The surprise came when Deshler *et al.* attempted to isolate the 75-kD protein from cytoplasmic extracts and found that the Vg1-binding activity (Vera) cosedimented with a large organelle fraction enriched with TRAPα, an integral protein associated with the protein translocation machinery of the endoplasmic reticulum. In stage 2 oocytes, the TRAPα distribution overlapped with the wedge-shaped, in situ hybridization pattern of Vg1 in stage 2 oocytes (*2*). Because Vg1 is not translated at this time and the endoplasmic reticulum is of the smooth variety, it appears that preferential translation is not the major function of this interaction. Traditionally, the endoplasmic reticulum is viewed as an organelle involved in synthesis and secretion of proteins. The finding of Deshler *et al.* (*7*) demonstrates a novel function for a subdomain of this organelle—in the localization of RNAs during oogenesis.

How does this specialized region of the endoplasmic reticulum originate? The elaboration of this subdomain is a sequential process, first seen when the mitochondrial cloud and the associated METRO RNAs move toward the vegetal cortex (*14*). When the METRO RNAs are anchored, the wedge-shaped endoplasmic reticulum subdomain is fully delineated and Vg1 mRNA becomes associated with this structure. Thus, the function of this specialized region of the endoplasmic reticulum may be in the initial steps of localization of RNAs, such as Vg1, through the late pathway. The morphogenesis of the wedge-shaped endoplasmic reticulum structure is dependent on the functioning of the early pathway via the migration of the mitochondrial cloud. Vera may mediate the interaction between Vg1 mRNA and the endoplasmic reticulum.

Two alternative explanations are possible for the Vg1-endoplasmic reticulum association. (i) The wedge-shaped, endoplasmic reticulum-containing structure may serve as a substrate to orient the microtubule tracks used for Vg1 translocation during stages 3 and 4. (ii) Vg1 remains associated with the endoplasmic reticulum, and endoplasmic reticulum-containing vesicles are translocated to the vegetal cortex along microtubules. A close association between the endoplasmic reticulum and microtubules and the movement of membrane vesicles along microtubules have been observed in a variety of systems, supporting both possibilities (*15*). It is clear, however, that the wedge-shaped region of the endoplasmic reticulum is somehow unique; the Vg1 mRNA associates only with this subdomain of endoplasmic reticulum and not with the endoplasmic reticulum located elsewhere in the cortex. Future studies will focus on understanding the precise mechanism of this interaction and the universality of its use for RNA localization in other systems.

References and Notes

1. W. Jeffery, in *Developmental Biology, A Comprehensive Synthesis*, L. Browder, Ed. (Academic Press, New York, 1988), vol. 5, pp. 3–56; H. D. Lipshitz, in *Localized RNAs*, H. D. Lipshitz, Ed. (Landes, Austin, TX, 1995), pp. 1–5; D. St. Johnston, *Cell* **81**,161 (1995).
2. M. Kloc and L. D. Etkin, *Development* **121**, 287 (1995).
3. C. M. Forristall, M. Pondel, L. Chen, M. L. King, *ibid.*, p. 201.
4. M. Kloc, G. Spohr, L. D. Etkin, *Science* **262**, 1712 (1993).
5. L. Mosquera, C. Forristall, Y. Zhou, M. L. King, *Development* **117**, 377 (1993).
6. M. Ku and D. Melton, *ibid.* **119**, 1161 (1993).
7. J. O. Deshler, M. I. Highett, B. Schnapp, *Science* **276**, 1128 (1997).
8. D. Melton, *Nature* **328**, 80 (1987); J. K. Yisraeli and D. A. Melton, *ibid.* **336**, 592 (1988).
9. J. K. Yisraeli, S. Sokol, D. A. Melton, *Development* **108**, 289 (1990); M. Kloc and L. D. Etkin, *Science* **265**, 1101 (1994).
10. Y. Zhou and M. L. King, *Development* **122**, 2947 (1996).
11. K. L. Mowry and D. A. Melton, *Science* **255**, 991 (1992).
12. Z. Elisha, L. Havi, I. Ringel, J. K. Yisraeli, *EMBO J.* **14**, 5109 (1995); S. P. Schwartz, L. Aisenthal, Z. Elisha, F. Oberman, J. K. Yisraeli, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 11895 (1992).
13. K. Mowry, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 14608 (1996).
14. M. Kloc and L. D. Etkin, unpublished data.
15. M. Terasaki, L. B. Chen, K. Fujiwara, *J. Cell Biol.* **103**, 1557 (1986); V. Allan and R. Vale, *J. Cell Sci.* **107**, 1885 (1994); S. Dabora and M. Sheetz, *Cell* **54**, 27 (1988); C. Lee and L. B. Chen, *ibid.*, p. 37; C. Waterman-Storer, J. Gregory, S. Parsons, E. Salmon, *J. Cell Biol.* **130**, 1161 (1995).

16. The author acknowledges support from NIH and the helpful comments from the members of the Etkin laboratory.

UPDATE: CIRCADIAN RHYTHMS

As Time PASses: The First Mammalian Clock Gene

Steve A. Kay

Several molecular cogs of the circadian clock have been identified in the fungus *Neurospora* and the fruit fly *Drosophila* (*1*). One of these—the photoresponsive gene *wc-2* from *Neurospora* (*2*)—was recently described in *Science* and discussed in an accompanying Perspective (*3*). Significantly, this protein contains a PAS domain, found in many transcription factors including PER, a *Drosophila* clock component.

Additional support for PAS as a signature motif in clock components now comes from two papers published this week in *Cell* by Takahashi and his colleagues (*4*). (See also the News story on page 1030.) This laboratory has undertaken a truly heroic effort—and succeeded. They have carried out the brute-force screening for mutants of the clock in mice by observing wheel-running behavioral rhythms in the individual progeny of lines of mice treated with the mutagen ethylnitrosourea. Incredibly, mutant mouse number 25 displayed one of the desired phenotypes: lengthening of the period of cyclic behavior observed in constant darkness. The animals homozygous for the mutation eventually exhibited arrhythmicity in constant darkness (*5*). This locus was called *clock*, and further genetic analysis revealed that this allele was both semidominant and antimorphic, implying that the putative mutant protein was interfering with the function of the normal, wild-type *clock* gene (*6*). This notion has now been borne out by cloning of the *clock* gene by positional methods and gene rescue. The predicted CLOCK protein is 855 amino acids long and contains a basic helix-loop-helix–PAS motif, as well as a glutamine-rich carboxyl-terminus.

Thus, another protein that appears to be intimately involved in the circadian clock contains the PAS motif, making it the only conserved signature known so far among widely diverse clock molecules.

The author is in the NSF Center for Biological Timing, Department of Cell Biology, The Scripps Research Institute, La Jolla, CA 92037, USA. E-mail: stevek@scripps.edu

References

1. J. C. Dunlap, *Annu. Rev. Genet.* **30**, 579 (1996).
2. S. Crosthwaite, J. C. Dunlap, J. J. Loros, *Science* **276**, 763 (1997).
3. S. A. Kay, *ibid.*, p. 753.
4. D. P. King *et al.*, *Cell* **89**, 641 (1997); M. P. Antoch *et al.*, *ibid.*, p. 655.
5. M. H. Vitaterna *et al.*, *Science* **264**, 719 (1994).
6. D. P. King *et al.*, *Genetics*, in press.