provide more information on the core dynamics of this important family of enzymes.

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Early cryo-EM work

Visualizing the structure underlying a biological process provides a wealth of information. The need to 'see' biological macromolecules or assemblies in action has motivated the development of techniques that provide high resolution views of these molecules. In the 1950s, electron microscopy (EM) had defined the structures of organelles, giving us views of the Golgi apparatus and nucleus. Through the continuous development of instrumentation, specimen preparation and data processing methods together with the advance of powerful computers, EM has provided near atomic resolution structures of several important molecules (for example, the α/β heterodimer of tubulin) that are not easily amenable to studies by either X-ray crystallography or NMR.

An EM micrograph contains two-dimensional (2D) projections of the objects being imaged. To reduce sample movement and to increase the contrast of the image, biological specimens were usually dehydrated, fixed by crosslinking and stained with heavy metal compounds. However, this harsh treatment could easily distort structures and thus introduce artifacts into the image. In 1974, Taylor and Glaeser[1] reported the recording of electron diffraction data at near liquid N_2 temperature (~100 K) in an electron microscope from a frozen thin plate crystal of catalase in its hydrated state. This technique enables biological particles to be imaged under physiological conditions. Moreover, data collection at low temperature reduces sample damage by the electron beam, improving the resolution of the EM images. This paper thus marks the early development of cryo-EM.

Closely related to the development of EM data collection at low temperature was the design of control experiments to determine whether structures were affected in the freezing process. In 1983, Lepault *et al.*[2] carefully examined the effects of the amount of hydration and the formation of ice crystals during different freezing procedures on structural preservation in different types of biological samples, including a thin plate crystal of catalase, the purple membrane from *Halobacterium halobium* containing bacteriorhodopsin, and T4 bacteriophage. Their results clearly demonstrated that particles embedded in a thin layer of amorphous ice were better preserved than those containing ice crystals. This finding made it possible to freeze molecules at different stages of a biological process for imaging, and the procedure is in widespread use today. Cryo-EM complements X-ray crystallography and NMR to provide pictures of biomolecules in action — the advances in this field have established a solid tool for structure determination.

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