Topic: 3. Heart Failure and Cardiomyopathy

Curcumin Analogue GO-Y030 Significantly Improves Pressure Overload-induced Heart Failure in Vivo

Kana Shimizu,¹ Masafumi Funamoto,¹ Mai Genpei,¹ Yoichi Sunagawa,¹ Yasufumi Katanasaka,¹ Yusuke Miyazaki,¹ Hiroyuki Shibata,² Hiromichi Wada,³ Koji Hasegawa,³ Tatsuya Morimoto³

1. University of Shizuoka - Division of Molecular Medicine, Graduate School of Integrated Pharmaceutical and Nutritional Sciences,

2. Akita University - Department of Clinical Oncology, Graduate School of Medicine,

3. Kyoto Medical Center - Clinical Research Institute, National Hospital Organization

Keywords: Curcumin, Analogue, p300, Acetylation, Heart failure

Introduction and Objectives

Signals activated by increased hemodynamic overload to the heart finally reach the nuclei of cardiac myocytes and induce maladaptive hypertrophy in them. Nuclear acetylation, which is controlled by histone deacetylases and the intrinsic histone acetyltransferase p300, is a critical event in this process. We previously found that a natural p300 HAT inhibitor, curcumin, can inhibit cardiomyocyte hypertrophy and the development of heart failure *in vivo*. However, curcumin is insoluble in water, and its bioavailability is low. Therefore, a more efficient system for heart failure therapy is desirable for actual clinical practice. To overcome this limitation, we recently synthesized a curcumin analog, GO-Y030, which possesses stronger anti-cancer activity than curcumin. However, the effect of GO-Y030 on heart failure is still unclear. The purpose of this study was to determine whether GO-Y030 inhibits p300-HAT activity and can be used as a therapeutic agent for heart failure.

Materials and Methods

First, to investigate whether GO-Y030 inhibits p300-HAT activity, an *in vitro* HAT assay was performed using a recombinant p300-HAT domain and histone H3. The histones were processed for western blotting with anti-histone H3K9 antibody. The 50% inhibitory concentrations (IC₅₀) for p300-HAT activity were estimated from dose-response curves. Second, primary cardiomyocytes from neonatal rats were stimulated with saline or phenylephrine (PE) in the presence of curcumin or GO-Y030 for 48 hours. Proteins isolated from these cells by acid extraction were subjected to western blotting for acetylated histone H3K9 or total histone 3. Measurement of hypertrophic response gene transcription was performed by RT-PCR. Cardiomyocytes were stained with anti- γ -MHC antibody, and the surface area of these cells was measured. Third, C57BL/6j male mice (8 weeks old) were

subjected to sham or transverse aortic constriction (TAC). One day after TAC, the mice were randomly assigned to daily oral treatment with curcumin (1 or 50 mg/kg), GO-Y030 (0.1, 0.5 or 1 mg/kg), and vehicle (1% gum Arabic) as a control, for 6 weeks. After treatment, the effects of Y030 on TAC-induced cardiac hypertrophy and systolic dysfunction were investigated by echocardiography. The mRNA levels of hypertrophic genes were measured by real-time RT-PCR.

Results

The results of the *in vitro* HAT assay revealed that GO-Y030 inhibited p300-HAT activity more strongly than curcumin: The IC₅₀ value of Y030 was 1.1 μ M, while curcumin was 9.4 μ M. In cardiomyocytes, 1 μ M of GO-Y030 suppressed the following effects to the same extent as 10 μ M of curcumin: PE-induced histone H3K9 acetylation, activation of hypertrophic response genes such as ANF and BNP, and increase in the surface area of cardiomyocytes. Echocardiographic analysis showed that 0.5 and 1 mg/kg of GO-Y030 and 50 mg/kg of curcumin suppressed TAC-induced increase in left ventricular posterior wall thickness and decrease in fractional shortening. Low doses of GO-Y030 (0.5 and 1 mg/kg) significantly suppressed TAC-induced increases in HW/BW ratio and hypertrophic response gene transcription to the same extent as 50 mg/kg of curcumin. One mg/kg of curcumin did not suppress these four effects.

Conclusions

These results indicate that, compared to curcumin, the curcumin analogue GO-Y030 strongly inhibits p300-HAT activity, hypertrophic responses, and pressure overload-induced development of heart failure. These findings suggest that GO-Y030 may be effective for heart failure therapy. ■

1. Yanazume T, Hasegawa K, Morimoto T, et al. Cardiac p300 is involved in myocyte growth with decompensated heart failure. *Mol Cell Biol* 2003 May; **23**(10):3593–606. PMID: 12724418
2. Morimoto T, Sunagawa Y, Kawamura T, et al. The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats.
3. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm* 2007 Nov-Dec; **4**(6):807–18. PMID: 17999464; DOI: 10.1021/mp700113r
4. Ohori H, Yamakoshi H, Tomizawa M, et al. Synthesis and biological analysis of new curcumin analogues bearing an enhanced potential for the medicinal treatment of cancer. *Mol Cancer Ther* 2006; **5**(10):2563–71. PMID: 17041101; DOI: 10.1158/1535-7163.MCT-06-0174