Study points to unexplored realm of protein biology, drug targets

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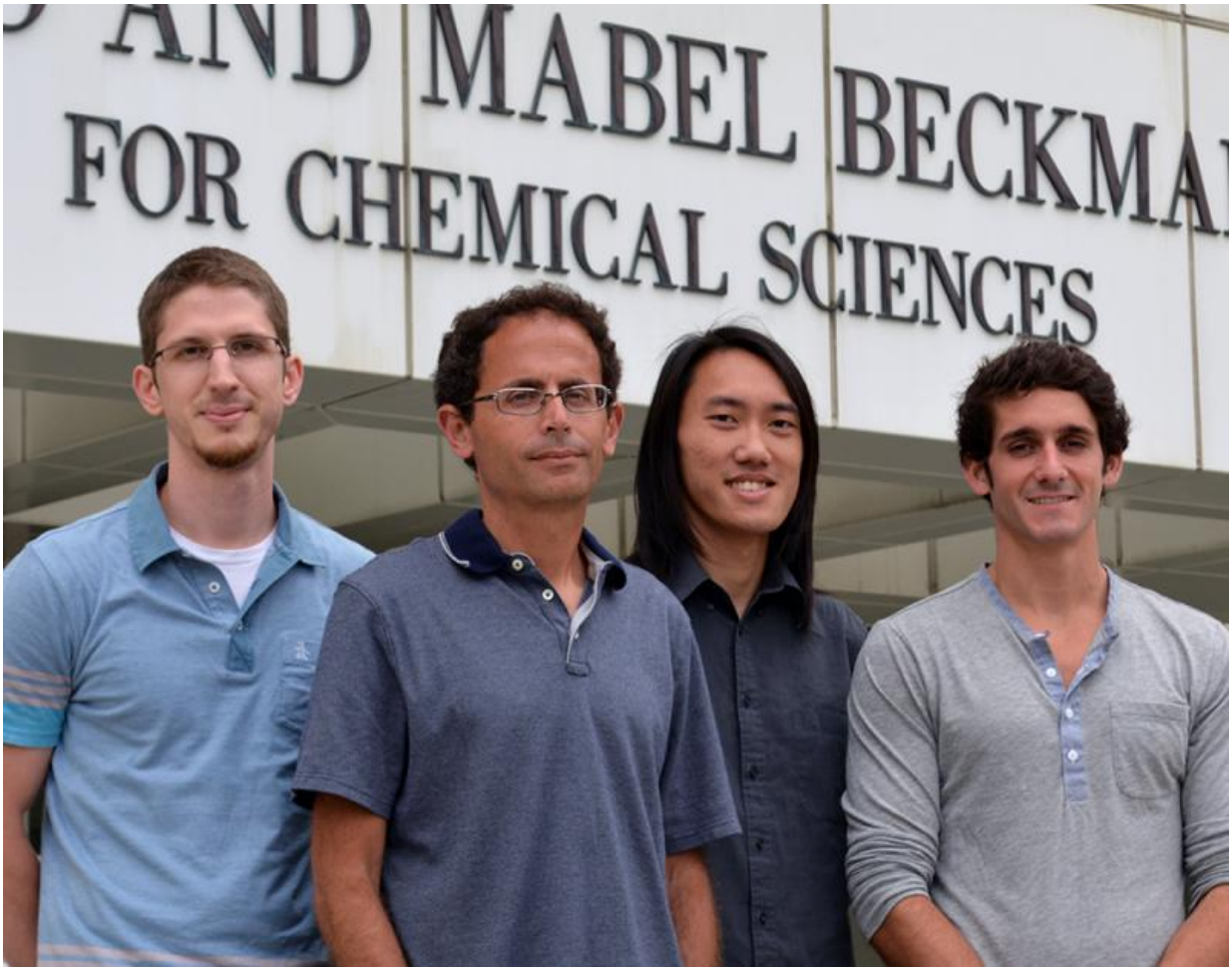

Authors of the new paper include (left to right) Micah Niphakis, Benjamin Cravatt, Kenneth Lum and Armand Cognetta III. Credit: The Scripps Research Institute

Scientists at The Scripps Research Institute (TSRI) have devised a powerful set of chemical methods for exploring the biology of proteins.

The techniques are designed to reveal protein interactions with lipids—a class of biological molecules including some vitamins (A, D, E), hormones (estrogen, testosterone), neurotransmitters (endocannabinoids) and components of fat (triglycerides, cholesterol).

'It has long been clear that lipids are important in biology, but it has been challenging to achieve a global portrait of how they interact with proteins,' said senior investigator Benjamin F. Cravatt, who chairs TSRI's Department of Chemical Physiology. 'This approach allows us not only to identify lipid-interacting proteins but also to discover small molecules or 'ligands' that selectively block these lipid-protein interactions, helping us to study their functions.'

In some cases, such ligands could become the basis for new drugs. In fact, initial surveys by Cravatt's team revealed a surprisingly large number of lipid-protein interactions—and while some of these interactions are already targeted by existing drugs, most are not.

'Traditionally, scientists have theorized fairly narrow limits on which proteins can be targeted with small-molecule ligands, but our results suggest that those boundaries are much wider,' said Cravatt.

The team's findings were reported in the journal *Cell* on June 18.

Surprising results

The study, whose co-first authors were Micah Niphakis, who at the time was a postdoctoral fellow in the Cravatt laboratory, and graduate student Kenneth M. Lum, emerged from an effort to discover protein-binding partners of arachidonoyl lipids, which are involved in many

physiological responses such as pain, inflammation, mood and appetite.

Niphakis began by making probe molecules that mimic the structure of arachidonoyl lipids and capture protein-binding partners when exposed to ultraviolet light. He found that each of the probes fastened to hundreds of distinct proteins in human and mouse cells. Probes mimicking other lipids also revealed large sets of protein interactions.

A big challenge in using the lipid probes was to determine which protein interactions were likely to be selective and biologically relevant and not just random, weak bindings. 'One way we addressed that challenge was to use multiple, structurally distinct probes to look at the differences in how they bound to a given protein,' said Niphakis.

As Niphakis and his colleagues worked with the probes, they found they could quickly generate extensive maps of a given lipid's protein-binding partners and, in many cases, even map the region of the protein that the lipid probes bound—information that could be put to multiple uses.

Profiling drug compounds

One was to profile the activities of any drug compound, essentially by comparing how lipid-protein interaction maps change in the presence of the drug. Such changes would be due largely to the drug's interference with lipid-protein binding events. The team found that, while some drugs they tested this way were highly selective in the sense that they bound only to their intended protein targets, others showed evidence of strong bindings to additional, 'off-target' proteins—which could produce their own biological effects.

Similarly, the TSRI researchers used their lipid probes to make a high-throughput screening assay to discover ligands that bind to proteins at their lipid interaction sites. In one case, the researchers screened a small-

molecule compound library and identified compounds that bind tightly to NUCB1, an otherwise little-known protein that showed strong interactions with the arachidonoyl probes. The researchers then employed these ligand compounds to study NUCB1's functions in detail, showing, for example, that it facilitates the breakdown of endocannabinoids and related lipids, perhaps by acting as a transporter.

The Cravatt laboratory is now using the same approach to study the functions of other proteins in their lipid interaction maps.

'There are a lot of proteins in our dataset that haven't been characterized, yet have strong interactions with our lipid probes,' said Cravatt.

In principle, a similar approach could be used to discover and study protein interactions with other, non-lipid types of biomolecules. 'Alternative probes would be valuable for surveying other types of metabolite-protein interactions,' said Niphakis.

More information: 'A global map of lipid-binding proteins and their ligandability in cells,' *Cell*, 2015.

Provided by The Scripps Research Institute

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