Regulatory Toxicology and Pharmacology 60 (2011) 112–119

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Protective effects of *Chlorella*-derived peptide on UVB-induced production of MMP-1 and degradation of procollagen genes in human skin fibroblasts

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ARTICLE INFO

Article history:
Received 28 October 2010
Available online 11 March 2011

Keywords:
UVB
MMP-1
CYR61
Procollagen
TbRII
c-fos
c-jun
MCP-1
Skin fibroblasts
Chlorella

ABSTRACT

UV exposure is known to induce premature aging, which is mediated by matrix metalloproteinase-1 (MMP-1) activity. MMP-1 mRNA expression is up-regulated by elevated cysteine-rich 61 (CYR61) and monocyte chemoattractant protein-1 (MCP-1) via action of transcription factor AP-1. Collagen is degraded by MMP-1 activity but synthesized by transforming growth factor-β (TGF-β) signal. *Chlorella* has been shown to inhibit UVB-induced MMP-1 level, however its regulatory molecular mechanisms have not been studied. In this study, *Chlorella* derived peptide (CDP) was added to skin fibroblasts after UVB irradiation and the expression of MMP-1, CYR61, procollagen, *c-fos*, *c-jun*, and TGF-β receptor (TbRII) mRNA and MCP-1 production were investigated. CDP (10 or 5 mg/ml) diminished UVB-induced MMP-1 and CYR61 mRNA expression and MCP-1 production, whereas, UVB-suppressed procollagen and TbRII mRNA was restored by CDP treatment. UVB-induced *c-fos* and *c-jun* expressions were also inhibited by the CDP treatment. Taken together, CDP inhibits UVB-induced MMP-1 expression in skin fibroblasts by suppressing expression of AP-1 and CYR61 and MCP-1 production.

1. Introduction

When skin is excessively exposed to solar ultraviolet (UV), this leads to photoaging. The photoaging process displays the prominent alterations in the skin through stimulation of multiple signal transduction pathways, which lead to activation of transcription factors or target genes (Fisher and Voorhees, 1998). UVB is known to induce the expressions of MMP-1, -3, and -9 in the normal human epidermis in vivo (Fisher et al., 1996). Among them, MMP-1, which degrades collagen, is thought to be the major contributor to photoaging (Brennan et al., 2003). On the other hand, transforming growth factor (TGF)-β is a multifunctional cytokine that regulates cell proliferation and differentiation, tissue remodeling, and repair (Massague, 1998). In the dermis, TGF-β acts as a positive growth factor inducing the synthesis of extracellular matrix proteins, including procollagen mRNA (Massague, 1998; Massague and Wotton, 2000; Piek et al., 1999). Over-expression of TGF-β receptor (TbR) I or II increases collagen promoter activity in fibroblasts (Kawakami et al., 1998). In addition, TbRII is essential for the binding of TGF-β. Studies have shown that UV irradiation causes down-regulation of TbRII receptor mRNA and protein (Quan et al., 2001) which then proceeds to down-regulation of type I procollagen gene expression in human skin in vivo (Quan et al., 2004). Cysteine-rich 61 (CYR61) is an extracellular matrix-associated signaling molecule that belongs to the CCN gene family (Lau and Lam, 1999). The CCN family of genes plays a fundamental biological role in growth, differentiation, angiogenesis, migration, and extracellular matrix regulation (Chen et al., 2001; Kireeva et al., 1996; Perbal et al., 2003). Up-regulation of CYR61 in human skin fibroblasts also causes the alterations of type I collagen homeostasis that mimic those observed in chronologically aged and photoaged human skin (Quan et al., 2006). Elevated CYR61 down-regulates TbRII gene and protein expression thereby impairing the TGF-β pathway, which subsequently affects type I collagen homeostasis. Furthermore, elevated CYR61 induced transcription factor activator protein-1 (AP-1), which acts to stimulate MMP-1 expression. Oxidative stress caused by UV irradiation, ozone, hydrogen peroxide and free radicals may lead to activation of AP-1, thereby increasing MMPs expression and sequentially causing collagen degradation. (Watanabe et al., 2004). UVB irradiation has diverse effects on the production of cytokines, among them IL-8 and monocyte chemoattractant protein-1 (MCP-1)[1] were predominantly increased (Kang et al., 2007). The latter has been shown to up-regulate MMP-1 mRNA expression and synthesis in human skin fibroblasts at a transcriptional level (Yamamoto et al., 2000).

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[1] Abbreviations used: MMP-1, matrix metalloproteinase-1; TGF-β, transforming growth factor- β; CDP, *Chlorella* derived peptide; MCP-1, monocyte chemoattractant protein-1; CYR61, cysteine-rich 61.

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doi:10.1016/j.yrtph.2011.03.001