ane and prostacyclin have opposing functions in haemodynamics; and leukotrienes are pro-inflammatory, whereas lipoxins seem to act as endogenous anti-inflammatory eicosanoids[1]. So it will be of interest to learn whether these groups of eicosanoids also have opposing effects on the transcriptional machinery.

Devchand *et al.*[2] have also shown that a hypolipidaemic drug that lowers triglyceride levels can activate PPARα. This hitherto unknown mechanism of activation offers a molecular model for rational drug design, to synthesize selective lipid-lowering agents as well as potential anti-inflammatory agents (Fig. 2). It is likely that the mechanism by which eicosanoids bind to PPARs and activate transcription involves conformational changes in the ligand–receptor complexes that dictate the sites of interaction with target genes. It follows that the binding of individual eicosanoids to PPARα may yield unique ligand–PPARα complexes that lead to differential gene expression. Along these lines, several leukotriene-receptor antagonists have been developed that very effectively block LTB_4 binding and function, although the clinical effects of these agents are not yet known[7].

Given the findings of Devchand *et al.*[2], it may be worth screening existing synthetic libraries of LTB_4 neutrophil antagonists and mimetics which have structural similarities to LTB_4, to test for their ability to activate PPARα and to lower the levels of triglycerides. Certain hypolipidaemic drugs may also have an anti-inflammatory action, and it should be possible to design anti-inflammatory agents that increase PPARα, allowing the increased expression of particular genes. This new link between membrane-derived bioactive lipids and gene expression opens up many opportunities for investigations into cell signalling and new targets for drug design. □

Charles N. Serhan is in the Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.

1. Serhan, C. N., Haeggström, J. Z. & Leslie, C. C. *FASEB J.* **10,** 1147–1158 (1996).
2. Devchand, P. R. *et al. Nature* **384,** 39–43 (1996).
3. Schoonjans, K., Staels, B. & Auwerx, J. *Biochim. Biophys. Acta* **1302,** 93–109 (1996).
4. Otto, J. C. & Smith, W. L. in *Molecular Biology of the Arachidonate Cascade* (eds Yamamoto, S. & Smith, W. L.) 139–156 (Elsevier, Amsterdam, 1995).
5. Borgeat, P., Hamberg, M. & Samuelsson, B. *J. Biol. Chem.* **251,** 7816–7820 (1976).
6. Ford-Hutchinson, A. W. *et al. Nature* **286,** 264–265 (1980).
7. Metters, K. M. in *Molecular Biology of the Arachidonate Cascade* (eds Yamamoto, S. & Smith, W. L.) 413–427 (Elsevier, Amsterdam, 1995).
8. Fiore, S., Ryeom, S. W., Weller, P. F. & Serhan, C. N. *J. Biol. Chem.* **267,** 16168–16176 (1992).
9. Forman, B. M. *et al. Cell* **83,** 803–812 (1995).
10. Wong, P. Y.-K. & Serhan, C. N. *Cell–Cell Interactions in the Release of Inflammatory Mediators: Eicosanoids, Cytokines, and Adhesion* (Plenum, New York, 1991).
11. Huwyler, J., Bürgin, M., Zeugin, T. & Gut, J. *Mol. Pharmacol.* **39,** 314–323 (1991).

ION CHANNELS

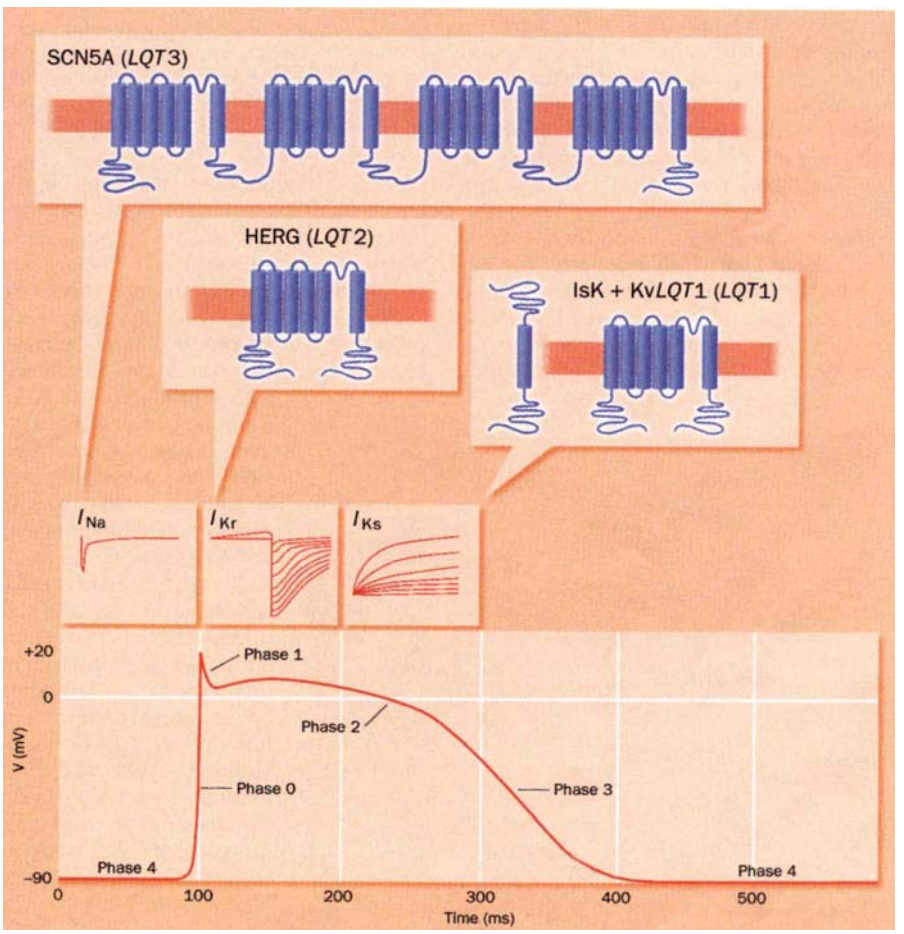
A new wave for heart rhythms

Bernard Attali

THE plasma membranes of cardiac muscle cells contain a complex repertoire of voltage-gated ion channels that are responsible for the generation of action potentials — travelling waves of electrical excitation. The delayed-rectifier K^+ channels are involved specifically in the repolarization of cardiac-cell membranes following an action potential, and abnormal behaviour of these channels is thought to cause deviations from the normal rhythms of the heart, so-called arrhythmias. Now, on pages 78 and 80 of this issue, Barhanin *et al.*[1] and Sanguinetti *et al.*[2] identify the molecular components of the slow delayed-rectifier K^+ channels, a crucial step in the search for new anti-arrhythmic drugs.

In many species, including humans, the K^+ current that passes through the cardiac delayed-rectifier channels corresponds to the sum of two distinct currents: a rapidly activating current, I_{Kr}, and a slowly activating current, I_{Ks}. Dysfunction of these channels causes the long-QT syndrome (LQT), an inherited disorder that increases the risk of sudden death from cardiac arrhythmias[3,4]. The I_{Kr} voltage-gated K^+ channel is the product of the *HERG* gene, mutations in which map to the *LQT2* locus[3]. Now I_{Ks} has also revealed some of its molecular secrets[1,2]. The new results show that the association of two structurally different membrane proteins, K_vLQT1 and IsK (minK), reconstitutes the cardiac slow delayed-rectifier I_{Ks} current.

The K_vLQT1 protein is a newcomer to the LQT club, and it was identified by positional cloning to the *LQT1* locus[4]. The



Following an action potential, mammalian cardiac cells are repolarized by the activation of a variety of K^+ channels. The molecular components of the channel that underlies the slowly activating current I_{Ks} have now been identified by Barhanin *et al.*[1] and Sanguinetti *et al.*[2]. The *LQT1* locus encodes the K_vLQT1 channel, which associates with IsK protein to form I_{ks}. The *LQT2* locus encodes the HERG K^+ channel, which underlies the rapidly activating current I_{Kr}. The outcome from the two channels is a small net outward current that increases with time, and mutations in *LQT1* and *LQT2* lead to a loss of channel function. The *LQT3* locus encodes the cardiac Na^+ channel, SCN5A, and mutations in *LQT3* lead to a gain of channel function. Despite their differences, mutations in K_vLQT1, HERG and SCN5A all lead to the long-QT syndrome, an inherited disorder characterized by delayed repolarization and cardiac arrhythmia.

partially cloned complementary DNA revealed that the *KVLQT1* gene encodes a hitherto undiscovered K^+ channel that is structurally similar to voltage-gated K^+ channels — it has a conserved K^+-selective pore-signature sequence flanked by six putative membrane-spanning segments. By contrast, IsK is a small, type-III glycoprotein that has a single putative membrane-spanning segment but neither sequence nor structural homology with any other cloned channels[5] (see figure). However, there is a remarkable correlation between the distribution of *KVLQT1* and *IsK* gene transcripts in heart, pancreas, kidney and salivary gland. This was, perhaps, the hint for the clever connection.

The *KVLQT1* complementary DNA has now been fully cloned and expressed in various heterologous systems[1,2]. Curiously, the expression of K_vLQT1 alone induces a voltage-dependent K^+ outward current that has very different biophysical characteristics from the native K^+ currents recorded in ventricular cells. For example, the K_vLQT1-activating kinetics are much faster than those of I_{Ks} and, in contrast to I_{Kr}, no inward rectification is apparent at positive potentials. However, with the exception of *Xenopus* oocytes, the expression of IsK alone does not produce detectable K^+-channel activity in transfected cells.

The breakthrough has been made by the coexpression of K_vLQT1 and IsK. This induces a slowly activating delayed-rectifier K^+ current that has similar gating kinetics to the native I_{Ks}, but a much higher amplitude than that observed with K_vLQT1 alone. Moreover, there is a +20-mV rightward shift in the voltage-dependence of activation when K_vLQT1 and IsK are coexpressed. Clearly, the biophysical properties of the K_vLQT1/IsK complex match those of the native I_{Ks} whereas those of K_vLQT1 alone do not.

To reach these conclusions, Barhanin *et al.*[1] used immunoprecipitation to demonstrate the physical interaction between K_vLQT1 and IsK, and Sanguinetti *et al.*[2] cloned the *Xenopus* analogue of K_vLQT1. These compelling data settle a long-running debate on two issues[6,7]. First, IsK alone is unable to form a functional K^+ channel. And second, IsK induces K^+ currents in *Xenopus* oocytes through interactions with endogenous K_vLQT1 channels. In a way, K^+ channels are more conformist than we expected, because they need a K^+-selective pore-signature sequence.

The clinical implications of these findings are numerous. The cardiac I_{Ks} channel is a target of class-III anti-arrhythmic drugs, and blocking it can delay repolarization and induce an acquired form of LQT. On the other hand, positive regulation of I_{Ks} by drugs such as fenamates might be helpful[8]. In either case, a sharp picture of the molecular contours of the K_vLQT1/IsK channel complex should provide clues for drug design. The status of K_vLQT1 and IsK should also be examined in the autosomal recessive form of LQT, known as Jervell–Lange-Nielsen syndrome, which is associated with congenital neural deafness. A careful study of the effects of *KVLQT1* mutations on channel function and their correlation with clinical symptoms should also be informative. Like mutations in the *HERG* gene, the *KVLQT1* mutations may act in a dominant-negative fashion and lead to a loss of channel function.

The biophysical impact of these stimulating data raise many questions that should stimulate innovative studies on channel gating, permeation, assembly and stoichiometry. By which 'unusual' mechanisms does IsK reduce the K_vLQT1 gating kinetics? To some extent, IsK bridles the activation of K_vLQT1, but in so doing renders the K_vLQT1 channel more efficient. Does the IsK protein form part of the channel pore, and if so, what are the interacting domains? Single-channel studies should be very helpful in addressing this question. Finally, what are the interface domains and stoichiometries involved in the physical interaction between K_vLQT1 and IsK, and how are these important for channel assembly? We should soon be able to open our gates to a flurry of reports addressing these questions. □

Bernard Attali is in the Department of Neurobiology, The Weizmann Institute of Science, 76100 Rehovot, Israel (e-mail: bnattali@weizmann.weizmann.ac.il).

1. Barhanin, J. *et al. Nature* **384,** 78–80 (1996).
2. Sanguinetti, M. C. *et al. Nature* **384,** 80–83 (1996).
3. Curran, M. E. *et al. Cell* **80,** 795–804 (1995).
4. Wang, Q. *et al. Nature Genet.* **12,** 17–23 (1996).
5. Takumi, T., Ohkubo, H. & Nakanishi, S. *Science* **242,** 1042–1045 (1988).
6. Goldstein, S. A. N. & Miller, C. *Neuron* **7,** 403–408 (1991).
7. Attali, B. *et al. Nature* **365,** 850–852 (1993).
8. Busch, A. *et al. Mol. Pharmacol.* **46,** 750–753 (1994).

DNA REPAIR

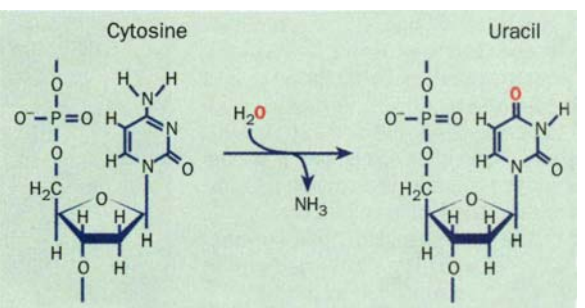
Push and pull of base flipping

Thomas A. Kunkel and Samuel H. Wilson

ENZYMES that are involved in the modification or removal of specific bases from DNA — such as methyltransferases and glycosylases — processively scan the DNA[1] in their search for what are often rare binding sites. These exquisitely specific enzymes recognize and process their substrates by binding target bases outside the double helix[2,3]. But we know very little about the mechanisms that could lead to such 'flipping' of bases to an extra-helical position by proteins that scan along a DNA molecule at rates approaching thousands of base pairs per second.

The report by Slupphaug *et al.*[4] on page 87 adds significant new insight to this interesting problem. They present the crystal structure of human uracil–DNA glycosylase (UDG) bound to uracil-containing DNA. Their detailed view of the UDG active site suggests that the enzyme pushes the target uracil base out from the DNA helix and then pulls the base into its substrate-binding pocket where the uracil is excised.

In the next 24 hours, the DNA in every cell in your body will be spontaneously damaged more than 10,000 times[5]. To deal with this, and with the additional challenges to genomic integrity that arise from external insults (for example, ultraviolet light or chemicals), cells have several different enzymatic DNA-repair pathways. These include mismatch repair for correcting DNA-replication errors, and nucleotide-excision repair for correcting bulky adducts that often distort the helix and block DNA replication. Also included is base-excision repair[6], which is initiated when DNA glycosylases recognize a variety of different modified bases and excise them from the DNA. These bases arise as a result of the deamination, oxidation and alkylation reactions that frequently occur in cells during everyday metabolism. One of the most extensively studied base modifications is cytosine deamination, which yields hundreds of uracil bases per human cell per day (see figure). These are highly mutagenic if unrepaired, leading to G–C to A–T transitions. So, to remove uracil and initiate repair, cells express UDG. ▶



Because cytosine normally pairs with guanine, cytosine deamination to uracil generates a G–U mispair. If the uracil is not corrected by base-excision repair before the next round of replication, then adenine will be incorporated opposite the uracil, ultimately yielding a G–C to A–T transition.