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MEETING REVIEW

The Palade Symposium: Celebrating Cell Biology at Its Best

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A symposium was held at the University of California, San Diego, to honor the contributions of Nobel Laureate, George Palade, to cell biology. The speakers included Günter Blobel, on the structure and function of nuclear pore complexes; Peter Walter, on the unfolded protein response in health and disease; Randy Schekman, on human disease-linked mutations in the COPII machinery; Scott Emr, on the regulation of plasma membrane composition by selective endocytosis; Roger Kornberg, on the structure and function of the transcription machinery; Peter Novick, on the regulation of rab GTPases along the secretory pathway; Jim Spudich, on the mechanism of the enigmatic myosin VI motor; and Joe Goldstein, on the function of the Niemann-Pick C (NPC)-linked gene products, NPC1 and NPC2, in cholesterol transport. Their work showcased the multidisciplinary nature, diversity, and vitality of cell biology. In the words of George Palade, their talks also illustrated "how cell biology could be used to understand disease and how disease could be used to discover normal cell biology." An integrated understanding of the cellular machinery will be essential in tackling the plethora of questions and challenges posed by completion of the human genome and for understanding the molecular mechanisms underlying human disease.

A SYMPOSIUM IN CELEBRATION OF CELL BIOLOGY

With the advent of electron microscopy (EM) in the 40s and 50s, George Palade, Keith Porter, and their colleagues were discovering new structures and organelles within the cell with each new micrograph. These pictures were displayed outside their labs along the hallways of Rockefeller University: each one posing new questions and opening new doors of investigation for the current and next generation of scientists to explore. The excitement and challenges of the burgeoning field of cell biology led them to found the American Society for Cell Biology in 1960.

Fifty years later, a symposium was held at the University of California, San Diego (January 28, 2010) to celebrate George Palade's accomplishments and contributions to cell biology. It attracted some 40 disciples and more than 300 colleagues and admirers of Palade, who passed away in October 2008. It was also a splendid celebration of cell biology. The field is alive and well, and more relevant than ever. Organized and hosted by Gordon Gill, Larry Goldstein, and Marilyn Farquhar, the speakers included three Nobel Laureates, Günter Blobel, Roger Kornberg, and Joe Goldstein, as well as other cell biology luminaries, Peter Walter, Randy Schekman, Scott Emr, Peter Novick, and Jim Spudich. (Video recordings of their talks have been posted online at http://georgepalade.ucsd.edu.)

Cells are the fundamental unit of life; hence the overarching goal of cell biology is to unravel the complexity, paradoxical simplicity, and elegance of the mechanisms governing life. These goals and the success of cell biology in tackling them were evident in the talks presented. Although the speakers had spectacular individual stories, certain themes ran through the day that epitomized the past, present, and future of cell biology. Overriding each of the presentations was an esthetic sense of the beauty of the cell. Quoting from Palade's 1974 Nobel Lecture (Palade, 1974), Spudich recounted how Palade was inspired by the elaborate organization of the pancreatic acinar cell, "It's pictures had for me the effect of the song of a mermaid: irresistible and half transparent."

Theme 1: Use Structure to Reveal Function

Palade's Nobel Prize citation emphasized his discovery of the ribosome. Indeed, cell biology is rooted in identifying organelles and macromolecular machines and then asking the questions: what does this organelle/machine do?, how is it assembled?, and most importantly, how does it work? In his opening remarks, Günter Blobel quoted Frances Crick as stating, "If you don't understand function, study structure." Cell biologists continue to be guided by structures across all scales starting with the dynamic behavior of cellular processes visualized by live cell fluorescence microscopy, to super-resolution light microscopy, EM tomographic reconstructions of organelles, cryo-EM structures of protein complexes, and finally high-resolution x-ray and NMR struc-

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The videotapes of the full lectures of this Symposium are available at http://georgepalade.ucsd.edu.

Figure 1. Marilyn Farquhar introducing a speaker at the Palade Symposia, UCSD.

tures of individual molecules and large machines. The day's talks provided several striking examples of how high-resolution structures have provided mechanistic insights into the inner workings of the cell.

Günter Blobel described work by his and other labs on the structure and function of the nuclear pore complex (NPC), which he called "the most sophisticated and beautiful transport complex." In mammalian cells, NPCs are assembled from ~500 subunits of ~30 different proteins (called nucleoporins or Nups), and are a total of 120 MDa in size (Cook *et al.*, 2007). Eucaryotic cells segregate their genetic material in a double membrane-bounded compartment: the nucleus. Consequently, proteins (e.g., ribosomal subunits and transcription factors) and protein–RNA complexes must be continually shuttled from the nucleus to the cytosol and back through the pores. In mediating this huge volume of bidirectional traffic, NPCs face the challenge of efficiently transporting highly diverse cargos, while maintaining selectivity.

To understand how NPCs accomplish this task, Blobel and his colleagues have taken a "Lego" approach and solved high-resolution structures of key pieces from a heptomeric complex (the Nup84 complex) that forms the core of the NPC. They can then reassemble these pieces to provide insight into the operations of this complex cellular machine. Two striking findings emerge. The first is that the core components of the NPC are structurally related to coat components involved in vesicle budding from the endoplasmic reticulum (ER; Brohawn *et al.*, 2008; Debler *et al.*, 2008; Kampmann and Blobel, 2009) as previously predicted from bioinformatic analysis (Devos *et al.*, 2004). This may reflect the evolution of the nuclear envelope through coat-mediated invagination of the proto-eucaryotic plasma membrane. The second is the conformational flexibility of both the core constituents and the FG (phenylalanine-glycine) repeat-containing tentacles that fill the nuclear pore. Blobel speculated that the "wobblicity" of the NPC core could allow its diameter to fluctuate and accommodate cargos of varying sizes (Melcak *et al.*, 2007; Nagy *et al.*, 2009). The unstructured, hydrophobic character of the FG-repeat containing Nups, which interact directly with import factors, provides a fluctuating selectivity barrier (a highly dynamic molecular sieve) through which cargo must be escorted and actively transported (Terry and Wente, 2009).

Roger Kornberg described his structural and biochemical studies of other large cellular machines that work together for regulated transcription (Kornberg, 2007), which is at the heart of controlling cell differentiation and function. These include RNA polymerase II (PolII, 12 subunits; 513 kDa; Bushnell and Kornberg, 2003; Chung *et al.*, 2003), general transcription factors (GTFs, 25 subunits; 1558 kDa; Liu *et al.*, 2010), mediator (20 subunits; 1003 kDa; Davis *et al.*, 2002), and more recently, the RSC complex (15 subunits, 1000 kDa) involved in chromatin reorganization (Chaban *et al.*, 2008; Lorch *et al.*, 2010). Two meters of human DNA is tightly packed into the nucleus in the form of chromatin: the DNA is wound around nucleosomes to form the fundamental particle of the chromosomes. Yet nucleosomes inhibit transcription from the promoters wrapped around them. The RSC complex functions to unravel nucleosomes allowing access to the transcription machinery, which together determines which proteins are expressed in which cell and under which conditions (Boeger *et al.*, 2004).

Theme 2: Cell Biology Demands a Multidisciplinary Approach

Unraveling the mechanistic underpinnings of complex cellular processes requires a multidisciplinary approach, including genetics, biochemistry, biophysics, and structural biology. Importantly, the cell biologist's efforts are not complete until these mechanisms and processes are studied and integrated within the living cell. This fundamental principle was understood by Palade (Palade, 1974), who stressed the necessity of "obtaining detailed and-if possible-comprehensive data on the chemistry and function of the different membranes of the secretory pathway and on their interactions" and used the tools of the day (electron microcopy, cell fractionation, biochemistry, and pulse-chase autoradiography) in his classical work defining the secretory process in the pancreatic acinar cell.

Peter Walter's multidisciplinary work on the unfolded protein response (UPR) was guided, like all of cell biology, he said, "By looking at things," and then "explaining them in terms of chemistry." The UPR is a homeostatic pathway that ensures that the cell's membrane biosynthetic machinery is balanced to its needs (Bernales *et al.*, 2006b). Under stress, the UPR calls upon ~5% of the yeast genome to massively restructure the secretory pathway. ER expansion is counterbalanced with ER degradation through an autophagic pathway (termed ERphagy) that removes hopelessly unfolded proteins and aggregates (Bernales *et al.*, 2006a). Maintaining this balance is a life/death decision for cells and hence the UPR plays an important role in many human diseases. In health the UPR is a finely tuned homeostat: in diseases such as diabetes and retinal pigmentosa and in response to viral infections, it can become a roque cytoprotector and apoptotic executioner.

A key signaling mechanism required to trigger the UPR involves an ER-localized transmembrane kinase, Ire1. Oligomerization of the kinase, which is highly cooperative with respect to ATP levels, leads to activation of an RNAse domain and the cytoplasmic processing of an mRNA precursor encoding a transcription factor that triggers UPR. Identifying the components of this pathway and the mechanisms governing it required genetics, systems biology, biochemistry, chemical biology, structural biology, and, as recently recounted in Walter's E.B. Wilson Award Lecture, serendipity (Walter, 2010). Linking this pathway to cellular structure and organization, Walter described his lab's recent use of

GFP-Ire1 constructs in mammalian cells to visualize the UPR response as a coalescence of the kinase and mRNA splicing factors into localized factories that disperse at later time points. Once again, by looking at things, new questions arise. How are these sites organized? What signals their dispersal?

Randy Schekman has leveraged the high-degree of conservation between yeast and mammalian cell biology to identify key components of the membrane trafficking machinery. Among these are the COPII coat components and the small GTPase Sar1p, which mediate the first step of the secretory pathway: vesicle formation from the ER (Sato and Nakano, 2007). Importantly, mutations in human homologues of this conserved machinery have recently been linked to heritable diseases: sar1b to defects in chylomicron synthesis (Charcosset *et al.,* 2008), sec23b to craniofacial disease (Fromme *et al.,* 2007), and sec24b to craniorachischisis, a rare but severe birth defect (Merte *et al.,* 2010). Using a cell-free reconstitution system, Schekman and his colleagues have defined the molecular bases underlying these human diseases. How is that mutations in these essential genes cause tissue-specific diseases? The answer lies both in the tissue-specific expression of mutant isoforms and in the cargo-selectivity of the impairment. Schekman, described his most recent work on sec24b, an isoform of the COPII component responsible for cargo selection. Functional reconstitution of the protein-sorting activities of sec24b identified its cargo-selective role, relative to other sec24 isoforms, in packaging of Vangl2, a key component in establishing planar cell polarity during neural tube closure (Merte *et al.,* 2010).

Scott Emr turned our attention to components of the endocytic machinery that regulate cargo-selective sorting at the plasma membrane (PM) and within endosomes. Transporters that mediate uptake of nutrients, such as amino acids and glucose, are delivered to and removed from the PM in response to the cell's needs. Emr described his discovery of a family of arrestin-related trafficking adaptors, ARTs, involved in endocytosis of surface transporters (Lin *et al.,* 2008) through a chemical genetic screen of a library of yeast knockout strains for increased sensitivity to a toxic arginine analogue. The complexity of the ART family (there are nine members in yeast and ~10 in mammalian cells) reflects their role in remodeling the PM the key organelle for intracellular communication and interactions with the environment. The turnover of PM proteins is completed with the aide of the ESCRT machinery, a set of highly conserved endosomal protein complexes discovered in the Emr lab (Teis *et al.,* 2009). ESCRT complexes selectively package internalized PM receptors and transporters into small vesicles that bud into the interior of the endosome. On delivery to the yeast vacuole, or mammalian lysosome, the intralumenal vesicles and their content are degraded.

Twenty-five years ago as a student in Schekman's lab, Peter Novick conducted the first screen for defects along the yeast secretory pathway and identified 23 genes (Novick *et al.,* 1980; Schekman and Novick, 2004). Among these was sec4, the founding member of the rab-family of GTPases that function as master regulators of vesicular trafficking and organelle identity (Novick and Zerial, 1997; Segev, 2001). Ten rab family members in yeast have evolved to more than 60 rabs in mammalian cells that regulate vesicle delivery, tethering, fusion, and the organization of membrane domains. Novick described his genetic, biochemical, and live cell microscopy experiments that establish how the rab-dependent recruitment of rab GEFs (guanine nucleotide exchange factors:rab activators) and GAPs (GTPase activating protein:rab inactivators) can lead to the sequential activation and deactivation of rab proteins. Using a combination of yeast genetics, biochemistry, and live cell microscopy, Novick has established that rab GEF and GAP countercurrent cascades govern localized rab activity to define organelle boundaries and to regulate vectorial transport between compartments along the secretory pathway (Rivera-Molina and Novick, 2009).

Nowhere is the utility of an interdisciplinary approach more evident than in Jim Spudich's work elucidating the mechanisms governing molecular motors, nature's preeminent nanomachines. Spudich described the use of single molecule assays, force measurements, low-angle light scattering, structural analyses, molecular biology, and time-resolved fluorescence and electron-spin resonance spectroscopy techniques to elucidate the mechanisms governing force generation and movement by myosin motors (Spudich, 2001). However, he lamented that experiments "can only disprove a model, they cannot prove it." Myosin VI, unlike its many myosin cousins, moves backward on actin filaments with a step size that appeared inconsistent with the prevailing swinging lever arm hypothesis for the translocation of motors along actin filaments, given the predicted structure of this motor. Thus, the paradoxical behavior of this unconventional myosin brought into question the prevailing hypothesis. Spudich's studies reveal how a 180° rotation of myosin VI motor domains while they walk along actin filaments brings the mechanics of this wayward motor back in line with its cousins. Thus, myosin VI becomes the exception that might just prove the rule (Spudich and Sivaramakrishnan, 2010).

Theme 3: Cell Biology Is Needed to Unravel the Mechanisms Underlying Human Disease

In a congratulatory note to Joe Goldstein and Michael Brown after their 1985 Nobel Prize for Physiology or Medicine, Palade wrote that the award recognized "how cell biology could be used to understand disease and how disease could be used to discover normal cell biology." Schekman, Walter, Emr, and Spudich each provided examples of how their knowledge of cellular machinery could be used to elucidate the mechanisms underlying genetic diseases. With the completion of the human genome, the identification of mutations associated with disease has increased exponentially. This explosion in human genomics has provided a plethora of questions and challenges that only cell biologists are equipped to meaningfully address.

The work of the Brown and Goldstein lab over the past 40 years since their discovery of mutations in the LDLR that cause familial hypercholesterolemia by perturbing its endocytic trafficking has provided the quintessential guide to using multidisciplinary cell biological approaches to unraveling the molecular basis for disease (Brown and Goldstein, 1986; Goldstein *et al.,* 2006). At this meeting, in addition to summarizing their substantial progress toward understanding how cells regulate serum cholesterol, Goldstein reported their latest work on NPC1 and NPC2, proteins associated with Niemann-Pick disease (Infante *et al.,* 2008a; Infante *et al.,* 2008b). He described biochemical and structural studies that reveal mechanisms for the efficient and direct transfer of insoluble cholesterol molecules from the small, intralumenal lysosomal protein, NPC2, to the intralumenal N-terminal domain of the lysosomal membrane protein NPC1 (Infante *et al.,* 2008c; Kwon *et al.,* 2009).

Theme 4: The Legacy and Future of Cell Biology

Cell biology is a relatively young field and hence can be readily traced back to its ancestors. Two of the speakers were direct scientific descendents of George Palade (Günter Blobel, Palade's student, and Peter Walter, Blobel's student). Five were direct familial or scientific descendents of Arthur Kornberg (Roger, his son; Schekman and Spudich, his students; and Schekman lab alumni, Novick and Emr). Interestingly, both Novick and Emr were recruited and nurtured as young faculty members by George Palade. Similar long lineages can be traced back to Keith Porter, Don Fawcett, Charles LeBlond, Joe Gall, Harvey Lodish, Bruce Alberts, Mark Kirchner, and others, many of whom, including George Palade, have also served as ASCB presidents. These unique bonds, coupled to the increasing need for integration across complex cell biological processes (membrane trafficking, cytoskeletal dynamics, cell-matrix interactions, signal transduction, and nuclear structure and function) define the field of cell biology.

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