JCI The Journal of Clinical Investigation

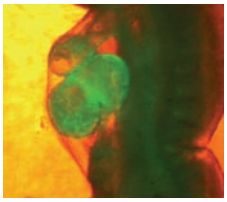
In This Issue

J Clin Invest. 2004;114(7):867-867. https://doi.org/10.1172/JCI120008.

In this issue

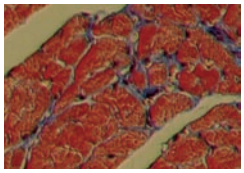
Changing channels Potassium channels are classified by their inward or outward rectifying current voltage relation. The membrane potential of several excitable and nonexcitable cells is maintained at the equilibrium potential for potassium (K+) by inward-rectifier K+ (Kir) channels. Reduction in heart rate through the parasympathetic nervous system relies on the acetylcholine-dependent activation of the G-protein-gated K+ channel (IK,ACh). This channel is composed of two Kir-channel subunits, Kir3.1 and Kir3.4, which have distinct functional properties. Bernd Fleischmann and colleagues (pages 994–1001) investigated the subunit composition of IK,ACh in young compared with adult cardiomyocytes and found that subunit composition changed during embryonic development. IK,ACh is primarily made up of Kir3.1 in the early stages and of Kir3.4 in later embryonic and adult stages. This change in subunit composition allows IK,ACh to generate the membrane hyperpolarization that underlies the strong negative chronotropy that occurs with the application of muscarinic agonists in late but not early stage atrial cardiomyocytes. Additionally, when the researchers virally expressed Kir3.4 in early stage cardiomyocytes, this enabled these cells to generate both negative chronotropy and membrane hyperpolarization. These data show that it is a switch in subunit composition that enables IK,ACh to achieve its functional role in adult cardiomyocytes. See figure ASK1 for whom Raf-1 tolls Heart failure can be the outcome of a variety of diseases and results […]

Changing channels



Potassium channels are classified by their inward or outward rectifying current voltage relation. The membrane potential of several excitable and nonexcitable cells is maintained at the equilibrium potential for potassium (K^+) by inward-rectifier K^+ (Kir) channels. Reduction in heart rate through the parasympathetic nervous system relies on the acetylcholine-dependent activation of the G-protein–gated K^+ channel ($I_{K,ACh}$). This channel is composed of two Kir-channel subunits, Kir3.1 and Kir3.4, which have distinct functional properties. Bernd Fleischmann and colleagues (pages 994–1001) investigated the subunit composition of $I_{K,ACh}$ in young compared with adult cardiomyocytes and found that subunit composition changed during embryonic development. $I_{K,ACh}$ is primarily made up of Kir3.1 in the early stages and of Kir3.4 in later embryonic and adult stages. This change in subunit composition allows $I_{K,ACh}$ to generate the membrane hyperpolarization that underlies the strong negative chronotropy that occurs with the application of muscarinic agonists in late but not early stage atrial cardiomyocytes. Additionally, when the researchers virally expressed Kir3.4 in early stage cardiomyocytes, this enabled these cells to generate both negative chronotropy and membrane hyperpolarization. These data show that it is a switch in subunit composition that enables $I_{K,ACh}$ to achieve its functional role in adult cardiomyocytes.

ASK1 for whom Raf-1 tolls

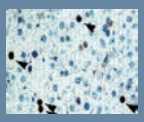


Heart failure can be the outcome of a variety of diseases and results in the loss or malfunction of cardiomyocytes. Recent work has suggested that apoptosis may play an important role in heart failure. Raf-1 inhibits apoptosis through the activation of the MEK/ERK pathway and has recently been implicated in a stress-response pathway involving apoptosis signal-regulating kinase–1 (ASK1) and mitogen-activated protein kinase kinase (MKK). To investigate whether Raf-1 dysfunction can affect heart function, Kinya Otsu and colleagues developed a cardiac-specific Raf-1–deficient transgenic mouse (pages 937–943). These mice had heart dilatation but without cardiac hypertrophy or lethality. Additionally, they showed left ventricular systolic dysfunction. TUNEL assay demonstrated a significant increase in apoptotic cells in the hearts of the transgenic mice. ASK1 kinase activity was higher in Raf-1–deficient mice, but there was no change in the expression level or activation of MEK1/2 or ERK. Knocking out *ASK1* in the Raf-1–deficient mice rescued all the heart defects. Taken together, these data provide evidence that Raf-1 promotes cardiomyocyte survival in a MEK/ERK–independent manner and that, in addition to having a role in early embryogenesis, Raf-1 functions at the organ level.

Giving a NOD to diabetes

The best-characterized model of human type I diabetes is the nonobese diabetic (NOD) mouse. In NOD mice, autoreactive T cells that recognize pancreatic islet antigens cause extensive islet damage. Recently, therapeutic strategies explored in this model have focused on dampening the activity of these autoreactive immune cells and in particular on targeting the CD28-B7 and CD40L-CD40 costimulatory pathways because previous work has shown that NOD–B7-2$^{-/-}$ and NOD-CD40L mice do not develop diabetes. Given the absence of diabetes in these mice, Jeffrey Bluestone and colleagues tested the hypothesis that specifically inhibiting CD28 versus CD40L pathways will differentially affect autoreactivity versus immune regulation (pages 979–987). Their data showed that in *NOD–B7-2*$^{-/-}$ mice, autoreactive T cell initiation was defective, but effector function was not. Furthermore, CD28-dependent $CD4^+CD25^+$ regulatory T cells inhibited the proliferation of any remaining autoreactive cells. CD28 loss resulted in a significant decrease in Tregs, which allowed partial restoration of the diabetes phenotype in *NOD–CD40L*$^{-/-}$ mice. The work here demonstrates that diabetes development in NOD mice is dependent on a balance of pathogenic and regulatory T cells that is controlled by costimulatory signals. The fact that even in the absence of costimulation, Treg loss resulted in diabetes indicates the need for investigation of alternative therapeutic strategies.

Obesity and cancer in the L-SACC1



Research has indicated that carcinoembryonic antigen–related cell adhesion molecule (CEACAM1) displays tumor suppressor activity, but its mechanism of action remains largely unknown. Sonia Najjar and colleagues used a transgenic mouse that carries a liver-specific overexpression of the phosphorylation-defective S503a CEACAM1 mutation (L-SACC1) to further dissect the means by which CEACAM1 carries out this antiproliferative effect (pages 944–952). The authors showed that, in addition to being a substrate for insulin receptor tyrosine kinase in the liver, CEACAM1 was also phosphorylated by EGFR in an EGF-dependent manner and its phosphorylated form reduced the mitogenic effect of EGF. Their analysis of the livers of wild-type and L-SACC1 mice revealed that phosphorylated CEACAM1 downregulates EGF-stimulated growth by binding to EGFR via Shc. This reduces Shc interaction with the ras/MAP kinase growth-promoting pathway. The researchers' analysis of L-SACC1 mice indicated that EGFR amplified cell proliferation in an EGF-independent manner. This growth-stimulating activity of EGFR began subsequent to the L-SACC1 mice developing visceral obesity and metabolic syndrome and therefore exhibiting increased amounts of free fatty acids and heparin-binding EGF-like growth factor. These data suggest that L-SACC1 mice provide an excellent model for further exploring the mechanisms underlying the previously noted link between visceral obesity and cancer.