Heme Oxygenase-1 Mediates the Anti-Inflammatory Effect of Curcumin Within LPS-Stimulated Human Monocytes

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Curcumin, a polyphenolic compound derived from plant, regulates heme oxygenase (HO-1) expression within certain cell types; however, the Curcumin-mediated signal transduction in the regulation of HO-1 expression within human monocytes/macrophages is unclear. Herein, we show that Curcumin dose dependently induced HO-1 expression and HO-1 activity through the activation of PKCα, PKCδ/ERK1/2, p38α, and PI3-kinase. In addition, H2O2 release is essential for Curcumin-mediated ERK1/2 and p38 phosphorylation and HO-1 expression. Further, Curcumin inhibited LPS-induced IL-1 and IL-6 secretion and blockage of HO-1 expression/activity by HO-1 siRNA or HO-1 inhibitor, SnPP reversed the inhibitory effects of Curcumin on cytokines secretion. HO-1 over-expression produced the same inhibitory effects of Curcumin on IL-1 secretion. Collectively, our results suggest that Curcumin inhibits cytokines secretion within LPS-stimulated monocytes through a mechanism that involves the action of HO-1.


Heme oxygenase-1 (HO-1) is an enzyme which catalyzes the rate-limiting step in heme degradation resulting in the formation of iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin by biliverdin reductase (Maines, 1997). HO-1 exhibited certain biological properties including anti-inflammation (Lee and Chau, 2002; Hegazi et al., 2005), anti-oxidant (Taille et al., 2004) and preventing apoptosis (Chow et al., 2005; Silva et al., 2006). HO-1 is inducible in response to various stimuli within monocytes/macrophages, including alcohol (Drechsler et al., 2006), thiol-containing dietary anti-oxidant (Ogborne et al., 2005), triterpenoid (Liby et al., 2005), and lipopolysaccharide (LPS) (Rushworth et al., 2005). The diversity of stimuli that induce HO-1 suggests that the molecular mechanisms that regulate HO-1 are complex. Several studies have described that signaling through nuclear factor-erythroid-2-related factor (Nrf2) and p38 is involved in HO-1 induction within alpha-6poic acid-stimulated human monocytes (Ogborne et al., 2005), cadmium-stimulated epithelial cells (Alam et al., 2000) and Curcumin-stimulated epithelial cells, breast cells, and monocytes (Balogun et al., 2003a; Andreadi et al., 2006; Rushworth et al., 2006). Having said this, however, the oxidized redox state and protein kinase-mediated signal transduction in the regulation of HO-1 expression within cultured monocytes/macrophages would appear to be unclear at time of writing.

Curcumin is a polyphenolic compound derived from the rhizomes of the plant Curcuma longa Linn with immuno-modulatory activities (Ammon and Wahl, 1991). Curcumin induces HO-1 expression within endothelial cells (Motterlini et al., 2000), astrocytes (Scapagnini et al., 2002, 2006), epithelial cells (Balogun et al., 2003a,b) and monocytes (Rushworth et al., 2006). Curcumin induce HO-1 by regulating the PKC-mediated activation of Nrf2 and p38 within human monocytes, but the role of other signaling molecules including ERK1/2, PI3-kinase, and reactive oxygen species (ROS) in the regulation of HO-1 expression is still in question (Rushworth et al., 2006). In this study, we found that Curcumin-mediated HO-1 expression within human monocytes via p38α, PKCα/δ, and PI3-kinase as well as ROS, upstream of ERK1/2 and p38α.

We have demonstrated that Curcumin inhibited LPS-induced IL-1 gene expression through suppressing JNK activation (Hsu and Wen, 2002); however, the role of HO-1 in Curcumin-mediated inhibition of cytokines expression within LPS-stimulated human monocytes is never been reported. Here we used SnPP, an inhibitor of HO-1 and HO-1 siRNA to inhibit Curcumin-induced HO-1 expression and activity and found that SnPP and HO-1 siRNA reversed Curcumin-mediated inhibition of cytokine expression.

Hsien-Yeh Hsu, Li-Chieh Chu and Kuo-Feng Hua contributed equally to this study.

Contract grant sponsor: National Science Council, Taiwan;
Contract grant number: NSC 96-2627-M-010-004, NSC 94-2120-M-010-002.

Contract grant sponsor: National Health Research Institutes, Taiwan;
Contract grant number: NHRI-EX93-9211SI (support for the cost of reprints).

Contract grant sponsor: Ministry of Education, Taiwan, on Program for Promoting Academic Excellence of Universities;

Contract grant sponsor: Ministry of Education, Aim for the Top University Plan;
Contract grant number: 95A-C-D01-PPG-10.

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Received 13 November 2006; Accepted 7 June 2007 DOI: 10.1002/jcp.21206