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In This Issue

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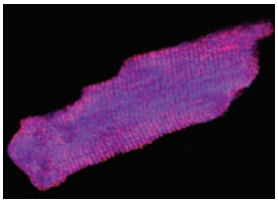
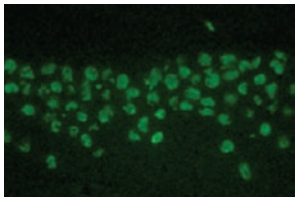
Healing a failing heart As heart failure remains a leading cause of mortality in the developed world, researchers continue to search for therapies targeted to the underlying molecular defects that lead to chronic ventricular dysfunction. While other systems contribute, there is substantial evidence that abnormal intracellular Ca2+ handling is a key component of the impaired contractile performance of the failing heart. Patrick Most and colleagues show that adenovirus-mediated gene delivery of the Ca2+-binding protein, S100A1 can restore contractile function in postinfarction failing rat myocardium. S100A1, a low-molecular-weight Ca2+-binding protein is especially interesting with respect to cardiovascular disease, as it is the most abundant S100 protein isoform in the heart and has been found to be downregulated in human and animal models of heart failure (pages 1550–1563). Restoration of cardiac S100A1 protein levels normalized intracellular Ca2+ transients and sarcoplasmic reticulum Ca2+ content, reversed diastolic Ca2+ overload, and disturbed Na+ handling in the failing myocardium. The beneficial S100A1-mediated effects were derived from direct actions on the SERCA/phospholamban complex and the sarcoplasmic reticulum Ca2+-release channel (RyR2). The S100A1-mediated rescue of contractile function and Ca2+ cycling was associated with reconstituted energy supply and silencing of reactivated fetal gene expression pattern that defines abnormal cardiac function. Restoration of S100A1 protein levels in failing myocardium by gene transfer may be a novel therapeutic strategy for the […]

Healing a failing heart



As heart failure remains a leading cause of mortality in the developed world, researchers continue to search for therapies targeted to the underlying molecular defects that lead to chronic ventricular dysfunction. While other systems contribute, there is substantial evidence that abnormal intracellular Ca^{2+} handling is a key component of the impaired contractile performance of the failing heart. Patrick Most and colleagues show that adenovirus-mediated gene delivery of the Ca^{2+}-binding protein, S100A1 can restore contractile function in postinfarction failing rat myocardium. S100A1, a low-molecular-weight Ca^{2+}-binding protein is especially interesting with respect to cardiovascular disease, as it is the most abundant S100 protein isoform in the heart and has been found to be downregulated in human and animal models of heart failure (pages 1550–1563). Restoration of cardiac S100A1 protein levels normalized intracellular Ca^{2+} transients and sarcoplasmic reticulum Ca^{2+} content, reversed diastolic Ca^{2+} overload, and disturbed Na^{+} handling in the failing myocardium. The beneficial S100A1-mediated effects were derived from direct actions on the SERCA/phospholamban complex and the sarcoplasmic reticulum Ca^{2+}-release channel (RyR2). The S100A1-mediated rescue of contractile function and Ca^{2+} cycling was associated with reconstituted energy supply and silencing of reactivated fetal gene expression pattern that defines abnormal cardiac function. Restoration of S100A1 protein levels in failing myocardium by gene transfer may be a novel therapeutic strategy for the treatment of heart failure.

Remember rolipram?

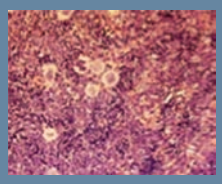


Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by mild cognitive impairment due to increased levels of amyloid β-peptides followed by deficits in multiple cortical functions in later stages of disease. There are only a few clinical options for AD patients, but now Ottavio Arancio, Michael Shelanski, and colleagues propose a new treatment to counter AD-associated memory loss (pages 1624–1634). The authors show that brief treatment of a transgenic mouse model of AD with the phosphodiesterase 4 inhibitor rolipram ameliorates deficits in both long-term potential (LTP) and contextual learning, which are measurements of neural function. Rolipram's protective effect is due to stabilization of synaptic circuitry via alterations in gene expression by activation of the cAMP/PKA/CREB signaling pathway that makes synapses more resistant to the insult caused by amyloid β. The beneficial effect of rolipram treatment extended beyond the duration of the administration: one course of long-term systemic treatment with rolipram improved LTP and basal synaptic transmission, as well as working, reference, and associative memory deficits for at least 2 months after the end of the treatment. This suggests that phosphodiesterase inhibitors have the potential to prevent the memory loss characteristic of AD.

At a LOS for gangliosides

Molecular mimicry of *Campylobacter jejuni* lipo-oligosaccharides (LOS) with gangliosides in nervous tissue can induce cross-reactive antibodies leading to the development of Guillain-Barré syndrome (GBS). Peggy Godschalk, Astrid Heikema, and colleagues examined the LOS biosynthesis gene cluster in *C. jejuni* strains associated with GBS and found that specific types of this gene cluster were associated with GBS and the expression of ganglioside-mimicking structures (pages 1659–1665). The authors then created *C. jejuni* mutants deficient in relevant LOS genes to establish the crucial causal role of these genes in the induction of autoimmune antibodies in mice. Specific bacterial genes were shown to be crucial for the induction of anti-ganglioside antibodies. These data provide new insights into and a better understanding of the pathogenesis of postinfectious autoimmune disease and create new opportunities for the development of diagnostic tests for rapid identification of neuropathogenic strains and early intervention in the course of human disease.

TYK-tock goes the lymphoid clock



The JAK-STAT signaling cascade regulates cell proliferation, differentiation, and survival in hematopoietic cells, and aberrant activation of JAK-STAT signaling had been shown in multiple solid tumors and leukemia. In their manuscript, Veronika Sexl and colleagues describe for the first time a central role of the JAK kinase TYK2 in the evolution of B lymphoid tumors (pages 1650–1658). Contrary to expectations, mice deficient for TYK2 developed Abelson-induced B lymphoid leukemia/lymphoma as well as TEL-JAK2–induced T lymphoid leukemia with a higher incidence and shortened latency compared with wild-type control mice. The high susceptibility of $TYK2^{-/-}$ mice resulted from impaired tumor surveillance. The increased rate of lymphoma and leukemia formation was linked to a decreased in vitro cytotoxic capacity of $TYK2^{-/-}$ NK cells and NK T cells toward tumor-derived cells. This defines NK cells as key players in tumor surveillance in Abelson-induced malignancies. The authors speculate that TYK2 deficiency in people is clinically silent (unless virus load is excessive) but predisposes to tumor formation. As patients with hematopoietic malignancies represent a population in which TYK2 deficiency is enriched, absence of TYK2 could predict a reduced responsiveness to type I IFNs, which are often used for the treatment of chronic myelogenous leukemia. Therefore, TYK2 deficiency may be relevant to the prognosis of patients as well as their proper treatment.