looked like the 'normal' Pacific. Figure 1 shows the behaviour of the subsurface water in the Indian and Pacific Oceans at a time when both oceans were in a highly anomalous state. It is tempting to think that it is no coincidence that a very strong dipole in the Indian Ocean occurred at the same time as one of the largest El Niños on record. But both Webster *et al.*[1] and Saji *et al.*[2] argue otherwise. They show that the conditions of 1997–98 are not unprecedented and that large amplitudes of the dipole occurred in 1961 (ref. 7), 1967, 1972 and 1994. Dipole variability is present to some degree most of the time but what kicks it into top gear is not clear. There is little statistical relationship between the Indian Ocean dipole and El Niño: the dipole occurs in both El Niño and non-El-Niño years, and Saji *et al.* show that it has also been evident even in a weak La Niña year such as 1967 (La Niña, the converse of El Niño, is when the east Pacific is anomalously cold).

Based on six major dipole events in the past 40 years, Saji *et al.*[2] have constructed a composite picture of the dipole mode showing its spatial structure at different phases. Their Fig. 2 (page 361) highlights the importance of wind and temperature changes first in the Indonesian region, initially to the south of the Equator but then, later, in September–October, westward along the Equator (sometimes, as in 1997, as far as Africa). They show that the dipole mode has a biennial character which may imply a certain predictability from one year to the next. The reliability and so usefulness of such predictions is likely to be limited, however, as we simply don't know how the dipole fits into the larger picture of climate variability and factors such as Himalayan snow cover and chaotic processes that are not directly linked to slow changes in sea-surface temperature.

How the dipole is related to monsoon rainfall is also unclear[8]; of the two biggest dipole events, that of 1961 was associated with the heaviest monsoon in 150 years[2], whereas in that of 1997 rainfall over India was normal[9]. In fact, Saji *et al.* find no statistical relationship between monsoon rainfall and the dipole. Nonetheless, the observations and analysis reported by Webster *et al.* and Saji *et al.* mean that the Indian Ocean jumps several rungs up the climate ladder of importance. We are still some way from understanding rainfall around the Indian rim, one of Lockyer's original goals, but identification of variability such as the dipole mode is a considerable step forward. ■

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Signal transduction

Mating, channels and kidney cysts

Scott W. Emmons and Stefan Somlo

Advances in human genetics have meant that the genes mutated in human diseases can be identified exclusively by their location in the genome. But how do we work out the cellular functions of the associated protein products? Reports on pages 383 and 386 of this issue[1,2] begin to address this problem for two proteins — polycystin-1 (PKD1) and polycystin-2 (PKD2) — that are defective in human autosomal dominant polycystic kidney disease. From their studies of the nematode worm *Caenorhabditis elegans*, Barr and Sternberg[2] present evidence that homologues of the polycystins act together in a signal-transduction pathway in sensory neurons. Chen *et al.*[1], by contrast, have used an oocyte-expression system in the frog *Xenopus laevis* to show that a homologue of PKD2 is associated with the activity of a cation channel. These results support the hypothesis that polycystin-related proteins belong to a hitherto unknown class of signal-transduction molecules.

Autosomal dominant polycystic kidney disease affects more than one in 1,000 live births, and is the most common single-gene disorder leading to kidney failure. The children of affected parents have a one in two chance of inheriting the disease, and half of all sufferers need dialysis or a kidney transplant by the age of 60. Mutations in either PKD1 or PKD2 cause almost indistinguishable clinical symptoms. Although the kidney is the most severely affected organ, the disease is systemic and affects the liver, pancreas and cardio- and cerebro-vascular systems as well.

The PKD1 protein is a roughly 4,300-amino-acid integral-membrane glycoprotein with a large, amino-terminal extracellular domain and a small, carboxy-terminal

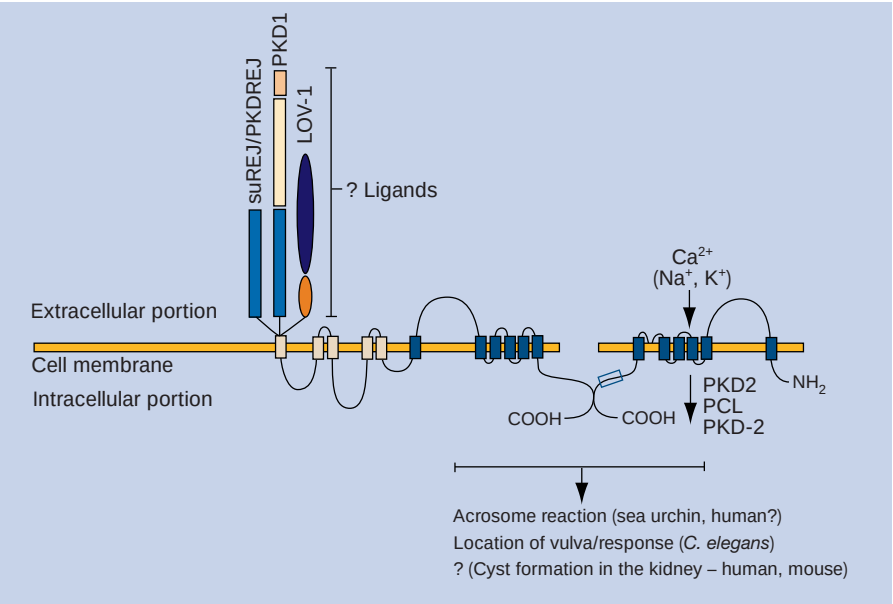

Figure 1 **Two components of the proposed polycystin signalling pathway. Proteins related to human PKD1 (refs 3, 4) include the *C. elegans* LOV-1, studied by Barr and Sternberg[2], the sea-urchin egg jelly receptor (suREJ)[8] and its human homologue PKDREJ (ref. 9). The large, extracellular domains contain different binding motifs: REJ module (blue); immunoglobulin-like PKD repeats (yellow); leucine-rich repeats and C-lectin-like domain (pale orange); serine/threonine-rich mucin-like domain (purple); ATP/GTP-binding domain (dark orange). The small cytoplasmic tails are thought to mediate interaction with proteins related to human PKD2 (ref. 5), including the polycystin-like (PCL) protein studied by Chen *et al.*[1] and the *C. elegans* PKD-2. PKD2-related proteins are predicted to have six membrane spans (dark blocks) and a cytoplasmic EF-hand (open block). The dark blocks in the PKD1-related protein represent the region of sequence similarity with PKD2-related channels.**

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? ■

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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**