MAPPING MOLECULAR LANDSCAPES INSIDE CELLS BY CRYOELECTRON TOMOGRAPHY

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Electron Tomography (ET) is uniquely suited to obtain three-dimensional (3-D) images of large pleiomorphic structures, such as organelles or even whole cells. While the principles of ET have been known for decades, its use has gathered momentum only in recent years. Technological advances have made it possible to develop automated data acquisition procedures. This, in turn, allowed reducing the total electron dose to levels low enough for studying radiation sensitive biological materials embedded in vitreous ice. As a result, we are now poised to combine the power of high-resolution 3-D imaging with the best possible preservation of the specimen.

In the past, ET has mainly been used to examine thin sections of plastic-embedded materials. This approach has provided valuable insights into cellular architecture, but it falls short of revealing the macromolecular organization inside cells. ET of frozen-hydrated whole prokaryotic cells or thin eukaryotic cells grown directly on EM grids provides 3-D images of macromolecular structures unperturbed and in their functional environment at molecular resolution (2-4 nm).

Such tomograms contain vast amounts of information; essentially they are 3-D images of the cell's entire proteome and they should ultimately enable us to map the spatial relationships of macromolecules in a cellular context. However, it is no trivial task to retrieve this information, because of the poor signal-to-noise ratio of such tomograms and the crowded nature of the cytoplasm. Advanced pattern recognition methods are needed for detecting and identifying specific macromolecules based on their structural signature. Provided that high- or medium-resolution structures of the molecules of interest are available, they can be used as templates for a systematic interrogation of the tomograms. Once the challenges of obtaining sufficiently good resolution and comprehensive libraries of template structures become available, we will be able to map the supramolecular landscape of cells systematically.

References:

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