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Drug Discovery Using X-Ray Crystallography

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Introduction

Structure-based research relies heavily on X-ray crystallography. The validity, accuracy, and precision of a protein or nucleic acid structure determined by X-ray crystallography can be evaluated from three different perspectives: I the nature of the diffraction experiment; ii) the interpretation of an electron density map; and iii) the interpretation of the structural model in terms of molecular weight. X-ray crystallography, which offers the benefit of more precisely delineating ligand binding sites, has just lately proved relevant in lead discovery. New approaches to high-throughput methods, many of which have been pioneered by academic groups interested in structural genomics, have made this possible.

High-throughput crystallography can now be used to identify and define the binding sites of molecular fragments that bind to protein targets. It can then be used as a quick method to guide lead optimization. Crystallization experiments are required in drug design after the three-dimensional structure of the target Apo-protein is available in order to create appropriate crystals of the small molecule–protein combination. Even when crystallisation conditions for the ligand-free protein are well established, the production of crystals of the complex may not be straightforward, depending on the scenario under consideration. Furthermore, after obtaining crystals and solving the crystal structure, it is very common to discover that the ligand did not bind to the protein at all [1].

Description

High-throughput crystallography

Protein crystallography is a multifaceted endeavour. Automating all aspects of the protein crystallographic process, including protein expression, characterization, crystallisation, and structure determination, is becoming a hot topic. The expression system used can have a big impact on a protein's yield and activity. Because of its speed, low costs, high yields, and absence of post-translational modification, E. coli is frequently the first choice; nevertheless, many eukaryotic proteins express poorly, if at all, or form inclusion bodies that must be refolded. Switching to insect cell or yeast expression has resulted in significant gains. Microplate format growth and expression screening procedures have recently been detailed for both of these systems, allowing them to be better exploited. The purified target protein's biophysical characterization is a crucial step in the crystallisation process. Although solubility is an excellent indicator of a well-folded protein, NMR and circular dichroism can provide results that are more accurate. Heterogeneity can be determined using dynamic and static light scattering, and oligomer state can be determined using analytical ultracentrifugation [2,3].

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The art of interpreting electron density maps

In fact, an appropriate data-to-parameter ratio can only be obtained by using additional restrictions based on prior knowledge of macromolecule characteristics. The biggest distinguishing property of both proteins and nucleic acids is that they are linear polymers made up almost entirely of the same subunits. In the case of proteins, this results in well-studied stereochemistry of amino acids and peptide bonds, as well as a clear chemical identity. In fact, an appropriate data-to-parameter ratio can only be obtained by using additional restrictions based on prior knowledge of macromolecule characteristics. The fact that proteins and nucleic acids are linear polymers made up almost entirely of a small number of common subunits is their greatest distinguishing property [4,5].

This results in well-studied stereochemistry of amino acids and peptide bonds in proteins, as well as the chemical identity of the polymer represented by the polypeptide sequence being clear. However, because there are so many distinct organic compounds that could be discovered, creating a comprehensive library to span the chemical space is a difficult undertaking. Biological macromolecules (even recombinant ones) are virtually always separated from *in vivo* sources before crystallisation (or any other *in vitro* analysis). As a result, a given macromolecule may have been exposed to tens of thousands of different small molecule compounds endogenous to the expression organism, not to mention the dozens of compounds and reaction products found in the purification and crystallisation buffers, by the time a crystal has formed [1,2].

Lead discovery from high-throughput crystallography

The small molecules can then be visualized using difference Fourier techniques by collecting sets of X-ray data on each soaked crystal under identical conditions. Automatic procedures enable the rapid structure solution of protein–ligand complexes by interpreting and analysing the X-ray data without the need for manual intervention. For a cocktail, the various molecules can be fitted to the difference electron density and ranked. This then allows complete automation of the system once the initial protein crystals have been characterised and the structures solved. This necessitates the employment of a focused set of pieces. These could come from any of a number of places. A general set of fragments, chosen from successful drug-like molecules by expert medicinal chemists based on molecular weight, hydrogen bond donors and acceptors, and solubility, proved to be highly useful. Another set can be produced via target virtual screening, which is the process of systematically docking a huge library of candidate fragments into a three-dimensional model of the target protein's designated binding/active site in a computer [2].

Conclusion

Crystallography has long played a role in drug discovery by assisting with lead optimization. High-throughput techniques have been pushed by structural genomics consortia, which are generally coupled with synchrotron sources, and these are revealing the structures of more potential targets in human and disease species. However, one of the most intriguing developments is in lead discovery, where high-throughput structural screening identifies small compounds that bind tightly and could be fragments of larger molecules that could be candidates for new medications.

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Conflict of Interest

The author reported no potential conflict of interest.

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