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The Significant Role of Chemo Proteomics and its Applications

Rosemary Yates*

Department of Pharmacy, University of Zambia, Zambia, South Africa

Commentary

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***For Correspondence:** Rosemary Yates, Department of Pharmacy, University of Zambia, Zambia, South Africa

Email: y.rosemary@gmail.za

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DESCRIPTION

Chemo proteomics (also known as chemical proteomics) refers to a wide range of techniques used to detect and investigate protein-small molecule interactions. Chemoproteomics supplements phenotypic drug discovery, a paradigm in which lead compounds are discovered based on their ability to alleviate a disease phenotype, as opposed to target-based drug discovery (reverse pharmacology), in which lead compounds are designed to interact with predetermined disease-driving biological targets. Because phenotypic drug discovery assays do not confirm a compound's mechanism of action, chemo proteomics provides valuable follow-up strategies to narrow down potential targets and ultimately validate a molecule's mechanism of action. By analysing protein-small molecule interactions on a proteome-wide scale, chemo proteomics attempts to address the inherent challenge of drug promiscuity in small molecule drug discovery. Chemo proteomics assays are classified into three types. Drug analogues that chemically modify target proteins in solution, tagging them for identification, are used in solution-based approaches. Approaches based on immobilization seek to isolate potential targets or ligands by anchoring their binding partners to an immobile support. Derivatization-free approaches seek to infer drug-target interactions by observing changes in protein stability or drug chromatography as a result of binding. Computational techniques are used to generate structural models that inform lead optimization and complement the chemo proteomic toolkit by providing parallel lines of evidence supporting potential drug-target pairs. Several high-profile drug targets have been identified using chemo proteomics, and the continued advancement of mass spectrometer sensitivity and chemical probe technology suggests that chemo proteomics will play a significant role in future drug discovery.

Applications

Drug ability: Chemo proteomic approaches have been used to broaden the range of drug gable targets. While successful drugs in the past have targeted well-defined binding pockets of drug gable proteins, these only account for about 15% of the annotated proteome. Bold approaches to ligand discovery are required to continue expanding our pharmacopoeia. The use of ABPP has coincidentally re-energized the hunt for newly ligand able sites. ABPP probes, which are intended to label enzyme active sites, have been found to unintentionally label many nucleophilic regions on a variety of proteins. These unintended reactions, which were initially thought to be experimental noise, have led researchers to the discovery of sites that could potentially be targeted by novel covalent drugs. This is especially true for proteins with no enzymatic activity to inhibit or for drug-resistant proteins. Proteins in any of these cases may be targeted for degradation using the novel drug modality of Proteolysis-Targeting-Chimeras (PROTACs). PROTACs are small molecules with heterobifunctional functions that are designed to interact with a target and an E3 ubiquitin ligase. Because of the interaction, the E3 ubiquitin ligase is brought close enough to the target to label it for degradation. The presence of potential covalent binding sites throughout the proteome suggests that many drugs can be covalently targeted using such a technique.

Drug repurposing: Chemo proteomics is at the cutting edge of drug repurposing. This is especially important in the aftermath of COVID-19, when there was an urgent need to identify FDA-approved drugs with antiviral activity. A phenotypic screen is typically used in this context to identify drugs with a desired *in vitro* effect, such as inhibition of viral plaque formation. If a drug passes the test, the next step is to determine whether it acts on a known or novel target. Thus, chemo proteomics is a step after phenotypic screening. Friman et al investigated the off-target effects of Remdesivir, a broad-spectrum antiviral that was among the first repurposed drugs used in the COVID-19 pandemic. TRIP13 was discovered as a potential off-target of Remdesivir through thermal proteome profiling in a HepG2 cellular thermal shift assay, along with the controversial drug hydroxychloroquine.

High-throughput screening: Because the chemical libraries used in screening have not been optimized against any targets, approved drugs are never identified as hits in high-throughput screens. Methods such as affinity chromatography and affinity selection-mass spectrometry, on the other hand, are workhorses of the pharmaceutical industry, with AS-MS in particular producing a significant number of hits across many classes of difficult-to-drug proteins. This is largely due to the large number of ligands that can be screened in a single assay.