idea that this junction has a central role in cell polarity.

Bilder and Perrimon build on this base, identifying a protein called Scribble as another participant in maintaining epithelial polarity. In Scribble's absence, cells initially become polarized but, as embryo development proceeds, cell polarity is disrupted, epithelia lose their monolayered appearance, and adherens-junction proteins lose their polarized localization and become distributed around the cell periphery. In addition, apical proteins, including Crumbs, are no longer restricted to the apical surface. In contrast, septate-junction and basolateral proteins are less severely affected. So it seems that Scribble maintains the identity of the apical membrane region. As many consequences of the absence of Scribble are mimicked by deliberately mislocalizing Crumbs³, one function of Scribble may be to restrict Crumbs to the apical part of the cell.

But how does Scribble work? Bilder and Perrimon cloned the *scribble* gene, and in doing so spotlighted a family of proteins that act as molecular scaffolds on which other proteins are assembled. Scribble's protein sequence reveals a series of protein-protein interaction motifs. Its carboxy-terminal half contains four PDZ domains (named for the first three proteins in which they were found: PSD-95; the fly septate-junction protein, Discs large; and the mammalian tight-junction protein, ZO-1). A PDZ domain often recognizes specific amino-acid sequences at the carboxy termini of other proteins, but can also recognize internal protein motifs (reviewed in ref. 4). With four tandem PDZ domains, Scribble could bind four different partners simultaneously.

Moreover, Scribble's amino terminus contains leucine-rich repeats. Related repeats in other proteins bind small GTPases of the Ras superfamily. If this is true in Scribble, it might provide a mechanistic clue, as the GTPases RhoA and Rac are involved in epithelial polarity⁵ and junction function (reviewed in ref. 6).

Our knowledge of other PDZ proteins provides hints as to Scribble function. One such protein, InaD, which has five PDZ domains, brings together five proteins sequentially involved in transducing the light signal from the visual pigment rhodopsin (reviewed in ref. 7). The result is a functional signalling complex. A tripartite complex of PDZ proteins, Lin-2, Lin-7 and Lin-10, binds transmembrane proteins such as the receptor for epidermal growth factor and the glutamate receptor, mediating their targeting or retention in the basolateral region (reviewed in ref. 4). So PDZ proteins both assemble multiprotein complexes and localize them to particular cellular locations.

Many PDZ proteins are concentrated at cell junctions. The *Drosophila* PDZ proteins Canoe and ZO-1 localize to adherens

junctions⁸. Tight and septate junctions harbour many PDZ proteins, including Discs large in *Drosophila* and the ZO-1, 2 and 3 family in mammals (reviewed in refs 4, 9). Bilder and Perrimon find that Scribble also localizes to septate junctions. This contrasts with the PDZ protein Discs-large, also critical for cell polarity¹⁰, which is concentrated in the apical region. Bazooka/ASIP/Par-3, a PDZ protein essential for cell polarity in both *Drosophila* and the nematode *Caenorhabditis elegans*, is more complex: it localizes to tight junctions in mammals and the apical membrane in *Drosophila*^{11–14}.

Bilder and Perrimon propose two ways in which Scribble might work (Fig. 1c). Scribble might form part of a fence preventing apical proteins from straying into basolateral territory. Alternatively, it may help to direct basolateral and apical proteins to their proper locations.

More complex possibilities also suggest themselves. First, Scribble appears before septate junctions form, and at that time it localizes at the apical end of the lateral cell surface. So it might regulate the localization of apical proteins during this early period when it resides near them. Alternatively, if Scribble works later when it is a septate-junction protein, its effects at a distance on apical and adherens-junction proteins reinforces the idea that cell polarity results from the integrated action of proteins of the apical and basolateral regions and the junctional complex. As in home construction, if the foundations are compromised, the roof may collapse. To see which of these models best fits reality, we must identify and study Scribble's protein partners and other architects of cell polarity. ■

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Daedalus

Stirring the blood

Cardiovascular diseases are among the greatest killers of modern times. Solids precipitate out of our blood — either as dangerous deposits on arterial walls, or as clots which travel in suspension until they block some crucial capillary. Unlike human designers, nature has never invented the circulation-filter. She relies on the blood staying dependably fluid, an optimistic hope in view of the cells and solid particles densely suspended in it.

Indeed, says Daedalus, blood is only kept fluid by the continual stirring of its movement. Stagnant blood would settle out, deposit sediment, and clot. A narrowed heart valve, for example, can create a cul-de-sac of unstirred blood in the heart. Clots can form in it, and may slip out into the bloodstream with tragic consequences.

So Daedalus wants to stir our blood. He recalls the ultrasonic cleaning bath, whose intense high-frequency agitation shakes dirt off solid surfaces. Ultrasound seems biologically harmless. It is regularly used to image structures inside the body, even fetuses. Indeed, a lithotripter focuses it intensely enough to shatter kidney-stones inside the body. So stirring the blood ultrasonically should be simple and safe. The intimate agitation would break up any incipient clots and nuclei that might be forming, keeping the blood safely fluid.

DREADCO's prototype blood-stirrer is a bath equipped with piezoelectric sound-generators that launch a converging beam into the water. The patient sits in the bath. Since he is 70% water himself, the beam enters him with little refraction or reflection, and converges to the desired volume in his body. It might be the heart, or one of the wider arteries. The beam will be kept on for several minutes, until all the patient's blood has passed through the beam. Depleted of incipient clots and clumps, it will be perfectly homogenized.

Even people with very clot-prone blood can survive for years without incident. So one blood homogenization should ensure good health for a long time. But patients at high risk could be homogenized more often. They might even wear a personal ultrasound stirrer all the time. With luck, blood-stirring will have other benefits as well. Invigorated by their vibro-massage, red cells may exchange oxygen more freely, and white ones patrol the system for invaders with added vigilance. **David Jones**

The Further Inventions of Daedalus (Oxford University Press), 148 past Daedalus columns expanded and illustrated, is now on sale. Special *Nature* offer: m.curtis@nature.com