COMMENTARY

Pharmacological chaperones in the age of proteomic pathology

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In the age of "big data," where thousands of proteins or protein precursors can be interrogated and assembled into large-scale networks, it is still the case that in the setting of disease singular proteins act as hubs in driving pathology (1). Once identified, a pathogenic protein—which can be deficient, dysfunctional, or even overly abundant—becomes a legitimate target for drug discovery. In some cases the protein is an enzyme, receptor, or channel, with easily identifiable and functional binding sites against which pharmaceuticals can be designed with predictable effects (2). In fact, most currently available drugs are directed against this class of proteins. Many pathogenic proteins, however, do not neatly fall into this category. Among the ~20,000 proteins that make up our proteome, the vast majority falls outside of this rare category, and are therefore not easily "druggable" when implicated in a disease.

The Promise of Pharmacological Chaperones

It is for this reason that various technologies that affect transcription or translation, collectively and loosely called "gene therapy," have held such high clinical promise. The challenges inherent in gene therapy, for efficacy but mainly for safety, are well documented, and it has yet to transform the pharmaceutical landscape (3). At the other end of a protein's life cycle, drugs can target proteasome or lysosome degradation pathways. The trick for this class of agents is specificity: how to alter intracellular degradation mechanisms and yet only affect the levels of singular proteins (4). If these two general approaches target the "birth" or the "death" of proteins, a relatively new approach, termed "pharmacological chaperones" (5), is designed to specifically target proteins during their pathogenic lives.

As such, pharmacological chaperones seem well positioned to fill a major need in drug discovery. Moreover, these chaperones seem particularly timely, as they are a perfect match for current molecular technologies, such as gene expression and proteomic profiling, which often characterize diseases by the pathogenic deficiencies of select proteins (for example, refs. 6 and 7). However, since the concept of pharmacological chaperones was introduced just over a decade ago (8), a number of technical barriers have hindered their wide-scale application and utility in drug discovery. The paper by Oh et al. (8) in PNAS sets out to tackle some of these barriers head on.

Borrowing its name from chemical chaperones, in the original formulation the term pharmacological chaperones was used to describe small molecules that, when bound to a protein, prevent or correct its pathogenic misfolding (9). However, the term is now used more broadly. Pharmacological chaperones are small molecules that bind to proteins and by virtue of stabilizing their 3D structures, protect them from degradation, thereby increasing their steady-state concentration in the cell (5).

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Screening for Pharmacological Chaperones

The greatest challenge in isolating effective pharmacological chaperones is that most pathogenic proteins do not possess natural binding sites. Prior knowledge of a protein's 3D structure provides a tractable solution to this problem, as this information can be used to identify a protein's potential "docking sites," to which chaperones can bind (10, 11). Although in some instances whether a small molecule will act as a pharmacological chaperone can be inferred (12), high-throughput screening of a compound library carries with it greater flexibility and promise. Working together with Greg Petsko and Dagmar Ringe, we have recently showed how an in silico high-throughput screening approach was able to isolate pharmacological chaperones directed against retromer (13), a multiprotein assembly implicated in Alzheimer's disease (7).

The elegant study by Oh et al. (8) introduces a complimentary high-throughput method for the identification of pharmacological chaperones, particularly those related to protein–protein interactions. The motivating goal of the study was to generate a novel compound library enriched with pharmacological chaperones, which if achieved could potentially obviate the need to predetermine the 3D structure of a targeted protein. In doing so, the authors relied on the observation that short α-helical peptide segments, spanning two to three helical turns, often play key roles in protein–protein interactions. Oh et al. therefore reasoned that small molecule α-helix mimetics would constitute a family of pharmacological chaperones, and based on this logic they synthesized a small molecule library containing a diverse range of α-helix mimetics.

Providing proof-of-principle, Oh et al. (8) then applied this library to isolate putative pharmacological chaperones directed against proteins thought to play pathogenic roles in either cancer or in Parkinson disease. Myeloid cell leukemia-1 (MCL-1) is a protein that is apparently thought to play a role in cancer progression by binding members of the B-cell lymphoma-2 homology domain-3 family of proteins. Using a high-throughput screen, the authors were able to identify small molecule α-helix mimetics that inhibit this binding. Next, Oh et al. screened their library and successfully identified small molecules that reduced the aggregation of the protein α-synuclein, aggregates that are thought to play a pathogenic role in Parkinson disease. As the authors admit, it remains unknown whether the putative small molecule binding

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to α-synuclein "prevented it from aggregating, either by masking the surfaces that directly involve in aggregation or by preventing its conversion/misfolding into aggregation prone species" (8).

Based on the motivating logic of targeting α-helix peptides, and as Oh et al. argue is the case for MCL-1, the mode of action of these small molecules seem to at least in part interfere with protein–protein interactions. If true, this would expand the definition of pharmacological chaperones from small molecules that act primarily to stabilize proteins, to include small molecules that can also inhibit pathogenic protein–protein interactions.

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