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The pivotal role of Epac in the development of heart failure

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Abstract

Prolonged activation of sympathetic nerve has been reported to accelerate the development of heart failure. Cyclic adenosine monophosphate (cAMP) mediated induction of apoptosis in cardiomyocytes and subsequent cardiac fibrosis are thought to be involved in the mechanism. Adenylyl cyclase (AC) is the enzyme that synthesizes cAMP. Our previous studies indicate that type 5 AC (AC5), one of the major cardiac AC isoforms, plays important role in catecholamine-induced cardiac dysfunction. Protein kinase A (PKA) has been recognized as a critical mediator of cAMP signals in cardiomyocytes. However, recent studies revealed that cAMP also activates exchange protein directly activated by cAMP (Epac) independent of PKA, thereby regulating various cellular functions.

In order to elucidate the role of Epac in the development of heart failure, we have generated Epac1 deficient (Epac1KO) mice. Chronic isoproterenol (ISO) infusion-induced cardiac dysfunction was attenuated in Epac1KO mice. In addition, TUNEL assay and Masson staining revealed that cardiomyocyte apoptosis and cardiac fibrosis were prevented in ISO-treated Epac1KO mice compared with wild-type mice. Further, to examine the role of Epac1 in AC5 mediated cardiac dysfunction, we cross-bred cardiac-specific AC5 transgenic (AC5TG) mice with the Epac1KO mice to generate mice overexpressing AC5 in the Epac1 deficient genetic background (AC5TG-Epac1KO). AC5 overexpression promoted the chronic ISO infusion-induced cardiac dysfunction, cardiomyocyte apoptosis and cardiac fibrosis. However, the effects of AC5 overexpression were significantly attenuated by deficiency of Epac1.

These findings suggest that Epac, a novel cAMP target, plays pivotal role in the development of heart failure.

Biography

Fujita is currently working as assistant professor in Cardiovascular Research Institute at Yokohama City University, Japan. He received his M.D. and Ph.D. from Yokohama City University. His research mainly focuses on the role of adrenergic receptor mediated signaling in cardiomyocytes.