Mol Cell Biochem
DOI 10.1007/s11010-013-1896-z

Interleukin-6 inhibition of peroxisome proliferator-activated receptor alpha expression is mediated by JAK2- and PI3K-induced STAT1/3 in HepG2 hepatocyte cells

Guat-Siew Chew · Stephen Myers · Alexander Chong Shu-Chien · Tengku Sifzizul Tengku Muhammad

Received: 6 September 2013 / Accepted: 5 November 2013

Abstract Interleukin-6 (IL-6) is the major activator of the acute phase response (APR). One important regulator of IL-6-activated APR is peroxisome proliferator-activated receptor alpha (PPARα). Currently, there is a growing interest in determining the role of PPARα in regulating APR; however, studies on the molecular mechanisms and signaling pathways implicated in mediating the effects of IL-6 on the expression of PPARα are limited. We previously revealed that IL-6 inhibits PPARα gene expression through CAAT/enhancer-binding protein transcription factors in hepatocytes. In this study, we determined that STAT1/3 was the direct downstream molecules that mediated the Janus kinase 2 (JAK2) and phosphatidylinositol-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathways in IL-6-induced repression of PPARα. Treatment of cells with pharmacological inhibitors of JAK2, PI3K, AKT, and mTOR attenuated the inhibitory effect of IL-6 on PPARα protein in a dose-dependent manner. These inhibitors also decreased the IL-6-induced repression of PPARα mRNA expression and promoter activity. Overexpression of STAT1 and STAT3 in HepG2 cells cotransfected with a reporter vector containing this PPARα promoter region revealed that both the expression plasmids inhibited the IL-6-induced repression of PPARα promoter activity. In the presence of inhibitors of JAK2 and mTOR (AG490 and rapamycin, respectively), IL-6-regulated protein expression and DNA binding of STAT1 and STAT3 were either completely or partially inhibited simultaneously, and the IL-6-induced repression of PPARα protein and mRNA was also inhibited. This study has unraveled novel pathways by which IL-6 inhibits PPARα gene transcription, involving the modulation of JAK2/STAT1–3 and PI3K/AKT/mTOR by inducing the binding of STAT1 and STAT3 to STAT-binding sites on the PPARα promoter. Together, these findings represent a new model of IL-6-induced suppression of PPARα expression by inducing STAT1 and STAT3 phosphorylation and subsequent down-regulation of PPARα mRNA expression.

Keywords Acute phase response · Interleukin-6 · Peroxisome proliferator alpha · Cell signaling pathways · Human HepG2 hepatocyte cells

G.-S. Chew (✉) · A. C. Shu-Chien
School of Biological Sciences, Universiti Sains Malaysia, 11800 Penang, Malaysia
e-mail: h.chew@ballarat.edu.au

G.-S. Chew · S. Myers
School of Biomedical Science, University of Ballarat, Ballarat 3350, VIC, Australia

T. S. T. Muhammad (✉)
Faculty of Science and Technology, Universiti Malaysia Terengganu, 21030 Kuala Terengganu, Terengganu, Malaysia
e-mail: sifzizul@umt.edu.my

Introduction

Organisms respond toward changes in local or systemic disturbances in homeostasis caused by infection, injury, and trauma by triggering a highly complicated but precise gene regulation network. Acute phase response (APR) is one of the major reactions initiated in human liver to restore disturbed homeostasis to normal physiological levels [1–3]. APR mediates changes in the concentration of plasma proteins known as acute phase proteins (APPs) which act as effectors of APR [4–6]. APPs are modulated positively or negatively by cytokines especially interleukin-6 (IL-6) mainly by altering the rate of their synthesis in the liver [7–9]. The onset of APR triggered by IL-6 may

Published online: 16 November 2013