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Parthenolide induces apoptosis by activating the mitochondrial and death receptor pathways and inhibits FAK-mediated cell invasion

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Abstract The natural product parthenolide induces apoptosis in cancer cells. However, the mechanism of apoptosis in ovarian cancer cells exposed to parthenolide is not clear. In addition, it is unclear whether parthenolide-induced apoptosis is mediated by the formation of reactive oxygen species and the depletion of GSH contents, and the effect of parthenolide on the invasion and migration of human epithelial ovarian cancer cells has not been studied. Therefore, we investigated the effects of parthenolide exposure on apoptosis, cell adhesion, and migration using the human epithelial ovarian carcinoma cell lines OV-CAR-3 and SK-OV-3. The results suggest that parthenolide may induce apoptotic cell death in ovarian carcinoma cell lines by activating the mitochondrial pathway and the caspase-8- and Bid-dependent pathways. The apoptotic effect of parthenolide appears to be mediated by the formation of reactive oxygen species and the depletion of GSH. Parthenolide inhibited fetal bovine serum-induced cell adhesion and migration of OVCAR-3 cells, possibly through the suppression the focal adhesion kinase-dependent activation of cytoskeletal-associated components. Therefore, parthenolide might be beneficial in the treatment of epithelial ovarian adenocarcinoma and combination therapy.

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Introduction

Apoptosis has an essential role in chemotherapy-induced tumor cell death [1], and inducers of apoptosis have been used in cancer therapy. Several studies have attempted to induce apoptosis by triggering the tumor-necrosis-factor-related apoptosis-inducing ligand receptor and the BCL-2 family of proteins, while others have targeted the caspases, and proteins that inhibit apoptosis [1, 2]. Apoptosis in cancer cells is mediated by the activation of cell surface death receptors, leading to caspase-8 activation, and by the mitochondrial signaling pathway, cytochrome *c* release and the subsequent activation of caspases [3, 4]. Anticancer drugs cause cell death in cancer cells by inducing the activation of apoptotic caspases [1].

The natural product parthenolide has been shown to have anti-inflammatory and anti-tumor effects [5, 6]. It induces apoptosis in cancer cells, including human hepatocellular carcinoma cells, human stomach cancer cells, and glioblastoma cells [7–9]. Parthenolide induces apoptosis in cancer cells by inhibiting nuclear factor (NF)-κB [9, 10] and activating signal transducer and activator of transcription 3 (STAT3) [6, 7]. However, it is unclear whether parthenolide toxicity is mediated by the activation of cell surface death receptors. In addition, whether the apoptotic effect of parthenolide is mediated by the mitochondrial death pathway is unclear [7].

Reactive oxygen species produced from mitochondrial dysfunction cause changes in mitochondrial membrane permeability, leading to the activation of caspases [4] and