bodies, it is known that the carboxy terminus is found on the cytoplasmic side of the plasma membrane[15]. By comparison with homologous regions of other transport proteins, it seems likely that part of this cytoplasmic domain functions as a nucleotide-binding site, probably using ATP to provide the energy for active efflux[2-4]. As the sequence of P-glycoprotein consists of a tandem repeat, each molecule would provide two such sites.

In anticipation of a direct study of the function of P-glycoproteins for their role in multidrug resistance, two major mechanisms have been considered[2-4]: (1) direct efflux of hydrophobic drugs through a P-glycoprotein pore, perhaps involving other components of the membrane; or (2) protein-mediated efflux in which the drugs are first bound to a carrier protein which is then expelled from the cell. The latter possibility is suggested by the close homology to the haemolysin transport system, which is known to function in this way. The homology also raises questions about the normal function of P-glycoproteins.

Knowledge of the structure and functions of the P-glycoproteins should lead to new attempts at tackling multidrug resistance in patients. It may be possible to take advantage of the exposure of part of the overproduced P-glycoprotein on the cell surface to target cytotoxic antibody conjugates to these cells after the bulk of the tumour has been destroyed by conventional chemotherapy. As the details of the transport mechanism become better defined, it will be possible to consider the design of specific drugs which can interfere with it; compounds have already been discovered that interfere with efflux of drugs from multidrug-resistant cells[16].

An understanding of the mechanism of multidrug resistance presents the possibility of much greater clinical benefit from the enormous effort that has in the past been put into developing and testing chemotherapeutic agents. □

1. Gerlach, J.H., Kartner, H., Bell, D.R. & Ling, V. *Cancer Surveys* **5**, 25 (1986).
2. Gerlach, J.H. *et al. Nature* **324**, 485 (1986).
3. Gros, P., Croop, J. & Housman, D. *Cell* **47**, 371 (1986).
4. Chen, C. *et al. Cell* **47**, 381 (1986).
5. Riordan, J.R. *et al. Nature* **316**, 817 (1985).
6. Van der Bliek, A.M., Van der Velde-Koerts, T., Ling, V. & Borst, P. *Molec. cell. Biol.* **6**, 1671 (1986).
7. Stark, G.R. *Cancer Surveys* **5**, 1 (1986).
8. Schimke, R.T. *Cancer Res.* **44**, 1735 (1984).
9. Gros, P., Ben-Neriah, Y., Croop, J. & Housman, D.E. *Nature* **323**, 728 (1986).
10. Inaba, M., Kobayashi, H., Sakurai, Y. & Johnson, R.K. *Cancer Res.* **39**, 2200 (1979).
11. Lalande, M.E. Ling, V. & Miller, R.G. *Proc. natn. Acad. Sci. U.S.A.* **78**, 363 (1981).
12. Cornwell, M.M., Safa, A.R., Felsted, R., Gottesman, M.M. & Pastan I. *Proc. natn. Acad. Sci. U.S.A.* **83**, 3847 (1986).
13. Safa, A.R., Glover, C.J., Meyers, M.B., Biedler, J.L. & Felsted, R. *J. biol. Chem.* **261**, 6137 (1986).
14. Fry, D.W. & Jackson, R.C. *Cancer Surveys* **5**, 47 (1986).
15. Kartner, N., Evernden-Porcelle, D., Bradley, G. & Ling V. *Nature* **316**, 820 (1985).
16. Kessel, D. *Cancer Surveys* **5**, 109 (1986).

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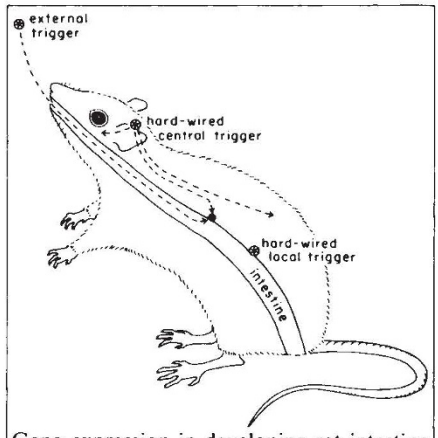
Developmental physiology

Hard-wired local triggering of intestinal enzyme expression

Jared M. Diamond

NORMAL development requires that each gene express itself at the right time and in the right cell. Is proper timing triggered by signals external to the animal, or is it 'hard-wired' within the animal (see figure)? If triggering is hard-wired, is the trigger local, within the tissue where expression will occur, or is it central, for example, in an endocrine gland whose hormones control many peripheral tissues? A recent report by K. Yeh and P. Holt (*Gastroenterology* **90**, 520; 1986) demonstrates the existence of a hard-wired local timer for sucrase expression in rat intestine, which will be a useful model for the identification of timers in other systems.

Infant rats are normally weaned from a diet of maternal milk to solid food around 25 days after birth. Starting around day 18, intestinal activity of lactase (which digests the milk sugar lactose) declines, whereas sucrase (which digests sucrose in solid food) first appears (Henning, S. *A. Rev. Physiol.* **47**, 231; 1985). These changes might be externally triggered by weaning and the resultant change of solutes entering the intestinal lumen: experimentally delaying the age of weaning, for example, is found to delay the decline of lactase.



Gene expression in developing rat intestine may be pre-programmed by a local timer in intestinal cells themselves; pre-programmed by a centrally released timer (for example, a thyroid or pituitary hormone); or not programmed at all but instead triggered by an external event.

The changes might also be under hard-wired central control by hormones that modulate many other developmental changes around the time of weaning. (Pituitary, thyroid and adrenal hormones affect development of intestinal lactase and sucrase, as well as that of many other functions.) Could a hard-wired local timer contribute as well?

Yeh and Holt transplanted isografts of mid-intestine from donor rat pups 0 or 5 days after birth to under the skins of newborn (day 0) host rat pups. Some of the grafts survived and exhibited normal migration rates of differentiating enterocytes along the crypt/villus axis. They found that the control of expression in the isografts differs between lactase and sucrase.

Isograft lactase does not begin to decline until after donor age 28 days (host age 28 or 23 days), although lactase in the host intestine begins to decline as usual around 18 days. Thus, the change in luminal solute input, which was experienced by the host intestine but not by the donor intestinal graft under the host's skin, is an important signal for turning off lactase expression. In agreement with this conclusion, the normal decline in lactase is delayed in bypassed intestinal loops (Tsuboi, K. *et al. Gastroenterology* **80**, 1550; 1981) and is accelerated in rat pups fed an artificial milk formula (Yeh, K. & Holt, P. *Pediatr. Res.* **19**, 963; 1985).

Sucrase activity begins to rise simultaneously around day 18 in donor and host tissue when day 0 donor tissue is transplanted into day 0 hosts. But when day 5 donor tissue is transplanted into a day 0 host, the isograft begins expressing sucrase when the host is only 13 days old and the donor tissue 18 days old. At this time the host tissue expresses no sucrase, which does not appear until 5 days later when the host reaches an age of 18 days.

Thus, donor sucrase expression is not triggered externally by luminal solute inputs (from which the donor intestinal graft was cut off), nor by a hard-wired central timer in the form of host hormones (which would have triggered host and donor expression simultaneously). Nor could the normal absence of sucrase expression at day 13 result from a systemic inhibitor present then, as the graft does express sucrase at a host age of 13 days. Instead, there must be a hard-wired local timer within the donor intestinal tissue that turns on sucrase expression at a tissue age of 18 days. In agreement with this conclusion, sucrase expression begins at the normal time in bypassed intestinal loops and in rat pups from which the pituitary, adrenal or thyroid gland is removed. □

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