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Compound K Rich Fractions Inhibit Inflammatory Signals in Response to Toll-like Receptor (TLR) 4 and TLR9 via Glucocorticoid Receptor

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Abstract

Compound K (C-K), a protopanaxadiol ginsenoside metabolite, demonstrated immunomodulatory effects in previous studies. In this study, we isolated the CK rich fractions (CKRF) from Korean Red Ginseng and investigated the regulation of CKRF-mediated inflammatory signaling during Toll-like receptor (TLR)-associated signaling modulation acting via glucocorticoid receptor (GR) engagement. Among various TLR ligands, CKRF considerably abrogated TLR4- or TLR9-induced inflammatory signaling. Of interest, pre-treatment of CKRF in either LPS/TLR4- or CpG-ODN/TLR9-stimulated macrophages substantially attenuated the TLR agonists-induced inflammatory cytokine production and mRNA expressions, as well as MAPK and NF-κB activation. CKRF competed for binding of the synthetic glucocorticoid dexamethasone to GR and activated GRE-containing reporter plasmids in a dose-dependent manner. Further, TLR4- or TLR9-dependent repression of inflammatory response genes by C-K was mediated through disrupting p65/interferon regulatory factor (IRF) complexes. Collectively, these results demonstrate that CKRF, as a functional ligand of GR, specifically modulates distinct TLR4- and TLR9-mediated inflammatory responses, and further studies are urgently needed for their *in vivo* roles for potential therapeutic uses, such as in systemic inflammatory syndromes.