Ginsenoside metabolite compound K exerts anti-inflammatory effect via suppressing T cell activation

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Received: March 17, 2015
Published online: April 29, 2015

Ginsenoside metabolite compound K (CK) is a metabolite of ginsenoside, and belongs to dammarane-type triterpene saponins according to its structure. It has been reported that CK exerts anti-inflammatory activity. Our previous studies showed that CK alleviated adjuvant-induced arthritis (AA) and collagen-induced arthritis (CIA) via suppressing T cell activation. Our recent study showed that the inhibitory effect of CK on T cell activation was due to suppressing CCL21-CCR7-mediated migration of dendritic cells (DCs) and signals between T cells and DCs. In this brief review, we summarize recent studies on the anti-inflammatory effect of CK and highlight recent advances in our understanding of how CK contributes to the anti-inflammatory effect via suppressing T cell activation in autoimmune conditions. Elucidating the possible mechanism of CK responsible for the anti-inflammatory effect may provide a rationale for development of CK as new therapeutic agents in treatment of inflammatory and autoimmune disease.

Keywords: Ginsenoside metabolite compound K; inflammation; autoimmune; T cell activation; dendritic cell; collagen-induced arthritis; adjuvant-induced arthritis


Ginsenoside metabolite compound K (CK, \(C_{36}H_{52}O_{8}\)) is a kind of dammarane-type triterpene saponins. In vivo, it is a catalobolite of ginsenoside by bacteria in the intestine [1, 2], and it can be converted from ginsenoside by food microorganisms in vitro [3]. The pharmacological activities of CK have been reported in several studies, including anti-inflammation, anti-tumor, anti-oxidation, et al.

The significant anti-inflammatory effect of CK has been confirmed in macrophages via a down-regulation of the pro-inflammatory cytokines and inflammatory signaling in vitro [4-7]. CK markedly inhibited the production of the pro-inflammatory cytokines and suppressed the activation of interleukin-1 receptor-associated kinase-1 (IRAK-1), inhibitor κB kinase β (IKKβ), nuclear factor κB (NF-κB), and mitogen-activated protein kinases (MAPKs) (ERK, JNK, and p-38) [4]. The production of NO and prostaglandin E2, and the activation of NF-κB in LPS-induced RAW 264.7 cells were significantly suppressed by CK [5]. CK repressed Toll-like receptor (TLR) 2 and TLR4-mediated NF-κB and MAPKs activation and decreased the secretion of pro-inflammatory cytokines [6]. It has been reported that CK can bind to and activate glucocorticoid receptor (GR). In addition, the anti-inflammatory effects of CK can be markedly canceled out by the blockade of GR [6]. This result suggest that CK exerted anti-inflammatory effect through GR. CK also significantly inhibited superoxide generation, NADPH oxidase activities, and Ser345-p47phox phosphorylation in macrophages [7]. In LPS-stimulated BV2 microglial cells and primary cultured microglia, CK
suppressed the activation of reactive oxygen species (ROS), MAPK, and NF-κB/activator protein-1 (AP-1), and activated heme oxygenase-1 (HO-1)/antioxidant response element (ARE) signaling [8].

The anti-inflammatory effect of CK also confirmed in animal models. CK alleviated 2,4,6-trinitrobenzene sulfuric acid (TNBS)-induced colitis by inhibiting the expression of pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, COX-2 and iNOS, and suppressing the activation of NF-κB[4]. CK markedly cured gram-negative bacterial-induced lethal shock via inhibiting systemic inflammatory cytokine production and reversing the lethal sequelae of sepsis [6]. CK decreased the number of activated microglia and reduced TNF-α and IL-1β levels in the LPS-induced sepsis brain [8]. CK alleviated colitis and suppressed the inflammation by inhibiting NF-κB activation [9].

Our previous studies showed that CK attenuated adjuvant-induced arthritis (AA) and collagen-induced arthritis (CIA) by suppressing T cell activation [10-12]. Our understanding of the immunopathology of autoimmune disease has been improved by recent progress in the research of T cells. Rheumatoid arthritis (RA) is a chronic autoimmune disease, and is generally regarded as T-cell-mediated inflammatory disease. The crucial role of activated T cells in the pathogenesis and progression of RA has been confirmed in numerous studies. Abnormal activation of T cells contributes to the immune damage and synovial pathological histology change in RA [13]. Animal models confirm the role of T cells in chronic inflammatory arthritis [14, 15]. A down-regulated percentage of naive T cells, an up-regulated percentage of activated T cells, and abnormal proliferation of T cells were demonstrated in AA and CIA [14-17]. Biological agents inhibiting T cells activation has been identified efficacy in the treatment of autoimmune disease including RA [18,19]. Our previous studies showed that CK reduced inflammatory cytokine levels including IL-1β, TNF-α, IL-2, and IL-17 [11,12,20]. In addition, CK decreased activated T-cells, and raised naive T-cells and Treg cells in spleen [11,12], reduced expression of T cell receptor (TCR), CD28, and CD25 on T cells [11,12,20].

To further clarify the mechanism of CK contributes to suppressing T cell activation, in our recent study, dendritic cells (DC), the most powerful APCs were investigated. DCs present antigens to T cells and induce T cell activation in inflammatory conditions [21-23]. It has been reported in numerous studies that DCs play important role in the pathogenesis of autoimmune disease such as RA [24-26]. The infiltrated DCs migrate from the inflamed synovium to the draining lymph nodes, present arthritogenic peptide to T cells and activate T cells [27,28]. In inflammation conditions, effector T cells such as Th1 and Th17 can be induced by the migration of DCs [29]. Migration of DCs from peripheral tissues to lymph nodes is mediated by chemokine receptor CCR7 and its ligand CCL21 [30]. During inflammation, expression of CCL21 massively increased in high endothelial venule, which promoted mature DCs migrate from peripheral to lymphatic nodes [31]. Our recent results showed that the percentage of DCs in the lymph nodes of CIA mice was downregulated by CK. These results suggest that reducing accumulation of DC in the lymph nodes may contribute to inhibiting T cell activation. Our results also showed that CCL21 level in the lymph nodes, CCR7 expression on DCs and CCL21-mediated migration of DCs were suppressed by CK. These results suggest that decreasing expression of CCL21 and CCR7 may be associated with the effect of CK on reducing DC accumulation in the lymph nodes. Based on our results and the studies mentioned above, we deduce that suppressing CCL21 and CCR7 may be responsible for the anti-inflammatory effect of CK. Signals provided by APCs is required for T cell activation, including MHC II -TCR and B7 (CD80, CD86)-CD28 [32]. Our recent study demonstrated that the expression of CD80, CD86, and MHCII on DCs were inhibited by CK. Consistent with this result, CK decreased the expression of TCR, CD28 and CD25 on T cells [11,12] and suppressed IL-2 secretion from T cells[111]. These results suggest that the effect of CK on suppressing T cell activation may be due to reducing the signals provided by DCs.

In our previous studies, it has been reported that CK up-regulated the percentages of Tregs in CIA mice [12]. The pivotal role of Tregs in autoimmune diseases such as RA has been established [33]. Tregs play a critical role in down-regulating adaptive immune response and limiting inflammation via controlling the interaction of APCs and effector T cells and the production of anti-inflammatory cytokines [33, 34]. Tregs and DC co-localized in the synovium of RA, but the activation and function of DC could not be inhibited by Tregs [35]. In our recent study, the result showed that CK exerts anti-inflammatory effect via suppressing DC priming T cell activation. Based on these data, we can suppose that the inhibitory effect of CK on DC may be related with the up-regulation of Tregs, but the exact role needed to be further studied.

In conclusion, these studies demonstrated that CK exerts anti-inflammatory effect via suppressing T cell activation and the mechanism may be due to inhibiting DC function. It should be noted that activation of T cells is complicated in vivo, the possible mechanisms of CK responsible for T cells activation needed to be future studied. Elucidated the potential mechanism for the anti-inflammatory effect of CK may provide a rationale for development of CK as new
therapeutic agents in treatment of inflammatory and autoimmune disease.

Acknowledgements

This work was supported by the National Nature Science Foundation of China [Grant 81330081, 31200675 and 81173075]; Anhui Province Nature Science Foundation in the University [Grant KJ2011Z180]; Foundation for Outstanding Young Talents in Higher Education Institutions of Anhui Province [Grant 2012SQRL268]; and Anhui Provincial Natural Science Foundation [Grant 1208085QH158].

Conflicting of interests

The authors declare that they have no conflicting of interests.

Abbreviations

AA: adjuvant-induced arthritis; AP-1: activator protein-1; APCs: antigen-presenting cells; ARE: antioxidant response element; CFA: complete Freund’s adjuvant; CIA: collagen-induced arthritis; CK, ginsenoside metabolite compound K; DCs: dendritic cells; GR: glucocorticoid receptor; IKKβ: inhibitor κB kinase; IRAK-1, interleukin-1 receptor-associated kinase-1; HO-1: heme oxygenase-1; MAPKs: mitogen-activated protein kinases; NF-κB: nuclear factor κB; RA: rheumatoid arthritis; ROS: reactive oxygen species; TCR: T cell receptor; TLR: Toll-like receptor; TNBS: 2,4,6-trinitrobenzene sulfonic acid.

Author contributions

WW conceived of the study and helped to write the manuscript. CJ designed and carried out the studies, performed data analysis and writing of the manuscript.

References


