IN THIS ISSUE

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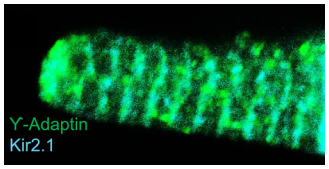
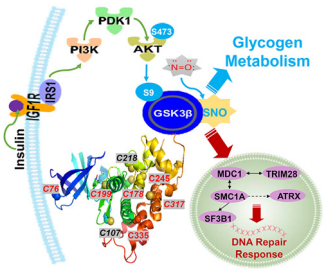


$Na_V1.5$ and Kir2.1 Channels' Common Trafficking Pathway (p 1501)

Sodium channel $Na_V1.5$ and potassium channel Kir2.1 team up to traverse the cell, report Ponce-Balbuena et al.

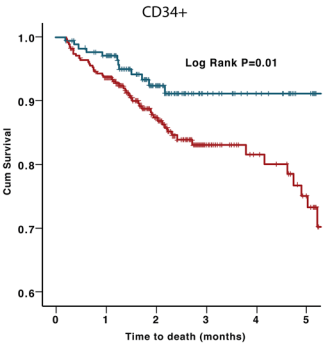
Kir2.1 is the major potassium channel responsible for the inward potassium current (I_{K1}) of ventricular myocytes, while $Na_V1.5$ generates the fast-inward sodium current (I_{Na}). As such, the 2 proteins are crucial for the normal electrical functioning of the heart. Both Kir2.1 and $Na_V1.5$ are parts of a large multiprotein complex, but when and where the channels come together was unknown. Ponce-Balbuena and colleagues have now shown, in cardiomyocytes and other cell types, that expression of a trafficking-deficient version of Kir2.1 not only affected the I_{K1}, but the I_{Na} too, suggesting the channels are trafficked together. Indeed, the team found that trafficking-deficient Kir2.1 did not alter $Na_V1.5$ expression levels, but instead interfered with the plasmalemmal localization of the sodium channel. Immunoprecipitation and immunostaining experiments confirmed the 2 channels interact, and showed they also partner with the trafficking factor AP1 (adaptor protein 1). Since both these channels are critical for normal electrophysiological functioning of the heart, these insights into their assembly and trafficking could inform arrhythmia research and the development of antiarrhythmic interventions.



S-Nitrosylation Controls GSK3β Function (p 1517)

S-Nitrosylation controls glycogen synthase kinase 3β (GSK3β), say Wang and colleagues.

Nitric oxide (NO) is a vasodilator, and a critical signaling molecule. And recently, NO has also been found to regulate protein function by *S*-nitrosylation. In a screen for *S*-nitrosylated proteins in the heart, Wang et al identified the kinase GSK3β. This enzyme is involved in a wide variety of cellular processes, and its dysregulation has been linked to several pathological conditions, including heart failure. GSK3β is a constitutively active enzyme, but is inhibited via phosphorylation at Ser-9. The researchers now show that *S*-nitrosylation also inhibits GSK3β, independent of Ser-9 phosphorylation, but that this form of inhibition is specific to GSK3β in the cytosol. *S*-nitrosylation of GSK3β induced nuclear translocation of the enzyme where the modification drove GSK3β-mediated phosphorylation of nuclear targets with a specific amino acid motif. The team went on to show that the abundance of nitrosylated GSK3β is increased in an animal model of heart failure. They conclude that post-translational modification of GSK3β by NO is a novel regulatory mode that could play an important role in heart failure, as well as other diseases associated with inhibition of GSK3β activity.



Progenitor Cells and Outcomes in Acute Coronary Syndrome (p 1565)

Levels of circulating progenitor cells predict clinical outcomes of acute coronary syndromes, report Tahhan et al.

Acute coronary syndromes (ACS), such as heart attacks and angina, are caused by intravascular thrombosis following rupture of an atherosclerotic plaque. Recent work has shown that circulating progenitor cells (CPCs) and resident stem cells contribute to myocardial recovery after ACS. Indeed, myocardial infarction is associated with both transient and prolonged elevation in CPC levels. Nevertheless, it is unknown whether the magnitude of a CPC response can predict long-term outcomes in ACS patients. Tahhan and colleagues examined CPC levels in more than 2000 patients with stable coronary artery disease (CAD), unstable angina (UA), and acute myocardial infarction (AMI). They found that CPC levels were significantly higher in AMI patients than in either UA or CAD patients, but that in all ACS patients (AMI and UA), subjects with low levels of CPCs had an ≈2.5-fold increased risk of all-cause mortality after 2 years. The team then validated this CPC-mortality link in an additional cohort of 238 ACS patients. These findings suggest that CPC counts could be used to identify high-risk ACS individuals and that novel strategies to boost CPC levels may be a way to improve clinical outcomes in such patients.

Written by Ruth Williams
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