The Ginsenoside Metabolite Compound K Inhibits Toll-like Receptor 4-mediated Inflammatory Signals Acting through Glucocorticoid Receptor

Running title: Compound K Regulates TLR4-dependent Signaling

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Abstract

Compound K (C-K), a protopanaxadiol ginsenoside metabolite, demonstrated immunomodulatory effects in previous studies. Here we describe a novel therapeutic role of CK for the treatment of lethal sepsis through TLR4-associated signaling modulation acting via glucocorticoid receptor (GR) engagement. Of various TLR stimulations, C-K significantly represses TLR4/lipopolysaccharide (LPS)-induced NF-κB and mitogen-activated protein kinase activation, and secretion of proinflammatory cytokines in mononuclear phagocytes. C-K competed for binding of the synthetic glucocorticoid dexamethasone to GR and activated GRE-containing reporter plasmids in a dose-dependent manner. In addition, blockade of GR with the glucocorticoid antagonist RU486 substantially reversed the anti-inflammatory effects of CK. Further, TLR4-dependent repression of inflammatory response genes by C-K was mediated through disrupting p65/interferon regulatory factor (IRF) complexes. Collectively, these results demonstrate that the C-K, as a functional ligand of GR, plays an essential role for controlling the distinct TLR4-mediated inflammatory responses.

Key Words: Compound K, toll-like receptor 4, MAPK, NF-κB