cytoplasmic tail[3,4]. The predicted structure of its domains suggested that it is involved in cell–cell interactions or in interactions with the extracellular matrix. The PKD2 protein has similarities to PKD1, but its topology and domain structure suggest that it might act as a subunit of a cation (perhaps calcium) channel[5]. An important clue to the relationship between PKD1 and PKD2 came from the discovery that they interact directly, suggesting that they act in a common pathway[6,7]. The possibility of a widespread function of related pathways was first suggested by the discovery of a structural relationship between PKD1 and a membrane receptor in sea-urchin sperm. This receptor mediates the acrosome reaction — an ion-channel-regulated membrane fusion event that is necessary for fertilization[8]. Human testes express a similar polycystin-related protein[9].

Now, quite unexpectedly, Barr and Sternberg[2] find that a mutation in *C. elegans*, which gives rise to males that are defective in mating behaviour, lies in a gene called *lov-1* (for 'location of vulva') — the worm homologue of human *PKD1*. Since research on *C. elegans* was initiated by Sydney Brenner in the late 1960s, work on this animal has, in part, been directed at understanding the genetic basis of development and the function of its nervous system. Male mating — in which males seek out the hermaphrodite partner and copulate with her — is probably the most complex behaviour shown by *C. elegans*.

Sternberg's laboratory had previously defined the six sub-steps of the stereotyped copulatory sequence, correlated these sub-steps with the function of individual neurons, and isolated behavioural mutants[10]. One of the sub-steps is to locate the vulva. As well as being unable to execute this step efficiently, *lov-1* mutant males are also defective in the first sub-step, termed 'response'. Response and vulva location depend on two types of male sensory structure. The first is a set of nine pairs of rays, which project out of the tail on each side. The second is a hardened cuticular structure called the hook, which contains two sensory neurons.

Knowing that PKD1 and PKD2 interact, Barr and Sternberg next used the recently completed *C. elegans* genome sequence to isolate *pkd-2*, the worm homologue of human *PKD2*. They then studied the expression patterns of both *lov-1* and *pkd-2*, and found that promoter sequences of both genes cause reporter genes to be expressed in the rays and the hook sensory neurons required for response and vulva location. Arguing (from a variety of evidence) that the defect in the *lov-1* mutant is not developmental, the authors concluded that the LOV-1 and PKD-2 proteins are involved in chemosensory or mechanosensory signal transduction in sensory neurons.

By contrast, Chen *et al.*[1] used cell-expression and electrophysiological approaches to examine the potential channel function of a polycystin-related protein. This protein, called PCL (polycystin-like), had been identified in the human expressed-sequence-tag database by its sequence similarity with that of PKD2. Although its function was not known, the authors knew that PCL, like PKD2, has the structural fingerprint of a cation-channel subunit related to a number of families (the transient receptor potential calcium channel and voltage-gated calcium-, sodium- and potassium-channel families). The PCL and PKD2 proteins both contain a calcium-binding EF-hand domain that may help to regulate channel activity.

Chen *et al.* expressed PCL in *Xenopus* oocytes by microinjecting synthetic messenger RNA for the protein. They then studied its channel properties using the two-microelectrode voltage clamp and patch-clamp techniques. The authors found that PCL is a non-selective cation channel that is permeable to sodium, potassium and calcium. Its calcium permeability is about five-fold higher than that of sodium, and calcium modulates the channel's activity. However, Chen *et al.* could not determine whether binding at the EF-hand domain is responsible for this calcium regulation. The high structural similarity between PCL and PKD2 provides indirect evidence that PKD2 is also a cation-channel subunit.

These data support the hypothesis that PKD1-related proteins act as receptors that regulate the activity of channels containing PKD2-related proteins (Fig. 1). The two proteins are part of a conserved signalling mechanism in which the translocation of ions acts as a second messenger. But the diversity of the processes in which this signalling mechanism seems to be involved highlights the remaining questions. What are the specific molecular cues that activate these pathways? What are their downstream effectors? And what additional factors are responsible for adapting this mechanism to the unique requirements of each tissue? ■

Scott W. Emmons is in the Department of Molecular Genetics, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA.
e-mail: emmons@aecom.yu.edu
Stefan Somlo is in the Section of Nephrology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06520-8029, USA.
e-mail: stefan.somlo@yale.edu

1. Chen, X. Z. *et al. Nature* **401,** 383–386 (1999).
2. Barr, M. M. & Sternberg, P. W. *Nature* **401,** 386–389 (1999).
3. Hughes, J. *et al. Nature Genet.* **10,** 151–160 (1995).
4. The International Polycystic Kidney Disease Consortium *Cell* **81,** 289–298 (1995).
5. Mochizuki, T. *et al. Science* **272,** 1339–1342 (1996).
6. Qian, F. *et al. Nature Genet.* **16,** 179–183 (1997).
7. Tsiokas, L., Kim, E., Arnould, T., Sukhatme, V. P. & Walz, G. *Proc. Natl Acad. Sci. USA* **94,** 6965–6970 (1997).
8. Moy, G. W. *et al. J. Cell Biol.* **133,** 809–817 (1996).
9. Hughes, J., Ward, C. J., Aspinwall, R., Butler, R. & Harris, P. C. *Hum. Mol. Genet.* **8,** 543–549 (1999).
10. Liu, K. S. & Sternberg, P. W. *Neuron* **14,** 79–89 (1995).

Daedalus

Fertile competition

The claim has been made that sperm counts in the West are declining alarmingly. A typical ejaculate might contain 100 million sperm; since only one is required to do the job, a reduction to (say) 50 million may not seem obviously critical. But human fertilization is chancy at best. Even trying hard, a couple can easily take many months to conceive. One explanation is that most sperm are infertile. Their job is to ward off or discourage rival sperm. In effect, they act as a large screen of warships escorting a small, crucial convoy of freighters.

Daedalus argues that both freighters and warships will put on a mighty spurt if challenged by a rival fleet. There is some evidence that a man with a sexual rival generates more sperm than he would do otherwise; but Daedalus reckons that the speed, efficiency and pugnacity of his sperm must rise as well. In many species sperm compete chemically, by putting out toxins or antigens against their rivals. Indeed, Daedalus once proposed to use human seminal toxins in a natural spermicidal contraceptive. He now has a converse strategy. DREADCO biochemists are studying human seminal toxins in the hope of developing a spermal 'vaccine'. It will be a derivative of such a toxin, modified just enough to be harmless, but still sensed as a deadly threat by sperm encountering it. Spurred by this challenge, they will drive towards the ovum with extra speed and energy. This ingenious 'conceptive' will be welcomed by couples trying hard to have children. It will boost their chances greatly.

But Daedalus goes further. The sperm in a given ejaculate must be immune to their own toxin. They should even tolerate quite well the toxin of a close genetic relative carrying many of the same genes. But toxin from a genetic stranger must be a terrible threat. The DREADCO team are therefore mixing semen samples from different types and races of men, and studying their competition under the microscope. They will then plot the semen donors on a map such that the more fiercely antagonistic the sperm of any two donors, the further apart they are on the map.

The resulting human distribution will be far more fundamental than one based (say) on blood groups or pigmentation. It will reveal the classes of mankind as sensed by genetics itself. It should powerfully illuminate the stages by which we emerged from Africa, and our diversification since then. **David Jones**