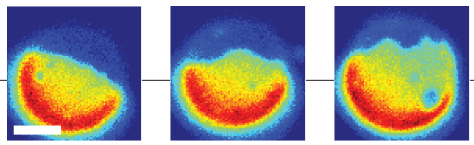
In this ISSUE

acs chemical biology

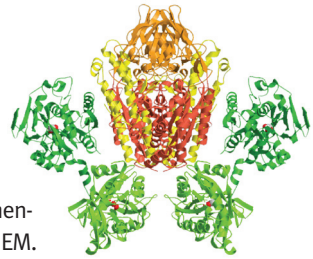


Vesicles Reach a Critical Point

Very little is known about the physical properties behind how plasma membrane lipids participate in various cellular processes. Further, because the physical properties of lipid raft domains of plasma membranes are by-and-large unknown, this has hindered the study of lipid-mediated lateral organization in membranes. Veatch *et al.* (p 287 and Point of View p 265) isolate giant plasma membrane vesicles (GPMVs) from living cells that show phase coexistence and temperatures of miscibility in the room-temperature range.

The authors analyzed the thermodynamic behavior of the isolated GPMVs and found that the critical fluctuations fit the 2D Ising model, a mathematical model that is applied to 2D phases near critical points. On the basis of these studies, the authors suggest that plasma membranes are adapted for existence near a miscibility critical point. The authors extended current knowledge to hypothesize that lateral heterogeneity in membranes corresponds with critical fluctuations.

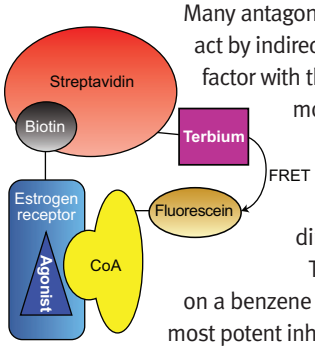
Molecular Electron Microscopy



Traditional electron microscopy (EM) has been used to determine the structure of cells or tissues, whereas molecular EM is used to visualize subcellular biological structures that are often difficult to see by other means. Stahlberg and Walz (p 268) present a comprehensive review on the state of the art in molecular EM. The review describes the use of the three approaches in molecular EM, namely, electron crystallography, single-particle EM, and electron tomography, in visualizing the structures of biological molecules. The review also highlights some of the challenges that currently exist in molecular EM and efforts in improving existing technologies.

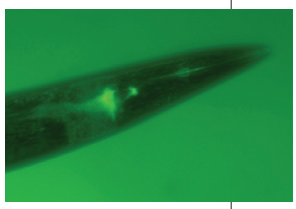
Blocking the Estrogen Receptor

Estrogen receptor α (ER), associated with breast cancer and a number of endocrine disorders, is activated upon binding of natural or synthetic estrogens. Many antagonists of ER, such as the cancer drug tamoxifen, act by indirectly hindering interaction of this transcription factor with the steroid receptor coactivators (SRCs) that modulate gene transcription. However, inhibitors that utilize this approach often suffer from drug resistance. Gunther *et al.* (p 282) describe a new class of potent inhibitors of ER that directly blocks SRC recruitment.



The authors synthesized small molecules based on a benzene core and found that these were among the most potent inhibitors of the ER–SRC interaction known *in vitro* and *in vivo*. These compounds increase the repertoire of chemical tools available for dissecting the activity of estrogen receptor action. In addition, these compounds may also serve as useful leads in the discovery of drugs for use in the clinic when resistance to current therapeutic agents is observed.

Arrested Development



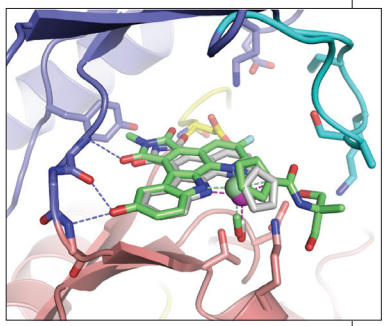
Chemical cues from the environment are particularly effective in influencing development and aging-related processes in animals. In the nematode *Caenorhabditis elegans*, a number of small molecules have been shown to elicit the induction of dauer, a resting state. Baiga *et al.* (p 294) elucidate the mechanisms of trafficking of fluorescent derivatives of naturally occurring small molecules in *C. elegans*.

The authors described the uptake and localization of a number of labeled small molecules and found that that those that triggered dauer accumulated in the cuticle of the pharynx. Subsequently, these molecules are transported to amphid neurons to induce the resting state. This study sheds light on how certain natural products can influence the development of a model organism.

Proving the Mettle of Organoruthenium

Organic compounds with metal centers are useful for designing drugs with anticancer properties. Drugs such as cisplatin that contain platinum have been used for decades now. More recently, there has been interest in the potential of organometallic compounds containing the metal ruthenium as scaffolds in drug discovery. Xie *et al.* (p 305) describe an organoruthenium compound that selectively inhibits the activity of phosphatidyl-inositol-3-kinases, a lipid kinase with oncogenic properties.

By resolving the structure of the target kinase complexed with a lead inhibitor, the authors were able to determine how to increase potency and specificity. The authors then took the most potent and selective inhibitor and probed the effects in cancer cells. The proliferative and migratory properties of these cells were reduced upon treatment. Ultimately, the extensive structural analysis of the target kinase with the new inhibitor should aid in the design of derivatives that could be used as cancer drugs.



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