Panax ginseng as a potential modulator of macrophages

Cuong Thach Nguyen1, 2, Dong-Kwon Rhee1

1School of Pharmacy, Sungkyunkwan University, Su-Won 440-746, South Korea
2Departments of Microbiology & Molecular Genetics, University of Texas Health Science Center, Houston, TX 77030, USA

Introduction

Panax ginseng has been well known as an immune modulator. In Asian countries, P. ginseng has been widely used as a traditional medicine for the treatment of several diseases such as respiratory, gastrointestinal, and cardiovascular diseases [1]. The major bioactive compound in P. ginseng is ginsenosides. Based on the position of sugar moieties, which are attached to a four-ring steroidal skeleton, ginsenosides are divided into 2 groups: protopanaxadiol (Rb1, Rb2, Rc, and Rd) and protopanaxatriol (Rg1, Rg2, Re, and Rf) [1].

Macrophages are important immune cells in the host defense against bacterial infections and cancer cells (lymphoma and mastocytoma). In different organs, macrophages have different morphologies and different names [2]. For instance, macrophages in the brain are called microglia, but are called Kupffer cells in the liver, Langerhans cells in the epidermis, alveolar macrophages in the lungs, and osteoclasts in the bones [2]. Macrophages are
activated when they encounter antigens, which are derived from pathogens or cancer cells [3]. They produce several pro-inflammatory mediators including interleukin-1β (IL-1β), tumor necrosis factor (TNF)-α, IL-6, and IL-12, or nitric oxide (NO) [3]. Macrophages also act as antigen-presenting cells by expressing class II major histocompatibility complex (MHC) molecules on their surface and presenting antigens to B or T cells to activate the adaptive immune system; thus, macrophages are considered as a “connector” of the innate and adaptive immune systems. For a decade, ginseng has been reported to possess potential antibacterial/viral and antitumor activity through the activation of macrophages. In the present study, we will mainly discuss the mechanism(s) by which P. ginseng or ginseng modulates the functions of macrophages upon bacterial/viral infection as well as in cancer diseases.

**How P. ginseng mitigates inflammation in macrophages?**

During inflammation, macrophages and other immune cells produce several inflammatory mediators such as cytokines and chemokines. These mediators are tightly regulated by host immunity. The inflammatory cytokines are one of the major...
Lipopolysaccharide (LPS), which is derived from gram-negative bacteria, is a potent inducer of pro-inflammatory cytokines. LPS is a well-known ligand of Toll-like receptor 4 (TLR4). Once LPS binds to TLR4 in macrophages, it triggers the inflammatory signals. Ginsenoside Rg1, one of the major components of P. ginseng, demonstrated anti-inflammatory effects in LPS-induced macrophages via inhibition of LPS binding to TLR4 [4]. Furthermore, ginsenoside Rg1 reduced the production of inflammatory cytokines TNF-α, IL-1β, and IL-6 via inactivation of nuclear factor (NF)-κB [4]. It also suppressed NO production via downregulation of inducible nitric oxide synthase expression (iNOS) in trinitrobenzenesulfonic acid (TNBS)-induced colitis [4]. Thus, ginsenoside Rg1 exhibited anti-colitic effects in mice with TNBS-induced colitis. Moreover, P. notoginseng flower saponins (PNFS) are the major active components of P. notoginseng, which was demonstrated to have anti-inflammatory activity in RAW264.7 macrophages [5]. PNFS inhibited inflammation via the suppression of TLR-4, mitogen-activated protein kinases (MAPKs), NF-κB, and iNOS expressions; however, it showed no effect on phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) expression [5]. Moreover, ginsenoside Rb1 and compound K inhibited expression of interleukin-1 receptor-associated kinase-1 (IRAK-1), inhibitor of nuclear factor kappa (IKK)-β, NF-κB, and MAP kinases (extracellular signal-regulated kinases (ERK), c-Jun amino-terminal kinases (JNK), and p38). However, it did not have any effects on the interaction between LPS and TLR-4, and activation of IRAK-4 and IRAK-2 [6].

Caspase-1 is a member of a caspase family, which is involved in apoptosis and inflammation. Caspase-1 cleaves pro-immature IL-1β to form mature IL-1β. In addition, ginsenoside, which is another compound from ginseng, showed inhibitory effects against caspase-1 activity, resulting in the inhibition of inflammation [7]. Moreover, activation of IL-1β is regulated by inflammasome, which includes NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome, interferon-inducible protein AIM2 inflammasome, and NLRC4 (NLR Family, CARD domain-containing 4) inflammasome [8]. P. ginseng suppressed IL-1β maturation by suppressing the activation of NLRP3 inflammasome in macrophages as well as the murine model [8]. In addition, P. ginseng strongly attenuated IL-1β secretion by inhibiting AIM2 inflammasome activation, suggesting that P. ginseng could act as a potential modulator of the inflammasome complex [8].

The transcription factor nuclear factor erythroid-2 related factor 2 (Nrf2) plays an important role in the regulation of antioxidant and anti-inflammatory response [9]. In a model of cardiomyocyte hypertrophy induced by inflamed macrophages, cytokines produced by macrophages caused hypertrophy of cardiomyocytes, and this is characterized by an increase in cell size and enhanced protein synthesis [9]. The ginseng-derived panaxynol acted as a suppressor of inflamed macrophage-induced cardiomyocyte hypertrophy [9]. In this model, panaxynol inhibited the production of cytokines such as TNF-α, IL-1β, and IL-6 as well as that of chemokine monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1β (MIP-1β), via stimulation of Nrf2 and inhibition of NF-κB [9]. These findings suggest that ginseng, ginsenosides, and particularly compound K, could be used as chemotherapeutic agents for the treatment of inflammation-related diseases such as colitis or chronic obstructive pulmonary disease (COPD) [1], by

### Table 1. Summary of anti-inflammatory effects of ginseng and ginseng compounds in macrophages

<table>
<thead>
<tr>
<th>Ginseng type</th>
<th>Models of inflammation</th>
<th>Target cytokines/proteins/enzymes</th>
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<tbody>
<tr>
<td>P. notoginseng flower saponins (PNFS)</td>
<td>LPS-induced inflammation</td>
<td>TNF-α, IL-6, NO/iNOS, TLR4, MAPK, NF-κB [5]</td>
</tr>
<tr>
<td>Igongsan</td>
<td></td>
<td>NO/iNOS, NF-κB, caspase-1, COX-2 [7]</td>
</tr>
<tr>
<td>Panaxynol</td>
<td></td>
<td>TNF-α, IL-1, IL-6, IL-8, IL-10, TGF-β [20]</td>
</tr>
<tr>
<td>P. ginseng</td>
<td></td>
<td>TNF-α, cAMP PDE [21]</td>
</tr>
<tr>
<td>Rb1, Rb2, and Re</td>
<td>TNBS-induced inflammation</td>
<td>TLR4, NF-κB, IL-1β [4]</td>
</tr>
<tr>
<td>Rb1 and compound K</td>
<td></td>
<td>IL-1β, NO/iNOS, COX-2, IRAK-1, IKK-β, NF-κB, ERK, JNK, p38 [8]</td>
</tr>
<tr>
<td>Rg1, Rb1, and 20(S)-protopanaxtriol</td>
<td></td>
<td>ERK, p38 MAPK, TNF-α, IL-6, IL-12, ROS, superoxide [22]</td>
</tr>
<tr>
<td>Rb1 and compound K</td>
<td>Zymosan-mediated inflammation</td>
<td>TNF-α, IL-1β, NO, PI3K/AKT [32]</td>
</tr>
<tr>
<td>P. ginseng</td>
<td>Infection-induced inflammation</td>
<td>TNF-α, IL-1β, IL-6, IFN-γ, IL-12, IL-18, TLR2, MyDD88, JNK, p38, NF-κB [11]</td>
</tr>
</tbody>
</table>

signals in cellular communication. Cells communicate with neighbor cells or transduce “danger signals” to other cells via the inflammatory cytokines or chemokines. However, excessive production of inflammatory cytokines could lead to inflammatory diseases, which is characterized by tissue damage or organ injury. Therefore, the balance of cytokines dictates the overall effect of an inflammatory response. We will discuss how P. ginseng impairs cytokine production in macrophages and inflammatory diseases, and summarize the recent studies that investigated the effect of ginseng in controlling inflammation in macrophage models (Fig. 1 and Table 1).
targeting TLR4/IRAK-1/NF-κB/MAPKPK activation.

P. ginseng modulates macrophage activity against infection.

P. ginseng is known to have anti-bacterial/viral properties. During infections, the immune cells (such as macrophages and neutrophils) recognize the presence of bacteria/virus via interaction with bacterial/viral components and produce cytokines (IL-1β, TNF-α, and IFN-γ) in response. These cytokines are part of the immune response and protects the host from infections. However, massive production of cytokines causes harmful effects to the host immunity, such as inducing immune cell apoptosis, cell damage, or tissues injury. Therefore, down-regulation of cytokine production would be beneficial for the host during fulminant pathogenic infection. Moreover, ginseng enhances macrophage phagocytic activity, which accelerates antigen processing and activates the immune system against infection [10, 11].

Upon infection, S. pneumoniae could invade the host defense system via several mechanisms. One of them is by inducing macrophages to undergo apoptosis, which may attenuate function of the innate immunity. Our studies found that P. ginseng enhanced the survival of macrophages via modulation of the PI3K/AKT signaling pathway [12]. Moreover, inflammation was involved in the pathogenesis of pneumococcal, particularly in pneumococcal sepsis. Pneumococcus-induced sepsis causes tissue damage, which might be harmful to the host. Unexpectedly, P. ginseng was found to exhibit anti-septic activity via inhibition of cytokine production in vitro and in vivo [12]. P. ginseng inhibited cytokine production in macrophages during pneumococcal infection. Furthermore, pre-treatment with P. ginseng abolished the inflammatory cytokines in infected mice [12]. Our study also elucidated the potential mechanisms by which P. ginseng inhibits the inflammatory cytokine productions in macrophage. P. ginseng could reduce TLR4 expression and subsequently caused attenuation of NF-κB expression [12]. Since NF-κB is an upstream regulator of inflammatory cytokine genes, it is possible that P. ginseng modulates the production of inflammatory cytokines via modulation of TLR4/NF-κB expression [12].

In addition, red ginseng saponin fraction-A (RGSF-A) suppressed adherence, internalization, and intracellular growth of Brucella abortus in macrophages, by downregulating F-actin density [13]. Moreover, RGSF-A enhanced phagosome-lysosome fusion within macrophage through suppression of MAPKs p-ERK1/2 and p38 signals during Brucella infection [13], suggesting that RGSF-A has a novel immune-modulating effect in B. abortus infection. In Staphylococcus aureus infection, ginsan, a P. ginseng-isolated polysaccharide, enhanced bacterial elimination by stimulating the phagocytic activity of macrophages [11]. Moreover, ginsan inhibited the expression of TLRs/NF-κB/MAPKs, which contributes to modulation of cytokines production in S. aureus-infected macrophages [11]. Furthermore, P. ginseng was involved in the activation of macrophages and conferred protection against Candida albicans infection, which causes candidiasis [14].

The protective effects of P. ginseng against respiratory syncytial virus (RSV) were also investigated [15]. In this study, P. ginseng limited the infection by suppressing the replication of RSV in human lung cells as well as mouse models [15]. In addition, P. ginseng inhibited the production of pro-inflammatory cytokines during the RSV infection [15]. Thus, pretreatment with red ginseng extract (an extract of steamed and dried P. ginseng) increased the survival rate of mice infected with RSV. Interestingly, ginseng was also demonstrated to have anti-malarial activity in vivo. Ginsenosides and ginseng-derived components were shown to inhibit replication of Plasmodium yoelii, which is responsible for malaria [10]. The possible mechanisms of its antimalarial activities involve enhancing the immune functions, which subsequently inhibit the proliferation of malaria parasites, as well as stimulating macrophage phagocytic activity.

P. ginseng potentiates macrophage functions against cancer diseases

As mentioned previously, ginseng inhibited inflammation via suppression of cytokine production to attenuate septic shock, which damage the host tissues during infection. In contrast, ginseng was shown to stimulate cytokine production in cancer models. This triggers signals to eliminate tumor cells for other professional immune cells such as lymphocytes, T, or B cells. Of note, treatment of Hepatoma-22 (H22) with water-soluble ginseng oligosaccharides (WGOS) enhanced phagocytosis of murine peritoneal macrophages from H22 tumor-bearing mice [16]. Also, WGOS increased NO production secreted by the macrophage [16]. Consistently, production of NO and TNF-α was induced by Woongjin fermented red ginseng extract (WGFR) [17] in RAW 264.7 cells. In a lung tumor murine model, ginsenoside Rg3-fortified red ginseng (Rg3-RGP) induced production of NO from peritoneal macrophages in vivo [18], thus Rg3-RGP reduced tumor size and improved the clinical outcome in cancer mouse models. Interestingly, peritoneal macrophages showed potential direct anti-tumor activity when ginseng polysaccharide (GPS)-pretreated macrophages were co-cultured with other cancer cell such as K562, HL-60, or KG1-α [19]. GPS also activated mouse peritoneal macrophages to produce TNF-α, IL-1β, IL-6,
IL-12, and NO [19]. These evidences suggest that ginseng enhance macrophage functions against tumors.

Conflicting interests

The authors have declared that no competing interests exist.

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References


