Extracellular signal-Regulated Kinases1/2 and their role in cardiac diseases

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Mitogen-activated protein (MAP) kinases are members of a well-studied family of serine/threonine protein kinases involved in signal transduction pathways, which control multiple cellular processes. The extracellular signal-regulated kinase (ERK1/2) cascade is a MAP kinase pathway that transmits signals from the cell surface to substrates either in the nucleus or in the cytoplasm. The transmission of the signal through the ERK1/2 cascade is mediated by serial phosphorylations and activations of protein kinases. Abnormal regulation of the ERK1/2 signals has been linked to diseases and recent work clearly implicated ERK1/2 signaling in the development of cardiac pathologies. Understanding the underlying mechanism and the consequences of the aberrant modulation of ERK1/2 cascade will lead to the development of pharmacologic inhibitors for the treatment of these cardiac disorders.

**Keywords:** Mitogen-activated protein (MAP) kinases; Lamin; cardiomyopathy; Extracellular signal-regulated kinases 1/2

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Introduction

A proportion of inherited cardiomyopathies display deregulated MAP kinase signaling. As these diseases are a major cause of cardiac disease in human, it is therefore not surprising that the MAP kinase signaling continues to be the subject of intense researches for future pharmacological intervention. The development of molecules targeting this pathway has focused mostly on the development of small-molecule inhibitors. This review will gather information on MAP kinase signaling, focusing on the ERK1/2 branch and will discuss important research progresses in the field of inherited cardiomyopathies. The recent years provided some clues to explain the pathogenesis of such disease, involving ERK1/2, which might open novel and promising perspectives for future clinical trials.

MAP kinases

Protein kinases are important players to achieve the integrated function of cells. Protein kinases are able to transfer phosphoryl groups onto target proteins, altering their activity [1]. This mechanism participates in the transmission of intra- and extracellular signals throughout the cell and to the nucleus. Thus, protein kinases play a pivotal role in signaling pathways that could regulate cell growth, differentiation, development, and death [2]. Hence, any disruption of the phosphorylation could alter cell functions and may cause diseases [3].
ERK1/2

ERK1 and ERK2 are ubiquitously expressed proteins of 44 and 42 kDa, which are nearly 85% identical in their amino-acid sequences [14-17]. Stimulation of different receptors can activate ERK1/2, e.g. receptors with intrinsic tyrosine kinase activity, cytokine receptors and G-protein-coupled receptors. Hence, ERK1/2 are stimulated by many extracellular ligands and cellular perturbations (e.g., mechanical stress, osmotic shock), with some cell type specificity enzymes that can phosphorylate serine/threonine and tyrosine residues. In spite of their ability to phosphorylate MAP kinases proteins, the substrate specificity of the known MEKs is very narrow: each MEK phosphorylates only one or a few of the MAP kinases. Much of the review highlights knowledge on extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2), two of the known MAP kinases.

ERK1/2 and inherited cardiomyopathies

Studies point to ERK1/2 as a maladaptive signaling pathway in cardiomyopathy. Cardiomyopathy is an anatomic and pathologic condition associated with muscle and electrical dysfunction of the heart, which may be confined to the heart or may be part of a generalized systemic disorder, often leading to heart failure-related disability. A well-known negative effect of ERK1/2 signaling in human heart function is highlighted by the fact that different mutations able to increase ERK1/2 pathway activation lead to cardiac pathologies in patients with Noonan and related syndromes, such as Costello, LEOPARD and cardio-facio-cutaneous syndromes [35-38]. Knock-in mice expressing a Noonan syndrome-associated mutation exhibit enhanced ERK1/2 signaling and an accelerated transition toward heart failure in response to pressure overload. Interestingly, postnatal treatment with MEK1/2 inhibition normalizes cardiac defects [39]. Based on these results, Novartis recently launched a clinical trial on Noonan syndrome using a MEK1/2 inhibitor (ClinicalTrials.gov Identifier: NCT01556568).

A further example is represented by mutations in the A-type lamin gene and causing dilated cardiomyopathy. Since 1999, scientists have unraveled the role of the nuclear lamina in the development of cardiac disease [40]. LMNA encodes...
nuclear A-type lamins via alternative splicing [41]. Lamins are intermediate filament proteins that polymerize to form the nuclear lamina, a fibrous meshwork underlining the inner nuclear membrane of most eukaryotic cells. We recently demonstrated an aberrant increase in ERK1/2 activity in hearts from a mouse model of the disease [42]. These results provide proof of principle for ERK1/2 inhibition as a therapeutic option to prevent or delay the onset of heart failure in LMNA cardiomyopathy. Pharmacological or genetic blockade of signaling in the ERK1/2 cascade in these mice improves left ventricular dilatation and deterioration in cardiac contractility [43-46].

Conclusion

Less than a decade ago the kinases constituting MAP kinase pathways were identified through intense efforts to understand the molecular events underlying cellular responses to extracellular signals. The kinases constituting ERK1/2 pathways appear to be key cellular signal transducers and thus attractive targets for drug development. These efforts are now beginning to bear fruit with the initiation of clinical trials in human cardiac diseases. Their positive outcome would be a triumph of translating basic scientific understanding of cellular function into successful human therapies.

Conflict of Interest

Dr. Muchir is inventor on a pending United States patent application on methods for treating and/or preventing cardiomyopathies by ERK inhibition filed by the Trustees of Columbia University in the City of New York.

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