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Revolutionising the field of structural biology with cryo-electron microscopy

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Cryogenic electron microscopy (cryo-EM) is a technique that involves flash-freezing solutions of biomolecules like proteins and then bombarding them with electrons to produce good quality images. Through these images, the three-dimensional (3D) structure of proteins can be developed, followed by their function and consequent changes in structure that may lead to malfunction and diseases. Although the sequences of the primary structure of many proteins have been formulated, not many 3D structures of proteins are known, thereby slowing down the progress towards using them as targets for various therapeutic purposes. The cryo-EM technique, developed by Joachim Frank, Richard Henderson and Jacques Dubochet won the Nobel prize in 2017 and has emerged as an indispensable tool towards solving this issue. It involves the use of electron microscopes that use electrons instead of light as a source of illumination. As the wavelength of electrons is much less than light, they give way better resolution and clarity. The first step involved in cryo-EM is the preparation of a purified protein sample which is then passed through a grid of tiny holes in a film supported by a metal frame. The grid is then plunged into a cryogen such as liquid ethane (flash freezing). This is followed by fixing the particles in amorphous carbon where they are also protected from radiation as well as evaporation of the buffer occurs. Transmission electron microscopy is carried out and images are collected using sophisticated software. Therefore, the 2D data generated is used to create a 3D map using image processing tools on a computer. The sequence of the protein is fitted into the map to create the final 3D model of the desired protein. There are various advantages of this method, such as no requirement of any stains/dyes as well as a variety of very small amounts of samples can be processed and studied. Cryo-EM has accelerated the process of drug discovery by determining structures of target compounds like receptors and ligands. It has helped in creating 3D models of various proteins including enzymes like beta-galactosidase, DNA gyrase, glutamate dehydrogenase and many other proteins, namely viral capsids and mitochondrial proteins. It has also helped in identifying molecular targets for the treatment of various diseases like cancer and many others. The development of cryo-EM has surely revolutionised the field of structural biology with a lot more structural and functional studies to be carried out in the future.

Keywords: Structural biology, Cryogenic electron microscopy, Electrons, Biomolecules Transmission electron microscopy, Cryogen, 3D modelling

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