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Application of Curcumin to Heart Failure Therapy by Targeting Transcriptional Pathway in Cardiomyocytes

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Heart failure is one of the leading causes of death throughout the world. During the development and deterioration processes of heart failure, cardiomyocytes undergo maladaptive hypertrophy by altering hypertrophy-related gene expression. The zinc finger protein GATA4 is one of the transcription factors involved in the regulation of cardiomyocyte hypertrophy. In response to hypertrophic stimuli such as the synaptic nervous and rennin-angiotensin systems, GATA4 forms a large complex with various functional proteins including an intrinsic histone acetyltransferase, p300, and the disruption of this complex results in the inhibition of hypertrophic responses in cardiomyocytes. While such a transcriptional signal pathway is recognized as a critical event during cardiomyocyte hypertrophy, pharmacological heart failure therapy that targets this pathway has not been established. In order to develop novel heart failure therapy targeting the pathway in cardiomyocytes, we have studied the potential of curcumin, a p300 histone acetyltransferase inhibitor, as an agent for novel heart failure therapy. In this review, we describe a recent study on the cardiac transcriptional signal pathway, especially p300/GATA4 pathway, and a novel heart failure therapy using curcumin.

Key words curcumin; heart failure therapy; p300; GATA4; cardiomyocyte; transcription

1. INTRODUCTION

Hypertensive heart disease and post-myocardial-infarction heart failure are the leading causes of cardiovascular mortality in industrialized countries, and cardiac hypertrophy is considered a hallmark of heart failure. Cardiomyocyte hypertrophy is the cellular response to an increase in various extrinsic and intrinsic stresses such as arterial hypertension, valvular heart disease, or familial hypertrophic cardiomyopathy. The hypertrophy is defined by an increase in cardiomyocyte size, enhanced protein synthesis, and a higher organization of the sarcomere. Various studies for resolving the molecular mechanisms have demonstrated that transcriptional regulation in the nucleus is an important signal pathway for the development of heart failure. Over the past two decades, there has been significant progress in our understanding of the molecular mechanisms of cardiac hypertrophy. Cardiac hypertrophy is accompanied by the reprogramming of fetal cardiac gene expression. The reactivation of fetal cardiac genes in response to stress signals such as the synaptic nervous and rennin-angiotensin systems suggests that the same transcriptional program is employed to control cardiac gene expression during development and to regulate hypertrophic cardiac growth. We investigated the co-operative functions of the cardiac transcription factor GATA4 and p300, a histone acetyltransferase (HAT) and a coactivator of GATA4, in the process of heart failure and the potential of curcumin, a HAT inhibitor of p300, for heart failure pharmacological therapy by targeting the transcriptional pathway.

Curcumin (diferuloylmethane) is a polyphenol extracted from the rhizomes of *Curcuma longa* (turmeric). A large number of papers suggest that curcumin has a diverse range of molecular targets, including transcription factors, growth factors and their receptors, cytokines, enzymes, and proteins regulating cell proliferation and apoptosis. It has been demonstrated that it exhibits multiple pharmacological activities including anti-oxidant, anti-inflammatory, anti-bacterial, and anti-viral activities, as well as a therapeutic potential for cancer and Alzheimer’s disease. At the time of the review, there are several ongoing clinical trials on curcumin in patients with different diseases, including several types of cancer, Alzheimer’s disease, epilepsy, psoriasis, rheumatism, and inflammatory bowel disease in the United States, Japan, and Taiwan. There is also interest in its potential cardioprotective properties. The protective effects of curcumin on the cardiovascular system have been previously described, and its use as a therapeutic agent to mitigate cardiovascular disease and other vascular dysfunctions is currently being investigated. This review focuses on the molecular mechanisms of transcriptional regulation in cardiac hypertrophy, especially the GATA4-related transcription pathway, and the effect of curcumin on heart failure therapy.

2. TRANSCRIPTIONAL REGULATION IN CARDIAC HYPERTROPHY

The changes in the cellular phenotype in cardiac hypertrophy are accompanied by the reinduction of the fetal gene program. The same transcription factors that are important for cardiac development, such as myocyte enhancer factor 2
(MEF2),2) serum response factor (SRF),14) GATA4,15) AP-1,16) neuron-restrictive silencer factor (nRSF),17) nuclear factor of activated T cells (NFAT),18) and myocardin,19) have also been implicated as mediators of the hypertrophic transcriptional program. Numerous pathways in cardiomyocytes have been implicated in the molecular response to the development of hypertrophy.20,21)

GATA transcription factors are characterized by the conserved double zinc fingers that are required for binding to the specific consensus DNA sequence (A/T)GATA(A/G). We previously demonstrated that GATA elements are necessary for the promoter activation of the β-MHC gene, a hypertrophic response gene.22) GATA transcription factors are known to bind to the GATA elements, and various reports show that cardiomyocyte-specific GATA proteins play important roles in hypertrophic gene transcriptions.23–26) GATA4 knockout mouse die at early embryonic stages,27,28) and the transgenic mice of GATA4 show significant cardiac hypertrophy.29) These data strongly indicate that the cardiomyocyte-specific transcription factor GATA4 regulates the gene transcription associated with hypertrophy.

GATA4 is an essential transcription factor for heart development and cardiac hypertrophy. The regulation mechanisms of GATA4 have been reported in some papers. Extracellular regulated kinase phosphorylates Ser 105 in GATA4, and the phosphorylated GATA4 increases its DNA binding activity and gene transcriptions.30,31) Moreover, calcineurin-NFAT or Rho-ROCK signals are also involved in GATA4 activation,32,33) and friend of GATA (FOG)-2 functions as a repressor of the activation.34) Acetylation of not only the histone tail but also some transcription factors is a critical process in the activation of gene transcription. We show that p300 binds and acetylates GATA4, and the acetylation enhances GATA4-induced hypertrophic gene transcriptions.35) The transgenic mice of intact p300 specifically expressed in cardiomyocytes lead to the exaggeration of left ventricular remodeling after myocardial infarction, but the remodeling in the transgenic mice of p300 lacking HAT activity is attenuated. These data indicate that the HAT activity of p300 is necessary for left ventricular remodeling after myocardial infarction.36) The details of p300 are described in a previous review.5) Concerning the acetylation of transcription factors in cardiomyocytes, we and others have intensively investigated GATA4. GATA4 acetylation is promoted by p300, and increases its DNA-binding capacity and transcriptional activity. The zinc finger domain of the C-terminal of GATA4 plays important roles in the DNA-binding capacity and binding to other factors, and contains some residual lysine groups. The acetylation of the lysine residues of GATA4 may be involved in its transcriptional activity. We analyzed the sites of p300-induced GATA4 acetylation, and found that four lysine residues: K311, K318, K320, and K322, were acetylated by p300, and the mutant GATA4 of these residual groups inhibited cardiomyocyte hypertrophy as a dominant-negative mutant.37) In order to further investigate the precise mechanism of the p300/GATA4 transcriptional pathway, we performed proteomic analysis of GATA4-binding proteins. The analysis identified 73 binding proteins including the transcription-regulated proteins such as cyclin-dependent kinase 9 (Cdk9), which is a component of positive transcription elongation factor b, SWI/SNF complex component protein, and chromatin assembly factor-1. We examined the Cdk9 function in cardiomyocyte hypertrophy and the p300/GATA4 pathway, and found that Cdk9 phosphorylates p300 and activates p300 HAT activity, and then promotes hypertrophic gene transcription (Fig. 1).36) Now, we are analyzing the functions of other novel GATA4-binding proteins.

The data showed that, when the acetylation of GATA4 was inhibited, post-myocardial-infarction remodeling was suppressed, suggesting that HF treatment should target the p300/GATA4 transcriptional pathway in the heart. In the heart, p300 works as a coactivator of other transcription factors such as MEF2 and plays an important role in cardiac hypertrophy.4,5,15,35,37) It has also been reported that histone deacetylases (HDACs), especially class II (HDAC 4, 5, 7, 9), suppresses hypertrophic gene transcriptions by MEF-2, NKX2-5, SRF, or NFAT, and cardiac hypertrophy.21,38)
specifically inhibits p300. Curcumin, a component of a natural substance, turmeric, inhibited the hypertrophy of cultured cardiomyocytes, preventing the onset of HF in rat models of hypertensive heart disease and myocardial infarction (Fig. 2). For the clinical application of curcumin therapy, we examined the combined effect of curcumin with an angiotensin-converting enzyme inhibitor (ACEI), enalapril, a conventional and standard agent for heart failure, using a myocardial infarction model. The effects of monotherapy with curcumin on heart failure were similar to those of enalapril. Combination therapy with these agents exhibited additive effects to improve the heart function, suggesting that the mechanism of action of curcumin differs from that of ACEI. Combination therapy with curcumin and these agents may be more effective for cardiac hypertrophy and heart failure.

Despite the multiple pharmacological effects and Phase I clinical safety even at high doses, curcumin possesses poor water solubility and, as a consequence, it exhibits poor bioavailability. Since it is rapidly metabolized in the liver, it has been revealed to show a low serum level and tissue distribution. These limitations of low solubility, rapid metabolism, and hence low bioavailability may prevent the success of curcumin in various animal and clinical studies. To overcome the problems, it is important to use the tools of drug delivery systems. Indeed, several drug delivery systems such as micelles, liposomes, nanoparticles, and nanoemulsions have been designed to improve the bioavailability of curcumin and to be used for pharmacological therapy. We have developed Theracurcumin (Theravalues Corporation, Chiyoda-ku, Tokyo, Japan), a highly absorbable curcumin formulation that is easily and stably dispersible in water, by nanoparticulation and surface-processing techniques. Theracurcumin shows significant improvement of the development of heart failure in rats at a low dose. In order to study the clinical effect of Theracurcumin on the left ventricular diastolic function of patients with hypertension and left ventricular hypertrophy, a clinical trial is now ongoing.

4. CONCLUSION AND PERSPECTIVE

It is interesting that curcumin, known as a component of healthy food, has therapeutic effects against various diseases such as cancer, Alzheimer’s disease, and cardiovascular diseases. To establish a fundamental pharmacological therapy for heart failure, we have examined the transcriptional pathway in cardiomyocytes, and ultimately identified the p300/GATA4 pathway as a target. In addition, we demonstrated that curcumin, a p300-specific HAT inhibitor, prevents hypertrophy in cultured cardiomyocytes and improves the development of heart failure in animal models, and a clinical study of heart failure patients with hypertension and cardiac hypertrophy is currently ongoing.

During the past two decades, most therapeutic agents have been developed for the treatment of patients with systolic heart failure. Long-term treatment with ACEIs, angiotensin II type 1 receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and β-adrenergic receptor antagonists (beta blockers) improves symptoms, hemodynamics, and clinical outcomes. In recent years, progress in basic research has resulted in the identification of new potential therapeutic targets for the treatment of heart failure, and many promising drugs have subsequently been developed. These above-described findings suggest that a new therapy targeting the transcription pathway has been developed, and we hope that the developed drug improves the quality of life and prognosis of patients with heart failure.

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