FoxO1 and NF-κB regulate cyclooxygenase-2 expression under lysophosphatidylcholine treatment in human cardiac fibroblasts

Hui-Ching Tseng (曾惠卿)1 and Chuen-Mao Yang (楊春茂)1,2,3,*

1Graduate Institute of Biomedical Sciences, Department of Physiology and Pharmacology and Health Ageing Research Center, College of Medicine, Chang Gung University, Kwei-San, Tao-Yuan, Taiwan; 2Department of Anesthesics, Chang Gung Memorial Hospital at Lin-Kou and College of Medicine, Chang Gung University, Kwei-San, Tao-Yuan, Taiwan; 3Research Center for Industry of Human Ecology and Graduate Institute of Health Industry Technology, Chang Gung University of Science and Technology, Tao-Yuan, Taiwan

Abstract

Introduction

Lysophosphatidylcholine (LysoPC) has been reported to accumulate in ischemic myocardium and regulates a variety of cellular events including proliferation, wound healing, and cell migration. Cyclooxygenase-2 (COX-2) has been demonstrated to participate in cardiac remodeling. In this study, we investigated the mechanisms of LysoPC-induced COX-2 expression in human cardiac fibroblast (HCFs), a major component of heart, leading to cardiac remodeling.

Methods

The levels of protein expression and phosphorylation of PKCα, p38, JNK1/2, and p65 were examined by Western blotting. The COX-2 mRNA was measured by quantitative real-time PCR. ROS levels were assessed by using DCFH-DA, DHE and MitoSox. The NF-κB and FoxO1 transcriptional activities were determined by chromatin immunoprecipitation and luciferase promoter activity.

Results

In this study, we found that LysoPC induced COX-2 protein and mRNA expression in a time- and concentration-dependent manner. Inhibition of COX-2 activity attenuated the release of pro-inflammatory cytokines including GM-CSF, IL-1β, IL-6, IL-8 and collagen secretion from HCFs challenged with LysoPC. Moreover, LysoPC-induced COX-2 expression was modulated by NF-κB and FoxO1 nuclear accumulation. The involvement of intracellular signaling components in LysoPC-mediated responses were mediated through intracellular mitochondrial ROS and NOX-derived ROS production. The elevated levels of ROS further stimulated phosphorylation of p38, JNK1/2 and PKCα. Overexpression of FoxO1 promoting COX-2 expression, contributing collagen secretion.

Conclusion

These results suggested that in HCFs, LysoPC-induced COX-2 expression leading to pro-inflammatory cytokines and collagens secretion is, at least in part, mediated through PKCα/JNK1/2 and NOX/ROS/mitochondrial ROS/p38 MAPK pathways via activation of NF-κB and FoxO1.