the more detailed explanations and proofs are relegated to the appendix. A useful common thread in this section and throughout the entire book is the comparison of the relative strengths of the multitude of forces that act upon small molecules. The first section will go a long way in guiding the less physically or mathematically inclined to a better understanding of principles critical to single molecule processes.

The second section advances beyond hypothetical proteins to the three major cytoskeletal filament systems—actin filaments, microtubules, and intermediate filaments. After concise chapters about the structure and mechanics of the cytoskeleton, the focus of the section is three chapters that discuss the forces and process of polymerization. Unfortunately, the first of these chapters discusses multiple simplistic models of polymerization that ignore the role of nucleotide hydrolysis in polymerization. While this was seemingly done to allow the reader to better appreciate the role of nucleotide hydrolysis discussed later, this approach may make the subject more difficult for those that are not already familiar with current models of dynamic instability.

The heart of *Mechanics* is definitely the five-chapter motor proteins section, where motility models are examined from four distinct points of view: structure, speed, ATP hydrolysis, and step forces of motor proteins. The structural chapter provides a synopsis of several decades of structural studies into the different motor families. As such, it does not provide all the details of structural conformations involved in the mechanochemical cycle, but it illustrates the similarities between kinesin and myosin and provides a good foundation for the following chapters. The next two chapters do a superb job relating the duty cycle of motors (the percentage of time they are bound to the cytoskeleton) to the speed and processivity of motors, and describing the ATP hydrolysis cycle of motors in an intelligent fashion. These concepts are not easy to convey, and Howard's treatment of these subjects is a strength of the book. Examinations of motor step sizes and the forces involved using optical tweezers are among some of the more glamorous experiments in biology, and the chapter describing these experiments both portrays how these experiments are carried out and provides the main conclusions of studies on multiple motors.

The last chapter examines myosin and kinesin motility and attempts to summarize and integrate concepts discussed throughout the book by relating the microscopic single molecule and macroscopic in vivo worlds of motors. Howard's personal model of how two-headed kinesin may move hand-over-hand is presented at the expense of other models that are present in the field. I would have preferred active and in depth discussion of the strengths and weaknesses of multiple models from the mechanical perspective provided throughout the book. For this reason, future readers of the book may want to remember that *Mechanics* does not always relate all sides of the motor story.

Mechanics is not meant to be an all-inclusive tome on motor proteins; it succeeds by focusing specifically on the mechanics of molecules involved in cellular motility. The book is a great launching point for gaining a biophysical understanding of the current detailed literature of motility which is increasingly filled with mathe-matical models describing motility data. As such, it will benefit students of a wide range of biological and physical backgrounds who are interested in understanding the nuts-and-bolts of cellular motility. The organization and reductionist theme of the book readily lend themselves to discussion of basic physical concepts and principles. In summary, *Mechanics* provides an oblique and refreshing perspective to the motility field that will guide those new to the field to an appreciation of the mechanics of cellular motility.

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Endocytosis: Molecules, Membranes, and Movements

Endocytosis
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In transmission electron micrographs, the peripheral cytosol of a typical eukaryotic cell is dominated by a profusion of membrane-bound organelles and small membrane intermediates. Several decades ago, these images, along with emerging subcellular fractionation techniques, led to the birth of the field of intracellular protein trafficking. In time, the internal membrane-bound structures that sparked this line of investigation were characterized, revealing a central tenet of membrane-based protein and lipid movements within the cell: the endoplasmic reticulum–Golgi complex–plasma membrane–endosome–lysosome interrelationship. We know now that the morphological complexity of these static images belies the dynamic nature of membrane traffic within the cell. Lipid and protein flux is relentless and organelle identity is only maintained by complex sorting decisions and precise targeting mechanisms.

Endocytosis is the process of internalization and subsequent sorting of macromolecules from the cell exterior. The endocytic pathway thus shuttles material along specific but varied itineraries between the plasma membrane, endosomes, lysosomes, and the Golgi apparatus. Endosome, of course, does not describe a single, morphologically homogeneous functional organelle, but is rather a blanket term for a malleable and pleiomorphic population of membrane structures charged with overseeing diverse trafficking operations with a high degree of fidelity. Here, form recapitulates function. Shortly after uptake, membrane-bound transport carriers fuse to form early endosomes. These peripherally located early endosomes quickly and efficiently segregate recycling plasma membrane proteins into thin tubular emanations

for passage back to the surface. Material destined for deeper endocytic elements remains within a central globular core. With ongoing membrane fission and fusion events and migration toward the perinuclear region of the cell, the central portion of an early endosome metamorphs into an elaborate network of internal whorls and vesicles, the multivesicular late endosome. Specific membrane regions of endosomal structures are thus embodied with distinct sorting, retention, and partitioning domains (Sonnichsen et al., J. Cell Biol. 125, 1015–1024, 2000). Molecular integration and kinetic interplay of these sorting domains determines individual trafficking circuits within the overall compartment. If one is left with a single overriding impression on completing Endocytosis, it must be that the diversity and operation of the protein machinery orchestrating these steps is truly remarkable, outstripping the morphological complexity of the endocytic compartment many fold.

One process that is considerably more complex than initially suspected is the formation of endocytic clathrin-coated vesicles. These vesicular carriers are perhaps the major portal of entry into most cell types and important developments in this area are chronicled in chapter 1, and also in chapter 2, which counterpoints clathrin-dependent and -independent uptake. It has long been established that, in vitro, the principle coat components, purified clathrin trimers and the AP-2 adaptor complex, can assemble into polyhedral structures remarkably similar in morphology to clathrin-coated buds and vesicles. With the demonstration of direct protein–protein interactions between AP-2 and select cargo proteins, the central working paradigm for coat-assisted vesicle transport was set: adaptors, living up to their name, provide the molecular link between coat assembly and cargo selection. Yet, in living cells, things are not quite so simple. While AP-2 binds to cargo (and clathrin) only weakly, interactions with other, previously unrecognized noncargo proteins are substantially more robust. Proteins like amphiphysin, eps15, dynamin, synaptojanin, epsin, numb, HIP1, and Dab2 arrived. Complex webs of protein-protein connections, driven largely via modular interaction domains, unearthed still more proteins—intersectin, endophilin, and syndapin. These additional proteins are known to have important functions in endocytosis and are not simply onlookers in the process. But why are so many endocytic cofactors, or accessory proteins as they have come to be termed (Slepnev and De Camilli, Nat. Rev. Neurosci. 1, 161–172, 2000), needed? Ideas on the role of some of the accessory proteins in clathrin-coat assembly are presented in chapters 1 and 2 and also briefly in chapter 9. No current model integrates mechanistically all of the accessory proteins into the process of clathrin-coat assembly and budding, but these chapters are clear and thorough, leaving the reader with a good overall picture of the process. Since the first portion of the book is structured as if progressing from the cell exterior to deep within the endocytic pathway, what is known of the molecular basis of alternate internalization routes, phagocytosis and macropinocytosis, is covered in the subsequent two chapters.

The section covering late endosomes and lysosomes (chapter 6) deftly highlights yet another important principle of intracellular trafficking—phylogenetic conservation and the complementarity of yeast and mammalian studies. We learn that material destined for lysosomal degradation transits the late endosome but must be segregated from the reused components that are spared destruction when the late endosome fuses with the lysosome. Morphological studies show that before encountering the lysosome, epidermal growth factor receptors (EGFR) move into intralumenal endosomal elements. In Saccharomyces cerevisiae, late endosomes are not usually discernible morphologically, but correct delivery to the yeast equivalent of the lysosome, the vacuole, also depends on the formation of multivesicular endosomes. Genetic screens have uncovered two lipid kinases, Vps34p and Fab1p (sequentially producing phosphatidylinositol 3-phosphate and phosphatidylinositol 3,5-bisphosphate), that are essential for involution of endosomal membranes and for proper targeting of vacuolar proteases. Homologs of these regulatory inositide kinases exist in mammals, and trafficking phenotypes remarkably similar to yeast kinase mutants can be induced in cultured cells with the lipid-kinase inhibitor wortmannin. Yet making the inwardly oriented buds is not sufficient to ensure delivery of appropriate cargo into intralumenal structures. Active sorting is of course required and here, it has just emerged, ubiquitin has been exploited (Katzman et al., Cell 106, 145–155, 2001). A molecular complex of three class E vacuolar protein sorting (vps) proteins, Vps23p, Vps28p, and Vps37p regulates passage of monoubiquitin-tagged molecules into the involuting vesicles. This sorting paradigm is clearly evolutionarily conserved because ubiquitination of the EGFR by the c-Cbl E-3 ligase propels the activated receptor toward the lysosome. This directed movement of the EGFR is counteracted by mutation of tumor susceptibility gene (Tsg) 101, the mammalian Vps23p ortholog. In Tsg101 mutants, activated EGFR spills back out onto the cell surface because they are not sorted properly into multivesicular endosomes. Broad phylogenetic conservation is also clear in the discussion of macropinocytosis (chapter 4) and in the consideration of endocytosis in learning and memory (chapter 9). The actin cytoskeleton plays a prominent role in endocytosis in yeast (chapter 10), but conservation of this aspect in higher organisms is only now becoming apparent.

Throughout the book, common principles are apparent: signal-dependent protein sorting, the prominent role of the cytoskeleton and, perhaps the most universal of concepts, SNARE and Rab-protein regulated membrane fusion underpinning compartmental specificity. Cell-specific adaptations, as in antigen presentation, are also carefully covered in Endocytosis. For the nonimmunologist, chapter 8 provides a particularly clear and well illustrated overview of how, within the endocytic compartment, antigenic peptides are produced from endocytosed macromolecules, loaded onto major histocompatibility complex class II, and then redirected back to the cell surface. In recent years, microorganisms have also provided some important insights, and subversion of the endocytic pathway by various pathogens is considered in the final chapter. Because the multivesicular endosome is a critical junction of trafficking paths, it is frequently a site of modulation. For example, it has just