Channelling our thoughts

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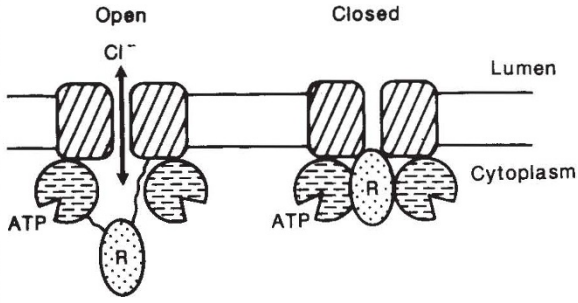
THE jury, it seems, is now in. After a period of hectic activity and a great deal of controversy, two papers in last week's *Science*[1,2] by the groups led by Michael Welsh and Alan Smith provide compelling evidence that the protein encoded by the cystic fibrosis gene is a regulated chloride channel. Earlier this year, as discussed in News and Views[3], it was shown that expression of the protein (known as CFTR) in several different cell types can generate a new cyclic AMP-regulated Cl^- channel[4,5]. In an elegant series of experiments, Welsh, Smith and their collaborators have now introduced specific amino-acid changes into CFTR which alter the characteristics of this channel. The results effectively exclude the possibility that CFTR activates an endogenous channel by acting as the transporter of some regulatory molecule.

Cystic fibrosis transmembrane conductance regulator (to give CFTR its full name) consists of five domains[6] (see figure). In the first of the two sets of experiments[1], positively charged amino acids in the transmembrane domains were, separately, replaced with negatively charged residues. This altered the ion selectivity of the channel in favour of I^- rather than Cl^-. The simplest interpretation is that these charged residues contribute to a transmembrane 'pore' and play a direct part in determining ion selectivity. But the effects of these charge reversals on the ion selectivity are, perhaps, more subtle than might have been anticipated. An alternative interpretation is that the amino-acid changes influence ion selectivity indirectly, through protein–protein interactions (dimerization of CFTR, or an interaction between CFTR and another protein).



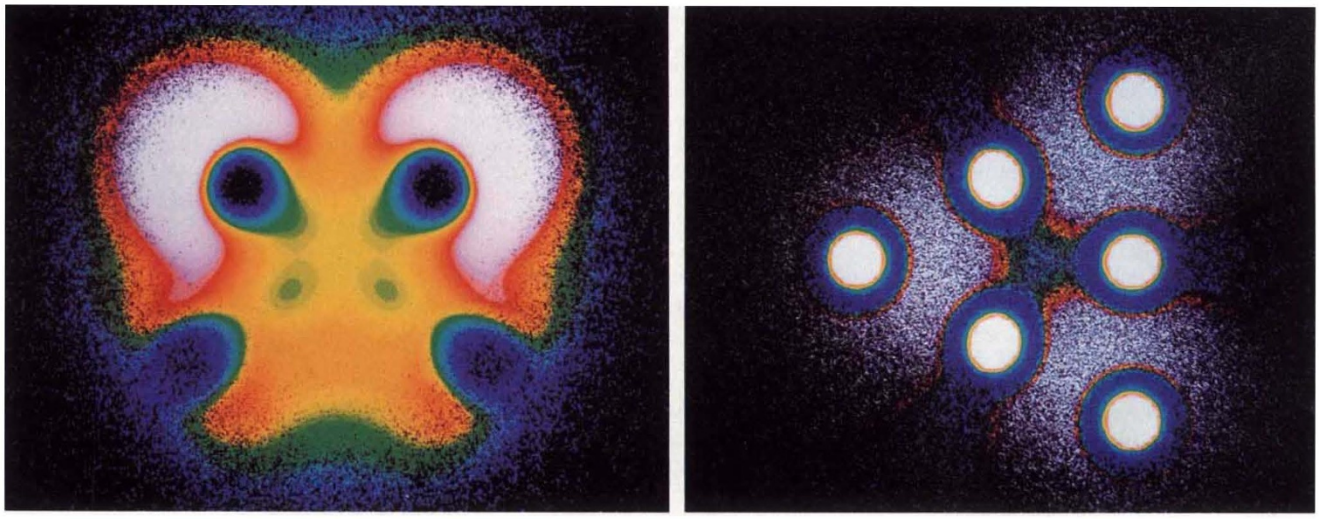
Model for CFTR function and regulation. Two transmembrane domains (hatched) form a pathway for Cl^- movement across the bilayer. The R domain opens and closes the channel in response to cAMP-activated protein kinases. The function of the ATP-binding domains (dashed lines) remains unclear.

In the second piece of work[2], deletion of the R domain of CFTR was found to leave the channel permanently open, implicating this domain in the opening and closing of the channel in response to cAMP-activated protein kinases (see figure). The observation that a mutation in one of the ATP-binding domains is suppressed by deletion of the R domain has been interpreted as showing that the ATP-binding domains may also have a regulatory role[2]: perhaps the R domain is moved into and out of the channel in an ATP-dependent fashion. In total, these data are convincing and strongly support the notion that CFTR is itself a regulated Cl^- channel or, at the very least, a component of a multisubunit channel.

Several riders must be added to this conclusion. First, the characteristics of the CFTR channel are very different from those of the voltage-gated, outwardly rectifying channel which has been associated with cystic fibrosis in the past; indeed, it now seems that the outward-rectifying channel may have little to do with cystic fibrosis[3]. Second, it remains to be shown that a channel with the characteristics of that conferred by CFTR is defective in cystic fibrosis cells; a similar channel has, however, been measured in normal epithelia[1,7]. Finally, most mutations to the cystic fibrosis gene alter the ATP-binding domains of CFTR, yet the function of these domains is far from clear.

Besides their obvious importance for cystic fibrosis research, the new results

Electron density maps with a difference



WITHIN every chemist, it seems, there lurks a Salvador Dali. What brings this repressed artistic bent out into the open is the need to depict some unusual trait of a complex molecule. A. Savin *et al.* (*Angew. Chemie Int. Ed. Engl.* **30**, 409–412; 1991) have turned their attention to the old problem of visualizing the distribution of electrons in molecular bonds. To emphasize the significance of localization of electrons in bonding, they have resorted to the electron-localization function, a mathematical measure, which they have colour-coded, of the probability of finding two electrons in the vicinity of one another. The two molecules shown here are (left) a slice through Cu_4Sn_4 in the heterocubane structure (made of intersecting tetrahedra of tin and copper) and a planar Li_6 cluster. Regions of highest density (the distorted lone pairs of tin in Sn_4Cu_4 and stable three-centre bonds in Li_6) are white. Density decreases through brown and blue to black. The tin nuclei appear black owing to the calculational method. The separation between the core and valence electrons of lithium is also apparent. (Courtesy A. Savin.)