ICER-Capades
Putting Cardiac Cyclic AMP Signaling “On Ice”
Mark A. Sussman

Koyaanisqatsi: ko · yaa · nis · katsi [from the Hopi language], n. 1 crazy life. 2. life in turmoil. 3. life disintegrating. 4. life out of balance. 5. a state of life that calls for another way of living.

In the complex interconnected world of myocardial cell signaling, structure and function depend on balancing of positive and negative regulatory stimuli, sequentially or in tandem, to promote homeostatic conditions. Transient variations in balance of signal transduction are the norm as the myocardium dynamically adjusts to physiological demands and conditions. Fortunately, a finely tuned array of antagonistic signaling molecules normally keeps each other from running amok. However, when myocardial signaling suffers from koyaanisqatsi, the resultant cellular alterations lead to cardiomyopathic disease.

A healthy heart is highly responsive to catecholamines that stimulate adrenergic receptor signaling to increase contractile force. β-Adrenergic receptors transduce signals through G proteins that stimulate the classic G(s)-adenyl cyclase-3'-5'-adenosine monophosphate (cAMP) signaling cascade. The cAMP pathway senses and amplifies β-adrenergic receptor activation, subsequently altering gene expression in conjunction with cAMP-response element binding (CREB) and cAMP-response element modulator (CREM) proteins. CREM-response elements (CREs) are found in the promoters of numerous genes regulating multiple facets of cell function. CRE-mediated transactivation in cardiomyocytes undergoes a rapid “burst,” peaking within 8 hours after induction followed by an attenuation phase characterized by a decrease in CRE-dependent transcription and refractoriness of transactivation by CREB, even in the presence of cAMP-elevating agonist. Several mechanisms have been explored to account for the attenuation phase including changes in phosphatase and kinase activity (reviewed in References 2 through 4). However, since the attenuation effect is impaired by blocking protein synthesis, a de novo–produced repressor was sought to account for transcriptional downregulation.

Enter the ICER (inducible cAMP early repressor), a small transcription factor CREM isoform associated with regulation of cell growth that functions as a powerful inhibitor of cAMP-induced transcription (Figure). ICER is rapidly induced by cAMP and then proceeds to shut off cAMP-inducible gene expression driven by CRE sequences, including its own ICER promoter that harbors two closely spaced CREs. Removal of ICER from the cell has been linked to mitogen-activated protein kinase (MAPK) activity that phosphorylates and targets ICER to ubiquitin-mediated degradation. ICER is present in a wide variety of tissues such as thyroid, pituitary, smooth muscle, testis, and liver, as well as cardiac cells. The work of Sadoshima’s group, in this issue of Circulation Research, opens a new door on myocardial β-adrenergic signaling as seen from an ICER perspective.

Results provided by Tomita et al examine ICER expression in response to various agonists as well as effects on hypertrophy. Adrenergic stimulation by isoproterenol (ISO; β-receptors) or phenylephrine (PE; α1 receptors) induced ICER mRNA expression as did forskolin (adenyl cyclase activator), whereas endothelin treatment (MAPK and protein kinase C activation) did not. Peak ICER protein production occurred approximately 12 hours after isoproterenol in cultured myocytes, consistent with the temporal development of an inhibitory response to cAMP activity. By 24 to 48 hours after induction, ICER localized in the center of stimulated cardiomyocytes, while adenovirally mediated overexpression of ICER resulted in strong nuclear labeling. Thus, ICER was being expressed at the right time and in the right place to inhibit cAMP-dependent transcription. Hypertrophic inhibition mediated by ICER was documented in cell culture, and adenovirally-mediated overexpression of an antisense ICER message enhanced hypertrophic responsiveness. Comparison showed the antihypertrophic effects mediated by ICER were similar to those of dominant-negative CREB protein expression. All of these studies were done in cultured cells, but implantation of an osmotic pump delivering a chronic infusion of ISO to rats also induced ICER mRNA to peak levels within 6 hours with sustained elevation for 48 hours. Collectively, these data support a role for ICER as an inhibitor of CRE-mediated hypertrophic signaling. But blunting hypertrophy is only part of the ICER story.

Connections between myocardial β-adrenergic signaling and apoptosis are well established, but an abundance of potential underlying molecular pathways obfuscate any simple mechanistic explanation. Based on results provided by Tomita et al, ICER may also promote apoptotic signaling pursuant to β-adrenergic stimulation. Not only did overexpression of ICER induce cardiomyocyte apoptosis, but antisense ICER also significantly reduced DNA fragmentation resulting from ISO stimulation. A mechanism for ICER-related apoptotic signaling is thought to stem from modula-
tion of Bcl-2 expression, which has been associated with cell survival. Bcl-2 levels in cultured cardiomyocytes were decreased by ICER overexpression as well as ISO treatment, whereas antisense ICER inhibited ISO-induced loss of Bcl-2. These findings are nicely supported by the presence of CRE sites in the Bcl-2 promoter. 18

ICER is distinguished as the first inducible negative regulator of β-adrenergic-mediated hypertrophy, but the results of this study suggest that ICER normally plays a transitory role in short-term regulation of CRE-dependent signaling. The peak of ICER expression arrives within minutes to hours after β-adrenergic stimulation both in vivo and in vitro. The β-adrenergic connection where ICER achieved chronologic notoriety was in the pineal gland, a key regulator of temporal synchronization physiological circadian rhythms. 19 In view of the prominent role that circadian rhythms play in the cardiovascular system, ICER participation in chronocardiology awaits exploration.

Quenching the rapid induction of immediate early genes such as c-fos and c-jun as an “anti-oncogene” is an important part of ICER function. 21,22 And, although ICER exerts action directly on CRE-dependent transcription, far-reaching upstream depression of β-adrenergic signaling could result from diminished receptor expression. 23 However, since ICER-mediated effects occur relatively quickly, participation in loss of β-adrenergic responsiveness observed with heart failure remains unknown. Long term elevation of ICER expression would surely be maladaptive, as chronic inhibition of CREB-dependent gene transcription provokes dilated cardiomyopathy and heart failure in transgenic mice. 24 Proapoptotic signaling mediated by ICER certainly dampsens prospects for beneficial application to inhibit reactive cardiac remodeling. 13,25 Alternatively, without appropriate ICER signaling, hypertrophic remodeling ensues by failing to put the brakes on CRE-mediated transcription in a timely fashion. The relevance, if any, of ICER in the pathogenesis of cardiomyopathy awaits further study. In summary, rather than acting as an initiator of change, ICER under normal circumstances provides the restraint that keeps cAMP signaling in a physiologically relevant realm.

Of course, the physiological role of ICER depends on appropriate moderation of activity. It is prudent to recognize that unrestrained alteration of myocardial signaling almost inevitably leads to undesirable consequences for cardiac structure and/or function. Adenoviral ICER overexpression that induces apoptosis in the Tomita et al. 25 study exposes the cardiomyocytes to levels of protein accumulation orders of magnitude higher than anything experienced by a healthy myocardium. Maintaining homeostasis in the myocardium depends on a finely tuned system with dynamic regulation, and adenoviral expression reagents are not particularly subtle. In attributing functional characteristics to ICER activity, we should remember that such molecules normally operate deftly and transiently and not as a sledgehammer. In myocardial signaling, what goes up must come down for preservation of cardiac structure and function. ICER-mediated attenuation is the critical counterbalance to the spike of cAMP-dependent gene transcription that, if left unchecked, leads to cardiac koyaanisqatsi.

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References


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