-cancer drugs," said Bourne. "It is hard not to believe that this broad-based systems approach represents the future of drug discovery, at least as far as small-molecule drugs are concerned."

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