the safety concerns associated with sparks and solvent vapors. An area that has emerged in the last several years combines film casting processability with electrochemical properties to make coatings of conducting polymers that are found to limit the corrosion of ferrous metals. If these preliminary and unexpected laboratory findings can be translated to a viable technology, the potential market applications are enormous.

The conductivity, permeability, and electrochemical activity of conducting polymers leads to their use as chemical sensors, and their compatibility with other organic materials may extend this usefulness to biological sensors. This is an area of extensive current research and incipient commercialization ["electronic noses" (*7*)] and one where Lonergan's work may potentially have the greatest impact. His hybrid device, combining an organic semiconductor with an electrochemically dopable polymer, forms a Schottky barrier junction whose electrical characteristics are exquisitely sensitive to the doping level of the polymer and therefore to the presence of reactive analyte species in contact with it. The cleverly embedded gold grid provides a means for controlling the baseline dopant level and thus perhaps the specificity and sensitivity of response.

Other applications of conjugated polymers are in various stages of research or technology transfer: nerve replacement for muscle stimulation, electroluminescence for (very) flat panel displays, and seed layers for electroless plating on printed circuit boards. There are also examples, like the batteries cited earlier, that showed great initial promise but have fallen, at least for the time being, by the wayside: nonlinear optics for use in fiber-optic switches and routers; photorefractive polymers for optical computing and holographic data storage; *pn* junctions, formed by donor and acceptor doping to make diode rectifiers; and electrochromic displays. The jury is still out on field-effect transistors for use in inexpensive smart cards.

All these examples illustrate the lesson that is to be learned: The successful commercialization of conjugated polymers has come (and presumably will continue to come) in applications that exploit additional unique properties. The lesson can be equally well applied to any new material. There is no economic advantage to the simple displacement of an entrenched manufacturing base. Rather, it pays to remember: One cannot spin-coat a transparent layer of copper from aqueous solution onto acres of celluloid film; nor can one change the Fermi level of silicon by immersing it in a solution of oxidant.

References and Notes

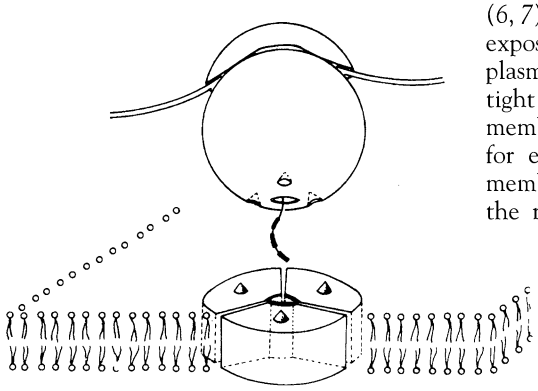
1. M. C. Lonergan, *Science* **278**, 2103 (1997).
2. T. Ito, H. Shirakawa, S. Ikeda, *J. Polym. Sci. Polym. Lett. Ed.* **12**, 11 (1974); C. K. Chiang *et al.*, *J. Chem. Phys.* **69**, 5098 (1978).
3. J. S. Miller, *Adv. Mater.* **5**, 587 (1993).
4. W. P. Su, J. R. Schrieffer, A. J. Heeger, *Phys. Rev. Lett.* **42**, 1698 (1979); *Phys. Rev. B* **22**, 2099 (1980).
5. For an extensive review of the field as it stood in the mid-1980s, see *Handbook of Conducting Polymers*, T. J. Skotheim, Ed. (Dekker, New York, 1986), vols. 1 and 2.
6. A. Dall'Olio, Y. Dascola, V. Varacca, V. Bocchi, *C. R. Acad. Sci. Ser. C* **267**, 433 (1968); A. F. Diaz, K. K. Kanazawa, G. P. Gardini, *J. Chem. Soc. Chem. Commun.* **1979**, 635 (1979).
7. H. V. Shurmer and J. W. Gardner, *Sens. Actuat. B* **8**, 1 (1992).

PROTEIN SYNTHESIS

A Ribosome at the End of the Tunnel

Ted Powers and Peter Walter

In all eukaryotic cells, proteins are sorted and delivered to final destinations inside and outside the cell. Those that are to be exported or inserted into membranes are first directed into a network of membrane tubes called the endoplasmic reticulum (ER). For many proteins, this process occurs early, while they are being created. In these cases the ribosomes together with their growing protein chains bind to pores in the ER membrane, forming the characteristic studded appearance of the rough ER seen under the electron microscope. The major constituent of the ER pore, or translocon, is the heterotrimeric Sec61 protein complex (*1*, *2*). The challenge at hand is to understand how the ribosome binds to the translocon and what happens during protein movement through the translocon and into the ER. On page 2123 in this issue, Beckmann *et al.* (*3*) rise to this challenge by describing the cryo–electron microscopic (EM) structure of the toroidal Sec61 complex bound to the ribosome.



Twenty-two years ahead of its time. "Hypothetical model for the formation of a transient tunnel through which the nascent chain would be transferred," as originally proposed by Blobel and Dobberstein (*4*, p. 848). [Reprinted from (*4*) with permission Rockefeller Press]

The idea that an aqueous, protein-conducting channel exists in the ER membrane was one of the original tenets of the signal hypothesis proposed in 1975 (see figure) (*4*) and has gained steady experimental support in recent years. Electrophysiological studies demonstrated that large ion-conducting channels appeared when ER-attached ribosomes were treated with puromycin, an antibiotic that causes release of nascent protein chains from the ribosome (*5*). Subsequent studies with fluorescence probes incorporated into the nascent chain showed directly that the translocating chain traverses the membrane through an aqueous environment (*6*, *7*). Moreover, the nascent chain was not exposed to small ions present in the cytoplasm, indicating that the ribosome forms a tight seal with the cytoplasmic face of the ER membrane. Now we know that sometimes—for example, during synthesis of integral membrane proteins—the tight seal between the ribosome and the membrane may be transiently broken to facilitate the lateral opening of the translocon. This brief opening would allow transmembrane segments of the protein access to the hydrophobic interior of the lipid bilayer, as well as provide entry for internal cytosolic domains into the cytosol during membrane protein integration (*8*). Thus, the ribosome-translocon interface must be both dynamic and tightly regulated.

In parallel studies, the components of the translocation pore have been identified (*9*). The basic translocon is astonishingly simple, composed principally of the heterotrimeric Sec61 complex. This complex is highly conserved; the Sec61α, Sec61β, and Sec61γ subunits from mammals are related to the yeast Sec61, Sbh1, and Sss1 proteins, respectively. Moreover, convincing homologs can be

The authors are in the Howard Hughes Medical Institute and Department of Biochemistry and Biophysics, University of California at San Francisco, San Francisco, CA 94143, USA. E-mail: tpowers@socrates.ucsf.edu

found for both Sec61α and Sec61γ in Eubacteria as well as in Archaea, pointing to a mechanism of protein translocation that is evolutionarily highly conserved. The Sec61 complex is required for the translocation of all substrate proteins so far tested (*10*). In addition, cross-linking studies have shown that Sec61α, the largest subunit of the complex with 10 membrane-spanning domains, is in close proximity to nascent chains throughout their translocation (*11*). The complex, isolated either from mammalian cells or yeast, can oligomerize in detergent to form a ringlike structure containing three or four copies of the complex and with an inner diameter of ~20 Å (*12*, *13*). Similar structures are seen in native membranes, providing compelling evidence that the Sec61 complex is in fact the protein-conducting channel seen in the biophysical studies.

Beckmann *et al.* (*3*) have now extended these observations by determining the EM structure of the heterotrimeric Sec61 complex bound to the ribosome, using components isolated from yeast. One key to their success was the observation that the Sec61 complex binds in a specific and saturable manner to 80S ribosomes in detergent solution, that is, under conditions that maintained the oligomerized state of the Sec61 complex. Another key was the use of three-dimensional image reconstruction, an approach used recently to produce wonderful low-resolution images of ribosomes from several organisms, including yeast. In these images, the Sec61 complex appears as a pentagon-shaped toroidal structure (or, put more simply, "a misshapen donut"), similiar in morphology to what had been observed before, with one surface of the Sec61 oligomer facing the surface of the large ribosomal subunit. The final outcome of this EM reconstruction (*3*) confirms the great insightfulness of the original model proposed in 1975 (*4*) (see figure).

Two important aspects of the mechanism of cotranslational translocation are suggested by this study. First, there is a single site of attachment between the Sec61 complex and the large ribosomal subunit. Therefore, most of the oligomeric Sec61 complex lies ~15 Å from the ribosome. Thus, as it stands, this structure cannot account for the tight seal between the ribosome and the translocon implied from fluorescence studies. It could be that additional components, either membrane or cytosolic in origin, create a "scarflike" seal around this gap. Alternatively, as the authors speculate, the nascent chain could induce a conformational change in the ribosome or the Sec61 complex so that the two structures would meet and a seal would be formed. The notion that the degree of attachment might be regulated by features in the nascent chain itself could begin to explain the dynamic behavior of the ribosome-translocon interface, which allows access of lipid to the growing chain of a transmembrane protein.

Second, the central pore of the oligomeric Sec61 complex aligns precisely with the exit site of a tunnel that runs through the large ribosomal subunit up to the subunit interface. Such a tunnel appears in other reconstructed images of ribosomes, prompting speculation that it forms the passageway for the nascent chain from its site of polymerization to the surface of the ribosome. Classic biochemical analyses showing that ribosomes protect distinct portions of the nascent polypeptide chain from proteolysis have seeded this idea (*14*). Although the existence of such a tunnel in the ribosome may still be controversial to some, the alignment of this cavity with the central opening in the Sec61 oligomer is too intriguing to discount.

These new results leave us with an image in which the translocon forms an extension of the ribosomal tunnel, connected in series to conduct the nascent chain from its site of synthesis to its final destination in the ER lumen. Indeed, ribosomes attached to translocon sites protect correspondingly larger fragments of nascent chains from proteolysis than ribosomes alone (*15*). Superimposed onto this simple conduit, however, is the likely dynamic behavior of the translocon that allows protein translocation and membrane protein integration, while strictly maintaining the permeability barrier of the membrane to other solutes. Thus, as remarkably intuitive as this new picture may appear, it is only a new beginning.

References

1. R. J. Deshaies, S. L. Sanders, D. A. Feldheim, R. Schekman, *Nature* **349**, 806 (1991).
2. D. Görlich, S. Prehn, E. Hartmann, K.-U. Kalies, T. A. Rapoport, *Cell* **71**, 489 (1992).
3. R. Beckmann *et al.*, *Science* **278**, 2123 (1997).
4. G. Blobel and B. Dobberstein, *J. Cell Biol.* **67**, 835 (1975).
5. S. M. Simon and G. Blobel, *Cell* **65**, 371 (1991).
6. K. S. Crowley, G. D. Reinhart, A. E. Johnson, *ibid.* **73**, 1101 (1993).
7. K. S. Crowley, S. Liao, V. E. Worrell, G. D. Reinhart, A. E. Johnson, *ibid.* **78**, 461 (1994).
8. S. Liao, J. Lin, H. Do, A. E. Johnson, *ibid.* **90**, 31 (1997); B. Martoglio, M. W. Hofmann, J. Brunner, B. Dobberstein, *ibid.* **81**, 207 (1995).
9. Reviewed in T. A. Rapoport, B. Jungnickel, U. Kutay, *Annu. Rev. Biochem.* **65**, 271 (1996).
10. D. Görlich and T. A. Rapoport, *Cell* **75**, 615 (1993).
11. W. Mothes, S. Prehn, T. A. Rapoport, *EMBO J.* **13**, 3973 (1994).
12. D. Hanein *et al.*, *Cell* **87**, 721 (1996).
13. T. A. Rapoport, *Pop. Mech.* **4**, 26 (1997).
14. L. I. Malkin and A. Rich, *J. Mol. Biol.* **26**, 329 (1967).
15. K. E. S. Matlack and P. Walter, *J. Biol. Chem.* **270**, 6170 (1995).

TRANSCRIPTION

Control of the Supply Line

Jeffrey Roberts

All cells undergo orderly duplication, harnessing many complex biochemical systems in the process. As it makes a copy of itself, the cell monitors its own economy in order to provide new cell components at the right rate. How does this happen so reliably? Such mechanisms of homeostatic regulation of basic cellular components have been very elusive. For example, well-characterized elements trigger DNA replication, but it is unknown how they are modulated to initiate replication precisely when the mass of a growing cell population reaches a certain value. It has also been difficult to discern how cells determine their investment in protein-making machinery—the ribosomes—according to need: When the growth rate varies in response to a change in the availability of nutrients, the number of ribosomes increases in proportion to the growth rate (*1*), implying that the rate of ribosome synthesis increases as the square of the growth rate. The mechanism of such regulation has been a matter of prolonged controversy, but an article in this issue on page 2092 from the laboratories of R. Gourse and C. Turnbough presents a model that will crystallize our existing views (*2*).

In his pioneering work, M. Nomura identified ribosomal RNA (rRNA) synthesis as the ultimate site of regulation of ribosome synthesis; enough ribosomal protein is produced to meet the cell's need for ribosome assembly, in response to the availability of rRNA (*3*). When a critical ribosomal protein accumulates in excess, it binds its own mRNA and inhibits further translation. This regulation entails many pleasing subtleties, including a binding site in mRNA for the critical regulatory protein that mimics the

The author is in the Section of Biochemistry, Molecular and Cell Biology, Cornell University, Ithaca, NY 14853, USA. E-mail: jwr7@cornell.edu