CHEMICAL BIOLOGY

Ligandable proteome mapping

Stereochemically defined chemical probes aid discovery of ligandable proteins.

Proteome-wide identification of proteins that can be specifically targeted by small molecules is crucial for the discovery of chemical probes and novel therapeutic targets. Fragment-based ligand discovery (FBLD) approaches have allowed the discovery of small-molecule binders for a variety of proteins, but traditional FBLD is challenging to scale. Benjamin Cravatt's and Christopher Parker's research groups at the Scripps Research Institute, along with collaborators from academia and industry, have been developing methods for proteome-wide identification of ligandable proteins. Their 2017 paper in *Cell* demonstrated that thousands of reversible fragment–protein interactions could be discovered directly in human cells. The initial approach, however, gave fragment–protein interaction profiles with complicated structure–activity relationships (SARs) that hindered confident assignment of some liganding events.

The researchers, led by graduate student Yujia Wang, have now improved the mapping by using enantiomeric probe pairs, or 'enantioprobes', that allow identification of stereoselective interactions across protein classes. They reasoned that after minimizing the physicochemical differences between fragment pairs, any observed differences in proteome-wide stereoselectivity would provide evidence of authentic ligand–protein interactions. Using eight pairs of enantioprobes to evaluate two human cell types (human peripheral blood mononuclear cells and HEK293T cells), they observed preferential enrichment of 176 proteins by at least one member of the enantioprobe pairs. Proteins identified in both cell lines showed consistent profiles and included not only the obvious targets such as enzymes, but also some surprising targets, such as scaffolding and adaptor proteins and transcriptional regulators. Binding details of four proteins showed that known ligands and enantioprobes shared binding sites on these proteins. The technique is amenable to multiplexing for quantitative mass spectrometry–based proteomics to enable higher throughput target identification with SAR analysis.

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Research papers
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