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# In This Issue

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Ion channel genes reshape the action potential (See article on page 1077–1084.) As cardiac action potentials proceed from rapid depolarization through the restoration of the resting membrane potential, a series of ion currents come into play, carried by distinct ion channels. Hoppe et al. focus here on a pair of voltage gated channels that mediate the Ca2+-independent transient outward K+ current, a component of the action potential that is commonly disrupted in failing hearts. Working both with cardiac muscle cell culture and with living mice whose hearts were injected with ion channel transgenes, Hoppe and colleagues show that a dominant-negative allele can block repolarization and extend the duration of the action potential. For their work in vivo, these authors constructed adenovirus vectors that can drive expression of wild-type or dominant-negative alleles of the ion channel genes under control of ecdysone, a factor that is foreign to mammals and is expected to be biologically inert in nontransgenic mice. This system should allow them to manipulate ion channel activity in a subtle manner and probe the immediate and long-term effects of perturbed ion flow in the living heart.Passive T-cell death protects mice from CNS damage (See article on pages 1109–1116.) T lymphocytes can activate their apoptotic pathways by at least 2 biochemically distinct routes. Activation-induced cell death (AICD) depends on stimulation of […]



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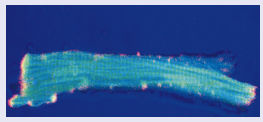
*By John Ashkenas, Science Editor*

## Ion channel genes reshape the action potential

*(See article on page 1077–1084.)*

As cardiac action potentials proceed from rapid depolarization through the restoration of the resting membrane potential, a series of ion currents come into play, carried by distinct ion channels. Hoppe et al. focus here on a pair of voltage gated channels that mediate the $Ca^{2+}$-independent transient outward $K^+$ current, a component of the action potential that is commonly disrupted in failing hearts. Working both with cardiac muscle cell culture and with living mice whose hearts were injected with ion channel transgenes, Hoppe and colleagues show that

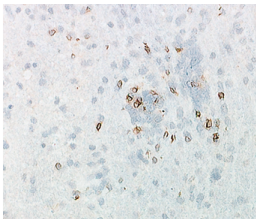


a dominant-negative allele can block repolarization and extend the duration of the action potential. For their work in vivo, these authors constructed adenovirus vectors that can drive expression of wild-type or dominant-negative alleles of the ion channel genes under control of ecdysone, a factor that is foreign to mammals and is expected to be biologically inert in nontransgenic mice. This system should allow them to manipulate ion channel activity in a subtle manner and probe the immediate and long-term effects of perturbed ion flow in the living heart.

## Passive T-cell death protects mice from CNS damage

*(See article on pages 1109–1116.)*

T lymphocytes can activate their apoptotic pathways by at least 2 biochemically distinct routes. Activation-induced cell death (AICD) depends on stimulation of receptors such as Fas, whereas passive cell death arises from the absence of survival signals and reflects the balance of intracellular proapoptotic factors, such as Bax, and anti-apoptotic factors, such as Bcl-$x_L$. Which of these pathways suppresses the immune responses in experimental autoimmune encephalomyelitis (EAE) has become controversial. Here, Issazadeh and colleagues show that Bcl-$x_L$ overexpression in T cells, which should specifically inhibit the passive apoptotic pathway in these cells, increases the severity of this condition in mice. When immunized with an epitope from a component of myelin, transgenic mice develop autoimmune disease more reliably than do similarly treated wild-type mice, and their neurons show a more severe loss of myelination. Active demyelination and heightened levels of inflammatory cytokines in the brains of transgenic mice correlate with reduced numbers of apoptotic cells, arguing that passive cell death by T cells is crucial for suppressing this disease process. As Issazadeh et al. note, other reports, including a recent paper in the *JCI*, have argued the converse, claiming that AICD is protective in this system. Some of these discrepancies may be explained, as the authors suggest, by effects on apoptosis in cell types other than T lymphocytes or by differences between mouse and rat in the pathogenesis of autoimmune disease. Still, the apoptotic pathway that is most relevant to multiple sclerosis, the human disease that EAE is intended to model, apparently remains undefined.



## The outRAGE of diabetic gum disease

*(See article on page 1117–1124.)*

Many of the vexing complications of diabetes mellitus, including microvascular injury and atherosclerosis, result from the accumulation in the tissues of advanced glycation end products (AGEs), proteins that acquire abnormal covalent modifications with sugars. RAGE, the cell surface receptor for AGEs, also binds specifically to the cytokine EN-RAGE, and stimulation of the receptor by either class of ligand promotes inflammation in various tissues. Lalla and coworkers now report that periodontal disease, another hallmark of diabetes, also results from activation of RAGE. This group previously documented that diabetic mice, like humans, are prone to oral inflammation and degradation of the alveolar bone when inoculated with a periodontal pathogen, and they now show that blocking RAGE function protects these mice from periodontal disease. Lalla et al. report that a soluble form of RAGE (sRAGE), administered systemically, has a number of effects on gingival tissue, one or more of which could account for the protective effect of this treatment. sRAGE inhibits expression of several secreted proteinases and also interferes with the accumulation of AGEs in this tissue. Interestingly, sRAGE also causes loss of RAGE and EN-RAGE expression. These latter effects occur even with doses of sRAGE that are too low to block periodontal disease, indicating that they are not sufficient to explain the beneficial effects of sRAGE in the gums. However, the loss of RAGE and EN-RAGE expression when RAGE signaling is blocked hints at a positive feedback mechanism that could operate in other tissues where RAGE activation leads to local inflammation and disease.