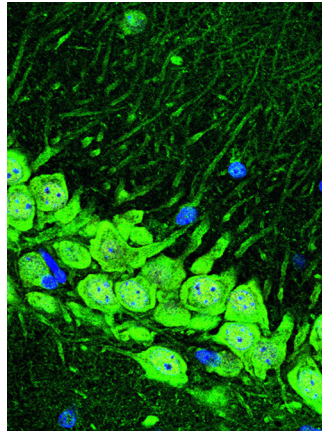


Fibroblast GRK2 Loss Limits Ischemic Injury (p 1116)

Fibroblast-specific GRK2 inhibition improves heart recovery after injury, say Woodall *et al.*

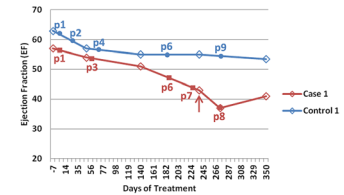
Upregulation of G protein-coupled receptor kinase 2 (GRK2) in heart failure reduces the contractile response of cardiomyocytes. Therefore, inhibiting GRK2 activity in cardiomyocytes to improve contractility and heart function might be a promising treatment for heart failure. However, cardiomyocytes are not the only cells affected by injury and heart failure. After infarction, cardiac fibroblasts—the supporting structural cells of the myocardium—form collagen-rich scars and secrete cytokines that promote inflammation. To determine whether GRK2 inhibition would affect fibroblast function, Woodall and colleagues examined responses to myocardial infarction in mice genetically engineered to conditionally and specifically lack GRK2 in their cardiac fibroblasts. They found that deletion of GRK2 specifically in fibroblasts promoted myocardial recovery after heart failure. These mice exhibited improved heart function, smaller infarcts, lower levels of fibrosis and less inflammation (reduced numbers of infiltrating neutrophils and lower expression of the proinflammatory cytokine TNF α). Taken together, these results suggest that inhibition of GRK2 in both myocytes and fibroblasts improves cardiac recovery after injury. The results also provide support for the idea that GRK2 inhibition could be a beneficial approach in the treatment of heart failure.



Endothelial NO Loss Promotes Tau Phosphorylation (p 1128)

Reduced endothelial nitric oxide production prompts tau phosphorylation in Alzheimer's model mice, report Austin and Katusic.

Alzheimer's disease (AD) is the most common form of age-related dementia that affects an estimated 5 million sufferers in the United States alone. Although specific causes underlying this debilitating, neurodegenerative disorder remain unclear, risk factors for cardiovascular diseases have been found to be associated with a higher incidence of AD. A risk factor common to several cardiovascular diseases is endothelial dysfunction, characterized by reduced bioavailability of nitric oxide (NO). Previous studies have shown that NO is an important neurological signaling molecule and that loss of NO in mice can lead to both cognitive impairment and increased abundance of amyloid precursor protein—an AD-related pathology. Now, Austin and Katusic have discovered that loss of NO promotes a second pathological protein. They found that the brain tissue of AD model mice genetically engineered to lack endothelial NO synthase (eNOS) showed significant accumulation of phosphorylated tau—a major component of the pathological tangles found in the brains of AD patients. The kinase p25, which drives tau phosphorylation, was also increased. The results, thus, identify a novel role of NO in AD pathology and support the idea that maintaining endothelial health may be important for the prevention and the treatment of AD.



IgE and Cardiac Dysfunction (p 1135)

Beer *et al* discover that immunoglobulin E is a potential biomarker for cardiovascular problems associated with cancer therapy.

Both the chemotherapy drug doxorubicin and the human monoclonal antibody trastuzumab (Herceptin) are widely used in the treatment of breast cancer. But both these therapies increase the risk of cardiovascular dysfunction. Early identification of patients who might be at a higher risk of developing such cancer therapeutics-related cardiovascular dysfunction (CTRCD) could minimize CTRCD risk by enabling timely intervention. Nevertheless, why some patients are more susceptible to CTRCD than others is, as yet, unknown. In the hopes of identifying potential biomarkers of CTRCD risk, Beer and colleagues examined the blood proteomes of breast cancer patients before, during, and after treatment with doxorubicin and/or trastuzumab. In an initial study of 7 patients—3 with and 4 without CTRCD—they found that high expression of immunoglobulin E (IgE) was significantly associated with low CTRCD risk (even before therapy started). A follow-up validation study in 35 patients then further confirmed that high IgE consistently equated with lower cardiovascular risk. These results not only suggest that IgE may be a potentially useful biomarker for identifying at-risk patients, but also reveal that the immune system influences the cardiovascular health of cancer patients.

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