INTRODUCTION

Lights, Camera, Action

AT THE END OF A LONG DAY IN THE LAB, WHAT WE’D ALL LIKE IS AN award-winning movie. What makes for a good movie? An engrossing story, deft cinematography, and an extraordinary ensemble of actors. The goal of single-molecule research is to produce a movie of the cell. Biochemistry and biophysics done in the test tube already provide an understanding of the dynamic behavior of molecules; from these studies, what goes on in cells, minute by minute or even second by second, can be inferred. Ultimately, however, the goal is to film single molecules in single cells, focusing in closely enough not only to observe spatial and temporal characteristics but also to decipher molecular mechanisms. We’re not there yet, but recent advances in single-molecule techniques bring us tantalizingly close to a molecule-scale movie of cellular life.

Because cells are optically transparent, light microscopy is ideal for noninvasive imaging of cells in three dimensions. However, until recently, the resolution of lens-based optical microscopes was constrained by the diffraction barrier, which gave a resolution cutoff at half the wavelength of light. In his Review, Hell (p. 1153) discusses concepts that show how the diffraction barrier can be broken in fluorescence spectroscopy and how these techniques have been applied to achieve nanoscale resolution. His Review gives hope that real-time three-dimensional imaging of live cells with electron-microscopy resolution may not be too far away.

Many single-molecule techniques remain in vitro, but take on the challenge of transferring the results into the realm of cellular systems. In their Review, Evans and Calderwood (p. 1148) describe how combining molecular cell biology with single-force spectroscopy provides a tool to explore eukaryotic cell adhesion, revealing how forces applied to cell-surface bonds affect intracellular interactions or chemical reactions. Although these techniques are a powerful probe of mechanical function, understanding molecular mechanisms generally requires molecular dynamics simulations of atomic structural molecules. Sotomayor and Schulten (p. 1144) describe in silico single-molecule experiments that use steered molecular dynamics simulations to explore how macromolecules respond to external forces at an atomic level.

Two Reports in this issue also highlight single-molecule techniques. In in vitro experiments, Shiroguchi and Kinohita (p. 1208) provide a clear view of myosin V motion, showing that it walks using a combination of lever action and Brownian motion. Elf et al. (p. 1191) use single-molecule imaging of the lac repressor to directly observe the function of this regulatory system in live Escherichia coli cells.

In related online resources, Science’s Signal Transduction Knowledge Environment (STKE) focuses on how single-molecule analysis is increasing understanding of cellular signaling (www.sciencemag.org/sciext/singlemolecules/). Chazin describes how x-ray crystallography and nuclear magnetic resonance studies have provided insights into the function of Ca\(^{2+}\)-sensing proteins. Navratil et al. discuss the application of microfluidic technology to the counting of low-abundance proteins in single cells, and Ghosh and Wirth present an algorithm for analyzing the movement of receptors in the plasma membrane.

We’ll be watching with interest as single-molecule approaches move us toward a quantitative and mechanistic understanding of cellular processes.

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