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EDITORIAL

Effect of inhibition of glycogen synthase kinase-3 on cardiac hypertrophy during acute pressure overload

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Abstract Myocardial hypertrophy has been recognized to be an adaptive response to a variety of external stimuli (e.g., myocardial infarction, pressure overload, catecholamine treatment, endocrine disorders) that are involved in several subcellular factors that mediate signaling pathways, from external stimuli to nuclear protein synthesis. Glycogen synthase kinase-3β (GSK-3β) is one of the subcellular factors that regulate nuclear transcription factors, such as activated T-cell (NFAT) proteins, that are related to gene programming during cardiac hypertrophy. On the other hand, GSK-3β, known as a regulator of cardiomyocyte growth in Wnt signaling of cardiogenesis, is involved in β-catenin degradation. Inhibition of GSK-3β has been reported to induce cardiac hypertrophy. Tateishi et al. demonstrated in an aortic constriction-induced acute hypertrophy model using 6-week-old Wister rats that if GSK-3b is inhibited by LiCl up-regulated β-catenin expression and additional hypertrophy were observed. They suggested that Li^{2+} had an additive effect on pressure overload-induced hypertrophy through the GSK-3β—β-catenin pathway. Their article provides promising information on the mechanism of hypertrophic myocyte growth during acute pressure overload.

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Introduction

Myocardial hypertrophy has been recognized to be an adaptive response to a variety of external stimuli such as myocardial infarction, pressure overload, catecholamine treatment, and endocrine disorders, which are involved in several subcellular factors that mediate signaling pathways, from external stimuli to nuclear protein synthesis. Intracellular signaling pathways contributing to cardiac hypertrophy have been reported to include G-protein isoforms (Gi and Gq), low-molecular-weight guanosine transpeptidases (Ras, RhoA, Rac), calcineurin (calcium/calmodulin-dependent protein phosphatase), protein kinase C, p38 mitogen-activated protein kinase (MAPK) isoforms, insulin-like growth factor I receptor, gp130–leukemia inhibitor factor receptor (LIFR) complex, basic fibroblast growth factor (FGF), transforming growth factor-β (TGFβ), and many others.[1]

Glycogen synthase kinase-3β (GSK-3β) is one of the subcellular factors regulating nuclear transcription factors such as activated T cell (NFAT) proteins, which are related to gene programming during cardiac hypertrophy.[1,2] If NFAT proteins are dephosphorylated by calcineurin, the dephosphorylated NFAT proteins are translocated from the cytosol to the nucleus (i.e., nuclear import), resulting in cardiac hypertrophy. In contrast, if NFAT proteins are phosphorylated by GSK-3β, the phosphorylated NFAT proteins are translocated in the reverse direction (i.e., nuclear export), antagonizing the calcineurin effect. In the unstimulated cell GSK-3β is in the active state, inhibiting the hypertrophic gene program, whereas in the stimulated cell GSK-3β is inactivated, NFAT proteins are dephosphorylated and translocated into the nucleus, and subsequently the hypertrophic gene program is promoted. In the

transgenic mice overexpressing GSK-3β, the heart weight/body weight ratio has been reported to be less than that in wild-type mice.[3] A variety of external stimuli such as isoproterenol (ISO), endothelin-1 (ET-1), and ventricular pressure overload are known to inhibit the activity of GSK-3β, inducing cardiac hypertrophy. Cyclosporin A, a calcineurin inhibitor, has been reported to counteract the effect of angiotensin II (Ang II), ET-1, or phenylephrine (PE) on inducing cardiac hypertrophy, suggesting that a calcium/calmodulin-dependent pathway through calcineurin may play an important role in the development of Ang II-, ET-1-, and PE-induced cardiac hypertrophy.[2] FK506 has been demonstrated to prevent pressure overload-induced cardiac hypertrophy by inhibiting calcineurin activity and its gene expression.[4]

On the other hand, GSK-3β plays an important role in the regulation of cardiomyocyte growth in Wnt signaling of cardiogenesis during embryonic development.[5] A GSK-3β molecule is coupled to a scaffolding protein (Axin) and an adenomatous polyposis coli (APC) protein, as well as phosphorylates β-catenin, resulting in ubiquitination and degradation of β-catenin. If GSK-3β activity is inhibited by its serine-9 residue phosphorylation, β-catenin is stabilized and translocated to the nucleus to promote a cardiogenic gene program. Haq et al. have reported that β-catenin can be stabilized after being exposed to external stimuli (PE, ET-1, LiCl, pressure overload) [6,7] in terminally differentiated cells, the mechanism of which is different from Wnt signaling.[8] This study suggests a possibility that β-catenin stabilization may be involved in the cardiac hypertrophic response in mature myocardium through the pathways of GSK-3β inhibition.

The article from Tateishi et al. demonstrated in an aortic constriction-induced acute hypertrophy model using a 6-week-old Wister rat that if GSK-3b is inhibited by LiCl up-regulated β-catenin expression and additional hypertrophy were observed, and suggested that Li^{2+} had an additive effect on pressure overload-induced hypertrophy through the GSK-3β—β-catenin pathway.

In this study, there seemed to be three possibilities in terms of the mechanism of the additive hypertrophy induced with combined treatment of 2-day aortic banding and LiCl injection in a 6-week-old rat. First, the extent of pressure overload might be insufficient for inhibition of GSK-3β activity and subsequent stabilization of β-catenin, and if so assessment in a rat with more severe aortic banding might provide useful information on the relative contribution of pressure overload to the development of hypertrophy. Second, a relatively short period (i.e., 2 days) of pressure overload might result in modest inhibition of GSK-3β activity, which might not be long enough to induce sufficiently β-catenin stabilization and resultant cardiac hypertrophy, requiring the adjuvant effect of Li^{2+}. Third, the inhibiting effect of Li^{2+} on GSK-3β activity might induce hypertrophy additively through the other pathways such as calcineurin–NFAT signaling. The involvement of calcineurin-NFAT signaling in the additive effect of Li^{2+} might not be able to be ignored, although its contribution to the hypertrophy gene program has been assessed in rats with a longer exposure of pressure overload (e.g., 3 weeks of aortic banding).

In conclusion, the article from Tateishi et al. provides promising information on the mechanism of hypertrophic myocyte growth during acute pressure overload. Further investigation may be required in terms of a more precise mechanism involved in the effect of β-catenin signaling or calcineurin–NFAT signaling during an acute phase of pressure overload-induced cardiac hypertrophy.

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