Intracellular transport is crucial to diverse physiological tasks. The cell employs multiple mechanisms to meet the demands of rapidly transporting cell contents of varying size over large distances, ranging from microns to up to a meter, to support specific physiological tasks. In a recent issue of Cell, Guo et al. (2014) developed a technique, force-spectrum microscopy, to measure intracellular forces and demonstrate that large motion of cellular components can be produced by random ATP-dependent fluctuations within the cytoplasm.

Intracellular transport of organelles and proteins is driven by multiple ATP-dependent processes. Recently in Cell, Guo et al. (2014) developed a technique, force-spectrum microscopy, to measure intracellular forces and demonstrate that large motion of cellular components can be produced by random ATP-dependent fluctuations within the cytoplasm.

Here, Guo et al. (2014) provide the first measurements to directly characterize these ATP-dependent yet random forces within the cytoplasm. The authors measured the mechanics of the cytoplasm using optical tweezers to apply forces to inert particles microinjected into the cytoplasm. The authors found that the cytoplasm was predominately elastic, meaning that particles tend to return to their original position after the force is removed. In the presence of solely thermal forces, this would result in constrained motion of large beads within the cytoplasm, as depicted in Figure 1B. However, when the authors measured the spontaneous (e.g., in the absence of external force) motion of particles and organelles within the cytoplasm, they observed motion that appeared diffusive (Figure 1D, dark blue).

This is a quite surprising result: how is diffusive-like motion produced in an elastic network? This diffusive transport could be explained by a model in which active forces build and release stochastic force buildups within an elastic network (MacKintosh and Levine, 2008), as has been previously observed in reconstituted actomyosin networks (Mizuno et al., 2007). While the forces still retain the random nature of thermal forces, the magnitude of their effect on object displacement is much larger. In order to test this idea, the authors developed a technique, termed force-spectrum microscopy (FSM), allowing them to utilize optical tweezer-based force measurements in combination with tracing spontaneous particle movements to deconstruct the stochastic force.
components that govern particle displacement. The authors demonstrated that these diffusive-like motions are highly ATP dependent and are eliminated upon depletion of the chemical energy source.

Guo et al. then made important connections to the transport of proteins and organelles within the cytoplasm. Using FSM, they found that the motions of endogenous organelles and vesicles matched those of microinjected particles. This indicates that this type of random active motion may drive the movements of large organelles within the cell body. Moreover, they observed that the diffusion coefficient of a soluble globular protein was also ATP dependent, indicating that similar processes may affect transport at much smaller scales, which may have implications for biochemical regulation (Figure 1D, dashed black). Intriguingly, they found that a malignant epithelial cell exerted higher stochastic forces than normal epithelial cells, with particles showing larger random movements in malignant cells. This suggests that these types of random active forces may influence physiological processes and contribute to disease progression.

Clarifying how the material properties of the cytoplasm are tuned to allow transport in response to active forces while maintaining mechanical integrity of the cell is a subject for future work. The cytoplasm of cells examined in Guo et al. (2014) has mechanical properties of an elastic solid yet retains (or improves upon) the ability of a fluid to transport objects via diffusion-like motion. Identification of the ATPases that regulate cytoplasmic noise may provide further insight into the regulation of this behavior in healthy and malignant cell types. For instance, such effects could alter cell metabolism or invasion. These results provide a new understanding of how cells make use of random ATP-dependent forces and cytoskeletal materials to support robust intracellular transport.

REFERENCES


Figure 1. Expected Motions for Small and Large Intracellular Particles

(A) Schematic of the crowded intracellular environment, including actin networks at the cell cortex (red rods) and microtubules (green). (B) Large particles in crowded environments (top left) or cytoskeletal networks (top right) are confined. Their MSD reaches a plateau at long timescales (bottom, solid cyan curve). Small particles may diffuse with random trajectories within gaps, as shown by dashed gray lines (top panels). This behavior produces an MSD that rises linearly with time (bottom, dashed black curve). (C) Molecular motors moving along tracks may transport objects along straight trajectories. In this case, the MSD is ballistic and rises as the square of the time delay (bottom). Similar motion is produced for large and small particles. (D) Addition of random ATP-driven fluctuations modifies the motion of objects from (B). Large particles are no longer trapped but may also show diffusive-like MSDs due to the random motions (bottom, solid cyan curves). Small particles still display diffusive-like behavior, but the larger amplitude of active compared to thermal fluctuations produces faster transport (bottom, dashed curves).