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Prostaglandins & other Lipid Mediators 78 (2005) 46–54

PROSTAGLANDINS & other LIPID MEDIATORS

Effect of peroxisome proliferator-activated receptor-γ ligands on the expression of retinoic acid-inducible gene-I in endothelial cells stimulated with lipopolysaccharide

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Received 28 October 2004; received in revised form 20 January 2005; accepted 20 February 2005
Available online 18 August 2005

Abstract

Retinoic acid-inducible gene-I (RIG-I) is a member of the DExH box protein family and designated as a putative RNA helicase. RIG-I is implicated in host defense and inflammatory reactions by regulating the expression of various genes. RIG-I is expressed in endothelial cells and upregulated with lipopolysaccharide (LPS). Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a nuclear hormone receptor and regulates gene expressions in response to its specific ligands. In the present study, we examined the effect of PPAR-γ ligands on the LPS-induced RIG-I expression in cultured human umbilical vein endothelial cells (HUVEC). 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), a metabolite of PGD_2, is a natural ligand for PPAR-γ and known to modulate inflammatory reactions by regulating the expression of various genes in PPAR-γ-dependent and -independent manners. LPS-induced RIG-I expression in HUVEC was inhibited by pretreatment of the cells with 15d-PGJ_2 in time-and concentration-dependent manners. However, ciglitazone and bisphenol A diglycide ether, authentic and specific ligands for PPAR-γ, did not affect the RIG-I expression. These results suggest that 15d-PGJ_2 inhibits LPS-induced RIG-I expression through a mechanism independent on PPAR-

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1098-8823/$ – see front matter
doi:10.1016/j.prostaglandins.2005.02.006

γ. 15d-PGJ_2 may regulate inflammatory reactions, at least in part, by inhibiting the expression of RIG-I.

Keywords: 15d-PGJ_2; RIG-I; Endothelial cells; LPS

1. Introduction

Peroxisome proliferator-activated receptors (PPARs), a family of nuclear hormone receptors, regulate expressions of various genes in response to specific ligands, and one of the major functions of PPAR-γ is regulation of inflammation. 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) is a metabolite of PGD_2 and a natural ligand for PPAR-γ [1]. It was originally described as a factor induces adipocyte differentiation through binding to PPAR-γ [2]. 15d-PGJ_2 has a wide variety of biological effects on various types of cells by regulating gene expressions in PPAR-γ-dependent or -independent manners [3]. In macrophages, 15d-PGJ_2 has been reported to inhibit the expression of inducible nitric oxide synthase, gelatinase B, scavenger receptor A [4], tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 [5] and macrophage chemoattractant protein-1 [6]. It also inhibits the expression of COX-2 in rheumatoid synoviocytes [7], GM-CSF in bronchial epithelial cells [8], and regulated on activation, normal T-cell expressed and secreted (RANTES) in astrocytes [9]. 15d-PGJ_2 induces c-fos in smooth muscle cells [10], IL-8 [6] and platelet-activating factor acetylhydrolase [11] in macrophages, heme oxygenase-1 (HO-1) in macrophages and smooth muscle cells [12], and nerve growth factor in astrocytes [13].

Vascular endothelial cells play an important role in host defense and inflammation. When stimulated with lipopolysaccharide (LPS) or cytokines such as IL-1, TNF-α and interferon-γ (IFN-γ), endothelial cells express various factors including adhesion molecules, chemokines, growth factors, and enzymes. These molecules are involved in inflammatory reactions, and dysregulation of their expressions may lead to inflammatory diseases. PPAR-γ is expressed in vascular endothelial cells [14]. In endothelial cells, 15d-PGJ_2 induces the expression of IL-8 [15] but inhibits the expression of IFN-γ-inducible protein-10, monokine induced by IFN-γ [16], vascular endothelial adhesion molecule-1, intercellular adhesion molecule-1 [17], fractalkine [18], galectin-9 [19], granulocyte-macrophage-colony-stimulating factor (GM-CSF) [20] and epithelial neutrophil activating peptide-78 [21]. Thus, 15d-PGJ_2 may play a regulatory role in inflammatory reactions at the vascular endothelium.

Retinoic acid-inducible gene I (RIG-I) is a member of the DExH box family protein and designated as a putative helicase from its amino acid sequence. RIG-I is involved in anti-viral response induced by intracellular double-stranded RNA [22]. Bacterial LPS induces multiple genes in human endothelial cells and other cell types, and RIG-I is one of the LPS-inducible factors in endothelial cells [23]. These observations suggest that RIG-I may play an important role in host defense mechanisms against microbial pathogens, in inflammatory reactions or inflammatory diseases. We have addressed the mechanisms regulating the expression of RIG-I in endothelial cells, and the present study was undertaken