Adora2b-elicted Per2 stabilization promotes a HIF-dependent metabolic switch crucial for myocardial adaptation to ischemia.

Eckle et al


In a recent issue of Nature Medicine, Eckle et al demonstrated that activation of an adenosine receptor (Adora2b) acts via the circadian clock protein, period2 (Per2), to induce a metabolic switch from fatty acid to glucose in cardiomyocytes, which is protective against ischemic injury. Indeed, stabilization of Per2 expression by exposure of mice to intense light has a similar cardioprotective effect as Adora2b activation.

Timing is everything, and it has long been known that there is a temporal variation in the incidence of clinical cardiovascular events—myocardial infarction, stroke, and perhaps even the response to angioplasty.2 Recently, genetic manipulations in mice have linked proteins relevant to the core molecular clock with regulation of blood pressure homeostasis1 and thrombogenesis,4 as well as the size of cardiac infarcts consequent to ischemia-reperfusion.5 Now, a report by Eckle et al in Nature Medicine implicates Per2, an important regulator of the negative limb of the molecular clock, in cardioprotection from ischemia in mice by inducing a metabolic switch away from fatty acid metabolism to anaerobic glycolysis. Adenosine has long been recognized as contributing to the protective effects of cardiac preconditioning, specifically acting via its receptor, Adora2b.6 Given this background, the authors performed a microarray to scan Adora2b targets in mouse heart, and Per2 topped the list. Activation of Adora2b increased both expression and stability of the Per2 protein, contributing to cardioprotection conferred by ischemic preconditioning by enhancing glycolysis via stabilization of hypoxia-inducible factor-1α. Provocatively, stabilization of Per2 expression by exposure of mice to intense light afforded protection from myocardial ischemia. Could this be a new therapeutic approach to heart disease in humans?

Despite its long being the focus of extensive studies, including its replication in humans,7 the fundamental mechanism of ischemic preconditioning remains unclear. Enhanced adenosine signaling is one of several pathways implicated in cardiac adaptation to ischemia.8,9 Adora2b is the only 1 of the 4 adenosine receptors whose cardiac expression is induced by ischemia in both mice and humans and whose function is implicated in ischemic preconditioning.1,6

These results are striking, but some fundamental questions remain. Although Per2 provides a seductive link between the molecular clock and cardiac function, the only other core clock gene altered by Adora2b activation was Per1, yet its deletion had no effect on the response to myocardial ischemia.1 The functions of Per1 and Per2 are partially redundant because both single mutant mice are rhythmic in behavior, but double gene deletion results in arrhythmia under constant darkness.8 In this article, however, Eckle et al describe a unique role for Per2 in mouse heart. Might this be a nonclock function of Per2 despite the temporal severity of the response to cardiac ischemia in mice and the temporal variation in clinical cardiovascular phenotypes? In contrast, genetic manipulation of multiple core clock genes influences both blood pressure3,10 and metabolic function11–13 in different ways, providing some reassurance against off-target effects. Similarly, is this a cardiac function of Per2 or does it reflect its actions elsewhere in the body? Ischemic preconditioning is disrupted by systemic factors, such as hypercholesterolemia, hyperglycemia, and hypertension,14 and Per2 plays roles in systemic metabolism and vascular function.15,16

A metabolic switch from the oxygen-dependent tricarboxylic acid cycle to oxygen-independent glycolysis is critical for cardiac protection from ischemia.17,18 Here, Per2 deletion decreased the capacity for hypoxia-enhanced glycolysis, and thus increased myocardial cell death by disrupting a direct stabilizing interaction with hypoxia-inducible factor-1α, a key regulator responsible for the induction of genes that facilitate adaptation and survival of cells to hypoxia.19,20 Hypoxia-inducible factor-1α increases virtually all the enzymes in the glycolytic pathway, including pyruvate dehydrogenase kinase isozyme 1 and lactate dehydrogenase, to improve glucose utilization and to decrease oxygen consumption by inhibiting mitochondrial respiration.21–23 Furthermore, hypoxia-inducible factor-1α is a member of basic helix-loop-helix-Per-ARNT-Sim protein family to which all canonical clock genes belong19 and interacts with at least some clock genes, including Bmal1, CLOCK, and Per1.24,25

The most provocative finding in this article is that stabilization of Per2 by exposure of mice to intense light
afforded cardioprotection. Although this will prompt a hunt for small molecules that might stabilize PER2, whether this precise manipulation would have some direct relevance to the human condition remains unknown. Phototherapy is used effectively for disorders as varied as psoriasis and neonatal jaundice and in some conditions with a temporal phenotype, such as seasonal affective disorder.26,27 Besides circadian variability, clinical cardiovascular events also exhibit seasonal variability, peaking in the winter months28 and are reported to increase with latitude as one moves from the equator.29,30 Although there are a host of potential confounding variables, these observations at least prompt us to consider the possible relevance of hours of exposure to sunlight as a modulator of cardiovascular risk. Perhaps there is indeed something new under the sun.

Disclosures

None.

References


(Almost) Everything is Illuminated: Adenosine Shines a Light on Cardioprotection
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