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. and Sanguinetti et al. 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. The \( I_{Ks} \) voltage-gated K⁺ channel is the product of the HERG gene, mutations in which map to the LQT2 locus. Now \( I_{Ks} \) has also revealed some of its molecular secrets. The new results show that the association of two structurally different membrane proteins, K₅LQT1 and IsK (minK), reconstitutes the cardiac slow delayed-rectifier \( I_{Ks} \) current.

The K₅LQT1 protein is a newcomer to the LQT club, and it was identified by positional cloning to the LQT1 locus. The

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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 \( I_{Kr} \) have now been identified by Barhanin et al. and Sanguinetti et al.. The LQT1 locus encodes the K₅LQT1 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 K₅LQT1, HERG and SCN5A all lead to the long-QT syndrome, an inherited disorder characterized by delayed repolarization and cardiac arrhythmia.
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. In either case, a sharp picture of the molecular contours of the $K_{LQT1}/IsK$ channel complex should provide clues for drug design. The status of $K_{LQT1}$ 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 $K_{LQT1}$ mutations on channel function and their correlation with clinical symptoms should also be informative. Like mutations in the HERG gene, the $K_{LQT1}$ 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 ‘universal’ mechanisms does IsK reduce the $K_{LQT1}$ gating kinetics? To some extent, IsK bridges the activation of $K_{LQT1}$ but in so doing renders the $K_{LQT1}$ 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 $K_{LQT1}$ 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.

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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 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.

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 C-to-T transition.

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