Trends in Biochemical Sciences | Technology of the Month

Emerging Role of Electron Microscopy in Drug Discovery

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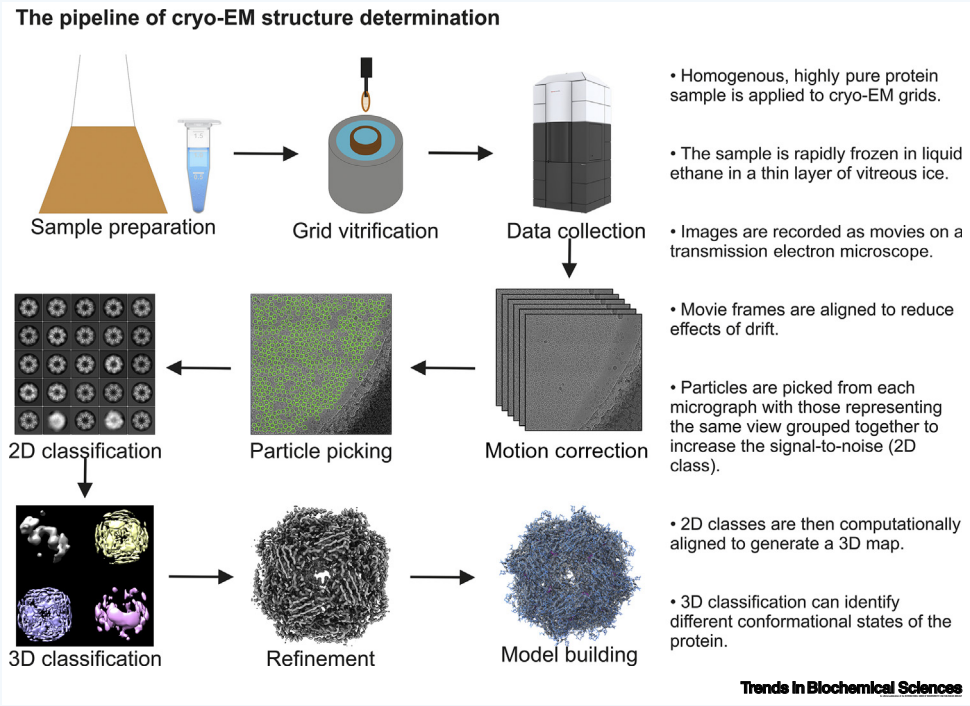
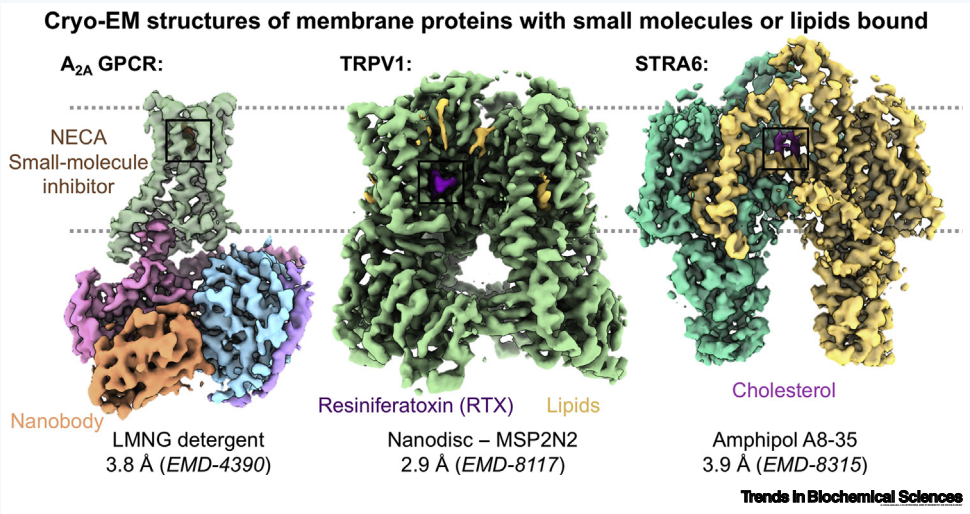


Electron microscopy (EM) has emerged as an invaluable structural technique with recent technological advances enabling high-resolution structures to be determined. This, in turn, has revolutionised potential applications of EM, particularly in the drug discovery field. Once the preserve of X-ray crystallography, cryo-EM now plays an important role in drug discovery programs, especially for difficult targets that had previously proved challenging for structural characterisation, such as membrane proteins.



Although membrane proteins represent approximately 30% of all known proteins and are over 60% of drug targets, they represent only 2% of existing crystal structures. Advances in cryo-EM have provided structures of therapeutically important targets including gamma secretase, human ether-à-go-go-related K^+ channel (hERG), Piezo, and cystic fibrosis transmembrane conductance regulator (CTFR) that had previously proved intractable to crystallography. Moreover, it is possible to study membrane proteins

ADVANTAGES:

Resolutions obtained in cryo-EM structures have enabled visualisation of small molecules, lipids, and antibodies bound to proteins, thus aiding drug discovery programs.

A wide range of systems can be studied including membrane proteins, viruses, ribosomes, large protein complexes, and filaments.

Different conformational states can be identified within a single data set.

Smaller amounts of purified proteins (microgram rather than milligram) are needed for EM compared with X-ray crystallography or NMR.

Boundaries are continuously being pushed with size (52 kDa) and resolution limits (1.6 Å) constantly decreasing, thus expanding the scope of the proteins of which cryo-EM can determine the structure.

CHALLENGES:

The timescale for structure determination is days to weeks, which is low throughput for structure-based drug discovery campaigns.

Cryo-EM cannot currently be used to screen large compound or fragment libraries as it would struggle to identify compounds with weak binding affinities (millimolar) in the same way that X-ray crystallography or NMR can.

Grid preparation can be challenging with inconsistencies in ice thickness and particle distribution.

Although getting better, resolutions attained are typically lower than X-ray crystallography–derived structures.

Instrumentation and access to EM facilities can be challenging.

Computational infrastructure for image processing can be a significant investment.

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in more native environments, improving drug design with structures in more physiologically relevant environments.

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