https://doi.org/10.1038/s41594-025-01510-y

From atoms to cells

We discuss work at the forefront of structural cell biology featured in this issue.

Molecular and structural biology are traditionally based on a reductionist approach to living systems: taking apart individual molecular components, pathways and processes to understand how they work as a part of a more complex whole. It is becoming increasingly clear, however, that a more cogent description of biological processes will need to encompass a systems-level logic that considers the complexity of organizational hierarchies across various scales, accounting for emergent phenomena, biological noise, redundancies and statistical effects.

In this issue, and featured on the cover, a study by Xue et al. from the Mahamid and Schacherl labs demonstrates how pushing the resolution limits of a technique called in-cell (in situ) cryo-electron tomography (cryo-ET) enables bridging the atomic and cellular scales.

As opposed to single-particle cryo-electron microscopy where biological molecules are studied in isolation, in situ cryo-ET examines molecules in their native environment. Whole cells are flash-frozen and sliced into exceedingly thin lamellae, which are then imaged under an electron beam in cryogenic conditions. Images taken at different angles allow 3D reconstruction of the molecular components inside this cellular slice.

Xue et al. imaged bacterial cells treated with the antibiotic chloramphenicol with cryo-ET. The resulting datasets not only confirmed previous in vitro structural studies that had unveiled the antibiotic's mode of action by context-specific inhibition of translation elongation but also showed that there were increased collisions between individual translating ribosomes upon chloramphenicol treatment and signs of activation of cellular stress response. As such, valuable contextual information allowed the researchers to not only understand the interaction between the antibiotic and ribosomes but also its molecular and cellular effect on the functional landscape of ribosomes and polysome arrangements. This is a remarkable example of work integrating the determinism of structural biology with the contextual cues of cellular-level complexity. The study is elegantly summarized in an associated Research Briefing.

As another example, in this issue, Lily Yeh Jan and Yuh Nung Jan discuss a family of proteins that can function as ion channels and/or lipid scramblases. While the proteins are structurally related within the protein family, their functions are diverse, and the Review highlights the need to study the channel and scramblase activities in cells at an organellar level if we are to decipher these functional disparities. We envision that in situ structural biology will likewise have a far-reaching effect on illuminating the roles of membrane proteins in their physiological environments.

Taking apart individual pathways and molecular components continues to be invaluable foundational knowledge. We are enthusiastic about studies advancing our understanding of structural and molecular biology, whether they analyze purified components or intact cells. While in-cell and single-particle structural biology occupy complementary niches, we are looking forward to more studies connecting the scales to construct more expansive paradigms.

Published online: 18 February 2025