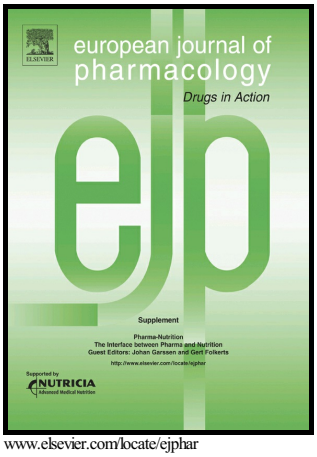

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Eun Ji Jo, Seong Ji Park, Byung-Chul Kim

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Propyl gallate sensitizes human lung cancer cells to cisplatin-induced apoptosis by targeting heme oxygenase-1 for TRC8-mediated degradation

Eun Ji Jo, Seong Ji Park and Byung-Chul Kim*

Department of Biochemistry, College of Natural Sciences, Kangwon National University, Chuncheon 24341, Republic of Korea

*Correspondence to. Department of Biochemistry. College of Natural Sciences. Kangwon National University. Kangwondaehakgil 1. Chuncheon-si, Gangwon-do 24341. Republic of Korea. Tel.: +82 33 250 8517. fax.: +82 33 259 5664. bckim@kangwon.ac.kr

Abstract

Heme oxygenase-1 (HO-1) significantly contributes to survival of cancer cells and is being considered as one of therapeutic targets for cancer treatment. Propyl gallate (PG) is a synthetic phenolic compound that possess a potent anti-oxidant and anti-inflammatory activities. In the present study, we investigated whether PG exhibit an anti-cancer effect through modulating HO-1 activation. In human non-small cell lung cancer (NSCLC) cells, treatment with PG dose-dependently diminished HO-1 protein levels without changing its mRNA levels and consequently decreased HO-1 activity. PG also significantly enhanced the sensitivity of NSCLC cells to cisplatin-induced apoptosis, and this effect was attenuated by overexpression of HO-1. Mechanistically, PG exerted its chemosensitization effect by down-regulating HO-1 protein expression through a TRC8 (translocation in renal carcinoma, chromosome 8)-mediated ubiquitin-proteasome pathway. Collectively, our data provide the potential application of PG in combination chemotherapy to enhance drug sensitivity in lung cancer by targeting HO-1.

Key words: propyl gallate; drug sensitivity; lung cancer; HO-1 degradation; TRC8 E3 ligase

1. Introduction

Heme oxygenase-1 (HO-1) is a rate-limiting enzyme that catalyzes oxidative breakdown of free heme (Kikuchi et al., 2005). HO-1 also confers cytoprotective functions to oxidative damage through potent antioxidant and anti-inflammatory actions of its metabolic byproducts, biliverdin and carbon monoxide (Lin et al., 2007; Lee et al., 2011). Therefore, HO-1 deficiency in normal cells may cause the incidence of genome instability and tumorigenesis.

HO-1 is an inducible protein and its expression is transcriptionally regulated by a nuclear factor-erythroid 2-related factor 2 (Nrf2) (Kobayashi and Yamamoto, 2005). Under oxidative stimuli, Nrf2 is