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Perspective

Chemoproteomics: Techniques to Identify and Interrogate Protein-Small Molecule Interactions

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DESCRIPTION

Chemoproteomics refers to a set of approaches for detecting and analysing protein-small molecule interactions. Chemoproteomics supports phenotypic drug discovery, a paradigm in which lead compounds are intended to interact with specified disease-driving biological targets rather than target-based drug discovery, in which lead compounds are designed to engage with disease-driving biological targets. Chemoproteomics provides essential follow-up tactics to narrow down potential targets and finally validate a molecule's mechanism of action, as phenotypic drug discovery assays do not provide validation of a compound's mechanism of action. By investigating protein-small molecule interactions on a proteome-wide scale, chemoproteomics seeks to solve the difficulty of drug promiscuity in small molecule drug discovery. Chemoproteomics aims to define the interactome of drug candidates in order to learn more about off-target toxicity and polypharmacology processes.

The use of pharmacological analogues that chemically change target proteins in solution, tagging them for identification, are used in solution-based methods. Immobilization-based techniques aim to isolate the targets or ligands by tying their binding partners to a stationary support. By examining changes in protein stability or drug chromatography upon binding, derivatization-free techniques try to infer drug-target interactions.

Computational approaches are utilised to develop structural models that inform lead optimization and augment the chemoproteomic toolset as parallel lines of evidence supporting prospective drug-target combinations. Chemoproteomics has been used to identify several high-profile therapeutic targets, and the on-going improvement of mass spectrometer sensitivity and chemical probe technology suggests that chemoproteomics will play a significant role in future drug discovery.

Broad proteome and transcriptome profiling has led to numerous improvements in the biomedical field; however RNA and protein expression characterisation is limited in its ability to provide information on protein functional properties.

Because transcript and protein expression data leaves gaps in our understanding of the effects of post-translational modifications and protein-protein interactions on enzyme activity, as well as the fact that enzyme activity varies across cell types, disease states, and physiological conditions, specialised tools are needed to profile enzyme activity across contexts.

Furthermore, many discovered enzymes have yet to be properly described to give actionable pathways on which functional tests might be based. Chemical methods are required to detect drug-protein interactions because there is no basis for a functional biological readout.

Activity-based protein profiling

The approach of activity-based protein profiling was created to track the availability of enzyme active sites to their endogenous ligands. The ABPP method employs specifically engineered probes that enter and make a covalent link with an enzyme's active site, indicating that the enzyme is active. Covalent labelling of an enzyme indicates drug binding because the probe is usually an analogue of the drug whose mechanism is being examined.

A site-directed covalent warhead (reactive group), a reporter tag, such as biotin or rhodamine, and a linker group are the three key functional elements in ABPP probes. The reporter tag might vary based on the downstream readout and is used to validate enzyme labelling with the reactive group. Fluorescent moieties, which permit imaging, and affinity tags, such as biotin, which allow for the pull-down of labelled enzymes and analysis via mass spectrometry, are the most extensively used reporters.

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Photo affinity labelling

Photo affinity labelling probes require activation by photolysis before covalent bonding to a protein, unlike ABPP, which results in protein labelling upon probe binding. This is made feasible by the presence of a photo reactive group. The drug scaffold is usually an analogue of the drug whose mechanism is being investigated, and it binds to the target reversibly, which better simulates how most medicines interact with their targets. Photo reactive groups come in a variety of forms, but they are essentially distinct from ABPP probes: ABPP labels nucleophilic amino acids in a target's active site, whereas photo affinity labelling is non-specific and so can be used to label a broader spectrum of targets.