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Functional mechanism of Ginsenosides on tumor growth and metastasis

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ABSTRACT

Ginsengs, has long been used as one medicinal herb in China for more than two thousand years. Many studies have shown that ginsengs have preventive and therapeutic roles for cancer, and play a good complementary role in cancer treatment. Ginsenosides, as most important constituents of ginseng, have been extensively investigated and emphasized in cancer chemoprevention and therapeutics. However, the functional mechanism of Ginsenosides on cancer is not well known. This review will focus on introducing the functional mechanisms of ginsenosides and their metabolites, which regulate signaling pathways related with tumor growth and metastasis. Ginsenosides inhibit tumor growth via upregulating tumor apoptosis, inducing tumor cell differentiation and targeting cancer stem cells. In addition, Ginsenosides regulate tumor microenvironment via suppressing tumor angiogenesis-related proteins and pathways. Structural modification of ginsenosides and their administration alone or combinations with other Chinese medicines or chemical medicines have recently been developed to be a new therapeutic strategy for cancer.

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1. Introduction

Ginsengs are the most popular herbal medicine drugs worldwide. Ginsengs have been reported to protect heart health (Jia et al., 2012), enhance immune function (Azike et al., 2015), increase tolerance (Sathiyaraj et al., 2014), enhance learning and memory capacities (Lee et al., 2008) and promote psychological health. Ginsengs have been widely used in cancer treatment.

Cancer is the primary public health problem in the world. Recently, the incidence and mortality of cancer has been increasing annually. Data from the World Health Organization (WHO) indicates that 14 million people were diagnosed with cancer across the globe in 2012, and the number of cancer patients will increase to 19 million by 2025 and 24 million by 2035. 8.8 million people died from cancer in 2015 across the globe, and It is predicted that the number will be increased to 13 million by 2030 (Jaffray, 2015).

Many studies have shown that ginsengs have preventive and therapeutic roles for cancer, and play the good complementary role in cancer treatment (Qi et al., 2010) . The preventive role of ginsengs on cancer was first found in 1983. The result had shown that oral administration of Korean red ginseng could effectively alleviate the incidence of lung cancer induced by urethane and aflatoxin B1 (Yun et al., 1983) . Clinical studies demonstrated that regular administration of ginseng products can distinctly prevent the growth of some types of cancer, such as gastric cancer, lung cancer, hepatic cancer, pancreatic cancer, ovarian cancer, and colon cancer (Yun and Choi, 1990, 1998). In the past three decades, many compounds with anti-tumor activity have been found in ginsengs, the most well-known compounds are ginsenosides Rg3 and Rh2 (Kim et al., 2004b; Liu et al., 2000). Since FDA classified ginsengs as Generally Recognized As Safe (GRAS) food, their inhibitory effect on malignant tumors has been widely accepted in the U.S. and Europe. In the review, we summarize the anti-tumor activity of ginsengs and their therapeutic mechanism in tumor treatment, providing novel therapeutic methods for clinical use.

2. Main active components in ginsengs

There are three key constituents of ginseng, namely saponins, polysaccharides, and phenolic compounds. Ginseng

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polysaccharides are the diverse groups of sugars that are composed of various types of glycosidic bonds. The phenolic compounds are known to have antioxidant ability. Some data reported that polysaccharides and phenolic compounds possess immunoregulatory and anti-cancer activities. However, their molecular mechanisms of anti-cancer are largely unknown (Wong et al., 2015). Ginseng's saponins, generally called ginsenosides (Rx), have been extensively investigated and emphasized in cancer chemoprevention and therapeutics. The regular ginsenosides will be metabolized by intestinal flora to undergo sequential de-glycosylation and finally converted to prosaposin or sapogenins within human body (Bae et al., 2002; Bae et al., 2005; Eunah et al., 2002). Many reports have demonstrated that most ginsenosides monomeric have antitumor activity. In those monomeric, Rb1, Rb2, Rb3, Rd, Rg3, Rg5, Rh2, Rs11, Rk1, F2 and CK belong to panaxadiol saponin, which contains one hydrogen, and Re, Rg1, Rg18, Rh1, Rh4, Rp1, Rf and F1 are panaxatriol saponin, which contains a sugar side-chain (Kim et al., 2008; Lee et al., 2015; Nakata et al., 2010; Shen et al., 2011; Yoon et al., 2012). The anti-cancer activities of those ginsenisides are related to their protein structure and sugar moieties.

3. Ginsenosides inhibit tumor growth

3.1. Ginsenosides regulate tumor cell cycle

The inhibition of tumor growth is a main methodology for cancer therapy. Ginsenosides have been shown to mediate cell cycles, including cyclin-dependent kinases (CDKs) and cyclins in the G0/G1 phase (Chung et al., 2013) (Fig. 1). Ginsenoside Rf induces cell apoptosis of human osteosarcoma cell in the G2/M phase via the mitochondrial pathway (Shangguan et al., 2014). Ginsenosides Rg3 (Park et al., 2014), Rg5 (Kim and Kim, 2015), Rh2 and CK (Zhang et al., 2013b) upregulate the expression of ataxia telangiectasia mutation (ATM), p53, p27, p21, p15, and pRb2/p130, and downregulate the expression of mouse double minute 2 (MDM2) and the transcriptional activity of E2F1 in the regulation phase of cell cycle-related proteins for a number of tumors such as breast cancer, gastric cancer, lung cancer, and prostate cancer. Those ginsenosides also downregulate the expression of cell division cycle proteins cyclinB1, CDC2, Cytc-B, CDK-4, and CDK-6 to block tumor cell cycles in the G0/G1 phase (Kim et al., 2012b; Nag et al., 2012). It is interesting that both Rg3 and Rh2 also inhibit the growth of prostate cancer cells through other different signaling pathways due to the difference of their C3 positions. Rg3 can significantly activate JNK in testosterone-independent PC3 cells while Rh2 can continually activate p38 mitogen-activated protein kinase (MAPK) in testosterone-dependent prostate cancer cell LNCaP (Kim et al., 2004a), suggesting that one kind of ginsenoside has multiple anti-cancer mechanism. Ginsenoside K also shows significant anti-proliferation and apoptosis-promoting activities in colon cancer cell experiments in vivo and in vitro (Zhang et al., 2013b).

3.2. Regulation mechanism of ginsenosides on tumor apoptosis

Some ginsenosides, such as 20(S)- ginsenoside Rg3 (Yuan et al., 2010) and ginsenosides Rg5, (Liang et al., 2015) Rh2, (Park et al., 1997) Rk1, (Hyeonseok et al., 2009) CK, (Kang et al., 2013) and PPD (Wang et al., 2009) can induce endogenous apoptosis, in the process of which those ginsenosides upregulate the expression of pro-apoptotic proteins of Bcl-2 family members Bad, Bid, Bim, Bax, and Bak and simultaneously downregulate the expression of pro-apoptotic proteins Bcl-2 and Bcl-xL, resulting in the decrease of mitochondrial transmembrane potential, the release of CytC, and the subsequent activation of caspase-9. Ginsenosides Rg3, Rh2, Rk1, CK, and PPD can also induce exogenous apoptosis of tumor cells by upregulating the expression of p53, TRAIL-R1 (DR4), TRAIL-R2(DR5), Fas, and its ligand (FasL) to activate Casp-8 (Cheng et al., 2005; Fei et al., 2015). These two pathways above

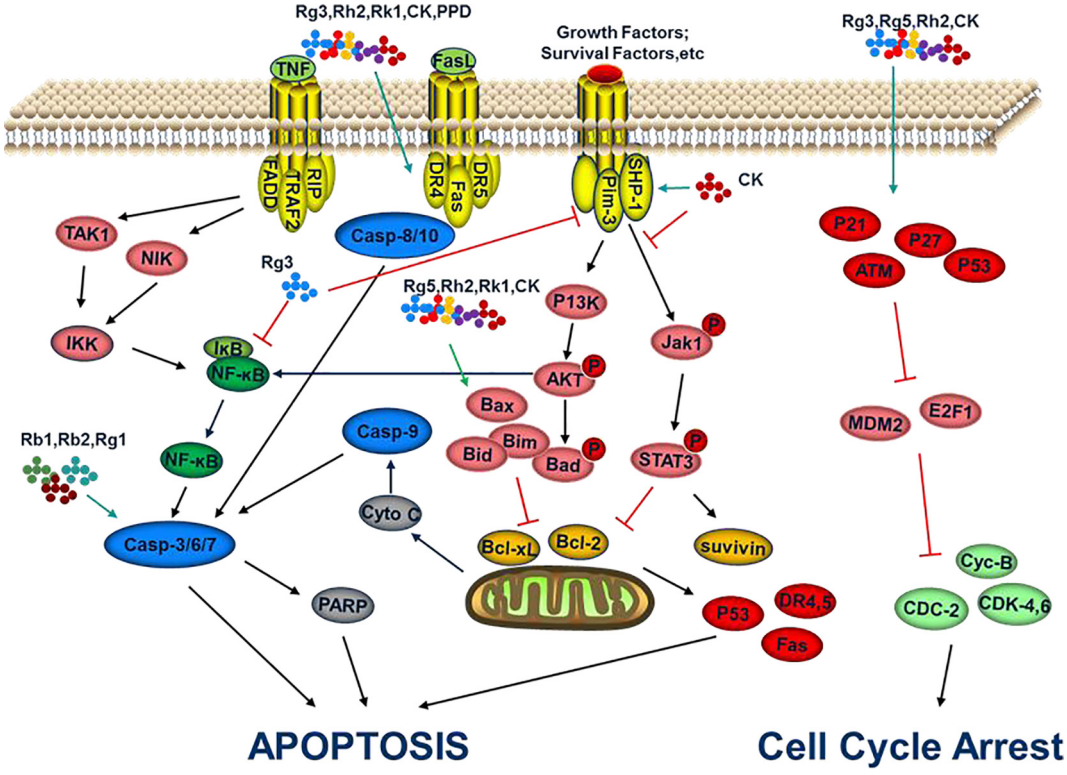

Fig. 1. Inhibition of ginsenosides on tumor growth Some ginsenosides induce tumor apoptosis through tumor cell membrane proteins, and block cell development via mediating cell cycle arrest.

can activate the downstream effector molecules Casp-3 and 7 and decompose PARP, leading to the apoptosis of tumor cells. Although ginsenosides Rb1, Rb2, and Rg1 substantially elevate the expression levels of Casp-3 and 8 in lung cancer cells, the levels of Casp-9 and anti-apoptosis protein Bax are not altered, indicating that these three ginsenosides induce tumor cell apoptosis via an exogenous apoptosis pathway rather than the endogenous mitochondrial pathway (Katsuda et al., 2002; Lee et al., 2016). In multiple myeloma cells, ginsenoside CK have been demonstrated that to inhibit the phosphorylation of Janus kinase 1 (JAK1) and Signal transducer and activator of transcription 3 (STAT3) by increasing the expression of protein tyrosine phosphatase Src homology region 2 domain-containing phosphatase-1 (SHP-1), and further downregulate the expression of STAT3 target genes, such as Bcl-2, Bcl-xL, and survivin, indicating that CK also mediate tumor cell apoptosis by inhibiting the JAK1/STAT3 signaling pathway (Park et al., 2011). Ginsenoside Rg3 also induce tumor cell apoptosis through other two pathways. The first one is that the ginsenoside downregulates the expression of proto-oncogene Pim-3 which phosphorylate many specific substrates in pancreatic cancer cells to promote the phosphorylation of downstream factor Bad (Jian et al., 2009). The Second is that It reduces the expression of Bcl-2 in breast cancer cells by inactivating the signals of extracellular signal-regulated kinase ERK/Akt and blocking the signals of NF-κB (Choi et al., 2014) (Fig. 1). Recently, Ginsenoside F2 has been shown to induce apoptosis of breast cancer stem cells by activating endogenous apoptosis pathways and mitochondrial dysfunction in conjunction with cell autophagy (Mai et al., 2012) . Those studies provide a new idea for developing F2 as a novel tumor therapeutic drug and conducting a subsequent pharmacological activity experiment.

3.3. Ginsenosides induce tumor cell differentiation

Many studies were involved in the leukemia therapy through ginseng-induced differentiation of tumor cells. Ginsenosides promote the production of hemoglobin and the aging of leukemia cells, and allow leukemia cells to differentiate into more mature cells. Ginsenosides Rh2 induces the differentiation of leukemia cells by upregulating the expression of TGF- β (Chung et al., 2013), or by inhibiting the activity of TLMA (Zeng and Tu, 2003). Ginsenoside Rh4 also induce leukemia cells to differentiate into granulocyte, monocyte, and megakaryocyte via PKC/ERK pathway (Kim et al., 2007). Ginsenoside Rh1 (Yu et al., 2015) and Rh2 (Wang et al., 2017) can effectively induce the differentiation of multifunctional F9 teratoma cells into endothelial cells by regulating the glucocorticoid.

3.4. Ginsenosides target tumor stem cells

Cancer stem cells (CSCs) are cancer cells with the similarity to normal stem cells and present the abilities of self-renewal and differentiation. CSCs appear to persist in tumors as a distinct population and CSCs are believed to be responsible for cancer relapse and metastasis after primary tumor resection (Perez-Losada and Balmain, 2003). There is the viewpoint that the standard therapy of inhibiting tumor recurrence is not to kill most tumor cells but to remove the tumor stem cells. Ginsenoside Rh2 dose-dependently reduced human skin squamous cell carcinoma (SCC) viability through reduced the number of Lgr5-positive CSCs. The Ginsenoside also reduces the growth of SCC by increasing autophagy and reducing β-catenin signaling in SCC cells (Liu et al., 2015). Ginsenoside Rb1 and its metabolite compound K can effectively inhibit CSC self-renewal without regrowth, and sensitize the CSCs to relevant doses of cisplatin and paclitaxel. The inhibition roles of Rb1 on CSCs were associated with the Wnt/β-catenin signaling pathway by downregulating β-catenin/T-cell factor-dependent transcription and expression of its target genes ATP-binding cassette G2 and P-glycoprotein (Deng et al., 2017). Recently, Ginsenoside Rg3 have been shown to repress the growth and stemness of colorectal cancer (CRC) cells both in vitro and in vivo (Tang et al., 2018). More and more reports have demonstrated that Ginsenosides may be effective treatment for CSCs.

4. Regulation of ginsenosides on tumor microenvironment

4.1. Ginsenosides reduce the product of reactive oxygen species (ROS)

Many evidences have shown that reactive oxygen species (ROS) play a pivotal role during tumor growth and metastasis. ROS are the primary cause leading to DNA mutation and instability of cell genome (Koshikawa et al., 2009). In the tumor microenvironment, the ROS produced by rapidly proliferated tumor cells can induce oxidative stress response due to cell-matrix entanglement, leading to the activation of angiogenic signals, the release of matrix metalloproteinases (MMPs), and the upregulation of cytokine expression, which promotes immune tolerance and tumor growth (Brown et al., 2004; Jackson et al., 2006; Lu et al., 2017; Singh et al., 2014). The ability of ginsenosides removing ROS is sorted in a decreasing order: Rc > Rb2 > Rg2 > Rh2 > Rh1 > Rf > Rg3 > Rg1 > Rb1 > Re > Rd (Chae et al., 2011). Ginsenoside Re were found to protect cardiomyocytes by removing hydrogen peroxide and hydroxyl radicals. Other Ginsenosides Rg6, and F4 have higher anti-oxidation activity and stronger anti-cancer activity with an action mechanism of regulating Bcl-2, Bax, and Caspase to induce cell apoptosis, compared with natural Re. Similarly, the products generated via a reaction of Rb2 in the presence of glycine have a stronger efficiency for ROS removal (Kang et al., 2007).

4.2. Ginsenosides suppress tumor angiogenesis

Angiogenesis refers to the development of new blood vessels from an existing vascular system. The rigorously mediated process is an important component of many physiological and pathological conditions, including tumor metastasis (O'Reilly et al., 1997). Angiogenesis is a multi-step process, including the growth, migration, and differentiation of endothelial cells (Liu et al., 2003). Many Ginsenosides have been found to suppress tumor angiogenesis through different pathways (Fig. 2). Ginsenoside Rg3 can downregulate the expression of VEGF (such as VEGF-A, VEGF-B, and VEGF-C) by repressing the signals of p38/ERK (Kim et al., 2012a), and also reduce the expression of VEGF in cancer cells by inhibiting hypoxia-induced multiple signals such as HIF-1α, COX-2, NF-κB, STAT3, ERK1/2, and JNK (Kim et al., 2009; Li et al., 2015a; Zeng et al., 2014). Recent data demonstrated that Ginsenoside Rh2 inhibited the translation of VEGF-A mRNA by elevating the level of miR-497 in glioblastoma multiforme (Li et al., 2015b). Ginsenoside CK inhibits the activation and expression of SphK1 in human umbilical vein endothelial cells and further inhibit SphK1 from catalyzing Sph to produce S1P (Shin et al., 2014). The decrease of S1P leads to an inhibition of the p38 MAPK signal and thereby reduces the expression of VEGF in the endothelial cells, thereby inhibiting neovascularization (Cui et al., 2014). Moreover, MMPs are associated with the expression of VEGF to some extent. For example, The reduced expression of MMP-2 suppresses the expression of transcription factor HIF-1α by downregulating the signal of PI3K/Akt, and further inhibits the expression of VEGF (Zhu et al., 2011). In addition to VEGF, ginsenosides also inhibit the expression of pro-angiogenesis factors such as bFGF and EphB2. Ginsenoside Rg3 can significantly inhibit bFGF-induced neovascularization (Yue et al., 2006), and effectively block the formation of

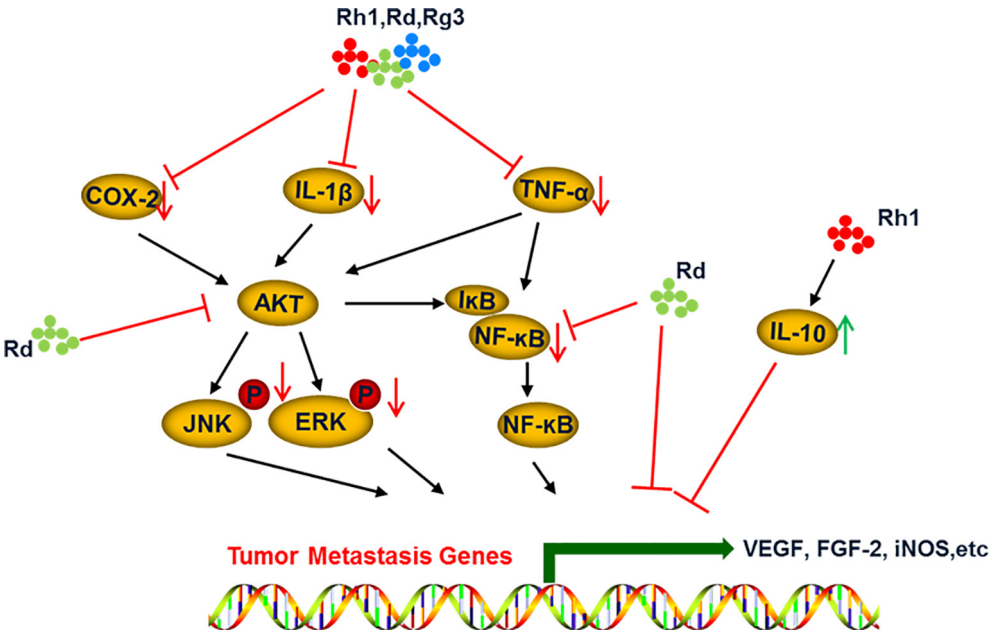

Fig. 2. Inhibition mechanism of ginsenosides on tumor metastasis Rh1, Rd, Rg3 negatively regulate AKT or NF-κB pathway through inhibiting COX-2 and some cytokines such as IL-1β and TNF-α. Finally, those ginsenosides regulate tumor metastasis proteins (such as MMPs, VEGF, FGF-2 and iNOS) to block tumor metastasis.

vasculogenic mimicry in pancreatic cancer by downregulating the expression of VE-Cad and EphA2 (Guo et al., 2014). In addition, Rg3 also reduces the expression of pro-angiogenesis factor EphB2 and its receptor EphB4 through the induction of miRNA-520h (Keung et al., 2016).

Cell adhesion molecules play an important role in tumor angiogenesis by regulating the adhesion and migration capabilities of endothelial cells (Hall and Hubbell, 2004). Some reports have shown that Ginsenosides Rg1 and Rg3 can inhibit the metastasis of melanoma cells to the lungs, and the likely mechanism is that these ginsenosides suppress the adhesion and migration of endothelial cells (ECs) by reducing the expression of Integrin β1 (Park et al., 2008). Ginsenosides Rh2 can inhibit tumor angiogenesis by downregulating the expression of JAM 1 and 2 in tumor cells (Wang et al., 2008).

4.3. Ginsenosides downregulate the activity of matrix metalloproteinases (MMP) on tumor metastasis

The matrix metalloproteinases (MMPs) are a family of >20 zinc-dependent endopeptidases that are capable of degrading the extracellular matrix (ECM) and basement membrane components under physiologic conditions (Fujimoto et al., 2001). Their activity is mainly regulated by tissue inhibitors of metalloproteinases (TIMPs). In oncology, MMPs have been considered as molecules necessary to promote tumor invasion and metastasis through the degradation of the ECM (Egeblad and Werb, 2002). The reports have shown that MMP-2 and 9 decompose type IV collagen, which is the primary pro-ECM component in basement membrane and has been considered to be the key target in this process (Heikinheimo and Salo, 1995).

Ginsenosides have been demonstrated to have negative roles on the expression of MMPs. Ginsenosides Rb2, Rg1, Rg3, Rh1, Rh2, Rd, and CK prevent ECM barrier damage by reducing the expression of MMP-1, 2, 3, 7, 9, 13, and 14 in cancer cells, thus Ginsenosides prevent invasion and migration of cancer cells. Moreover, Ginsenosides Rh1 and Rh2 reduce the expression level of AP-1 by MAPKs and PI3K/Akt signaling pathway and its downstream transcription factors NF-κB and AP-1 and also by recruiting HDAC4, which exerts a pivotal action on inhibiting the expression of the MMPs gene and the activity of its transcription factor (Yoon et al., 2012). For example, ginsenoside Rh3 can inhibit the expression of MMP-2 by inhibiting the activation of the p38MAPK pathway (Guo et al., 2014). Rh2 suppresses migration of pancreatic cancer cells by downregulating the expression of MMP-2 and 9. Similarly, Ginsenoside Rg3 inhibits angiogenesis induced by SKOV-3 tumor cells and highly invasive metastasis in ovarian cancer by reducing the expression of MMP-2 and MMP-9 (Cheng and Li, 2016). In addition, Rg3 have been demonstrated to downregulate AQP1 expression by activating p38 MAPK signals in prostatic cancer cells. Aquaporins (AQPs) are expressed in multiple human tumor cells and participate in the migration of tumor cells, thus Rg3 inhibits the migration of tumor cells via AQP1 (Pan et al., 2012). Another ginsenoside, RD reduces the expression of MMP-1, 2, and 7 to block migration of hepatic cancer cells by downregulating the ERK1/2 and p38 MAPK signaling pathways (Zhang et al., 2013a). Compound k reduces the expression of astrocytoma MMP-9 by blocking the MAPK signaling transduction pathway. In summary, ginsenosides suppress the activity and action of MMPs through difference pathways (Fig. 2).

5. Conclusion and future prospect

Given the increasing number of studies on ginsengs, ginsengs are likely to be used as antitumor drugs for controlling multiple types of cancer. Ginsenosides have been proven to regulate known oncogenes, such as Stat3. Since ginsenoside-induced death of cancer cells is achieved via multi-target pathways, it is difficult to some extent for cancer cells to develop drug resistance. Moreover, another advantage of ginsenosides is that the small side effect is shown when killing cancer cells. Thus ginsenosides may be considered as a good drug candidate for cancer treatment.

Given different kinds and places of origin of ginsengs and different cultivation methods of ginsengs, there are a variety of ginsenoside components different in quantity. Therefore, ginsengs have different pharmacological activities to cancer cells, which should be investigated further. Given the large number of ginsenosides and their synthetic compounds, a high-throughput screening

experiment is suitable for finding ginsenosides with different action mechanisms. In the screening experiments, it is necessary for our researcher to study how ginsenosides selectively act on tumor cells vs. normal cells. In summary, anti-cancer therapy of ginsenosides requires large-scale animal experiments as well as subsequent clinical observation of their therapeutic efficacy further.

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