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REVIEW

Oridonin: A promising anticancer drug from China

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Abstract Oridonin, a diterpenoid isolated from *Rabdosia rubescens (Hemsl.) Hara*, has been proved to possess remarkable anticancer activity, in addition to its potential in antiinflammation and antibacteria. The purpose of this article is to review current progress in oridonin concerned about a relationship between the chemical structure/modifications and its anticancer activity and to discuss the molecular mechanisms underlying its anticancer activity, such as suppression of tumor proliferation and induction of tumor cell death, and the cell signal transduction in anticancer activity of oridonin.

Keywords oridonin, chemical structure, antitumor, signal transduction

1 Introduction

Traditional Chinese medicines have been widely used for thousands of years in China and other Asian countries. Many herbs are claimed to exhibit anticancer and antiinflammatory activities. Given the complexity of the chemical composition and the multiple potential targets of herbs, traditional Chinese medicines could offer a new paradigm in future drug development for the treatment of complicated diseases. Plants of genus *Rabdosia rubescens (Hemsl.) Hara*, widely distributed in southwestern China, have been used as an antiinflammatory, antibacterial, and anticancer agent in local folk medicine in China and Japan since ancient times.

Oridonin, also called "Donglingcao," an ent-kaurene diterpenoid compound isolated from the leaves of *Rabdosia rubescens (Hemsl.) Hara*, was originally described *in the People's Republic of China Pharmacopoeia* in 1977. It has been widely used to treat swelling of the throat, insect bites, snake bites, and inflammation of the tonsils. Earlier in the 1970s, it was reported to possess anticancer activity. The purpose of this article is to review current progress in oridonin, especially the relationship between the chemical structure/modifications and its anticancer activity, and to discuss the molecular mechanisms underlying its anticancer activity.

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2 Structural requirements of oridonin for its anticancer activity

It is reported that the α-methylene cyclopentanone structure of oridonin, an ent-kaurane di-terpenoid, is the active site for its anticancer activity. Changes in this structure (e.g., split ring or saturated methylene) could counteract its anticancer activity (Fujita et al., 1976). The presence of a hydrogen bonding between the hydroxy group at the 6 position and the carbonyl group at the 15 position in the oridonin molecule (Fig. 1) has been shown critical for its anticancer activity because the carbon atom at the 17 position would be polarized to δ^+ and would increase the reactivity with the nucleophilic agents, such as sulfhydryl group (Node et al., 1983). Evidence indicated that all of the C-6-O-acyl derivatives synthesized from oridonin have no activity at the doses of 5 mg/kg and 10 mg/kg against Ehrich ascites carcinoma in mice, at which doses oridonin does exhibit activity. The 14-O-acyl derivative of oridonin showed increasing activity against Ehrlich ascites carcinoma cells in the acyl carbon chain length-dependent manner in mice. 14-O-benzoyl derivative was shown to have the same order of activity as oridonin. These results suggested that activity increases in proportion to the lipophilicity of the oridonin derivatives. The ester side chain in oridonin 14-O-acyl derivatives may play a carrier role in the processes related to its penetration into cells (Fujita et al., 1981). Recently, Xu et al. have synthesized series 1-O and 14-O-derivatives of oridonin and evaluated their activities in six cancer cell lines (BGC-7901, SW-480, HL-60, BEL-7402, A549, and B16) *in vitro*. The 1-O-acetyl-derivatives displayed more potent

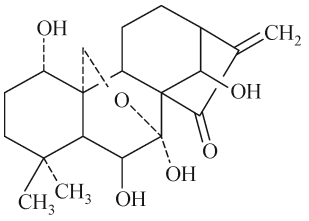

Fig. 1 The chemical structure of oridonin

anticancer activity than the 1-O-propylsulfonyl derivatives, whereas the derivatives of oxidation of 1-hydroxyl of oridonin showed slightly less potent anticancer activity than that of 1-hydroxyl with acetyl group. The authors suggested that 1-hydroxyl of oridonin would be an available site target for its anticancer activity (Xu et al., 2008).

By modifying the side chain vinyl in oridonin, Yan's group synthesized the aromatic amino-derivatives of oridonin via the Mannich reaction and studied their anticancer activity against the proliferation of KB cells. They demonstrated that addition reaction products with electron-withdrawing group boost anticancer activity against KB cells. Additionally, the presence of electron donating group on the side chain of oridonin produced poor activity against tumors (Yan et al., 2007). In order to improve its solubility, they also explored the oridonin-6-O-β-D-glucopyranoside (Yan et al., 2005). All the literatures suggest that the structural modifications of oridonin would produce novel drug candidates with improved solubility and higher potency than oridonin in cancer therapy.

3 Mechanisms of anticancer activities of oridonin

3.1 Suppression of tumor proliferation

Previous studies have shown that oridonin inhibited cell growth and proliferation in a variety of human cell lines, including those from the breast, lung, and prostate (Ikezoe et al., 2003). Cell cycle, an intricate sequence of events that enable cells to grow and replicate, can be divided into four stages: G1 phase, S phase, G2 phase, and M phase. Oridonin inhibits cell cycle progression, suppressing tumor growth. Hsieh et al. have tested oridonin's effects in MCF-7 and MDA-MB-231 cells. They observed that proliferation of MCF-7 and MCF-10A were inhibited by oridonin. Flow cytometric analysis revealed that oridonin elicited a G_1/S block in MCF-7 but an S-G_2/M arrest in MCF-10A. To further elucidate the biochemical basis for the observed results, they analyzed changes in cell cycle regulatory proteins. They found that oridonin reduced the expression of phosphorylation of retinoblastoma protein (Rb) and lowered the levels of transcription factor E2F in MCF-7 cell lines, whereas cyclin B1 and cdc2 expression in MCF-10A (Hsieh et al., 2005) was diminished. Oridonin exhibited antiproliferative activity toward DU-145 and LNCaP cell lines. Moreover, oridonin induced a G1 phase arrest in androgen receptor-positive LNCaP cells; however, it blocked the cell cycle at G2 and M phases in androgen receptor-negative DU-145 cells (Chen et al., 2005). Recent studies demonstrated that oridonin induced cell cycle arrest in G2/M phase during the early time of treatment in L929 cell through downregulation of cell-cycle-related cdc2, cdc25c, and cyclin B levels, as well as up-regulation of p21 and p-cdc2 levels (Cheng et al., 2009b). The anticancer activities of oridonin were associated with cell types concomitantly with its different effects on the expression of cell cycle regulatory proteins.

Furthermore, high levels of telomerase activity may contribute to promote tumor proliferation. Strategies targeting telomerase activity would contribute to cancer treatment. Li et al. investigated the effect of oridonin on telomerase activity and cell cycle in human leukemic cell line K562. It was indicated that oridonin at low dose exerted more potent anticancer activity. The telomerase activity is high in the S stage of cell cycle. The percentage of G0/Gl or G2/M stage cells decreased and that of the S stage cells increased after oridonin treatment. This suggests that oridonin significantly inhibits telomerase activity and redistributes cell cycle (Li and Wang, 2004).

3.2 Induction of tumor cell death

3.2.1 Oridonin and apoptosis

More than 50% of carcinomas have defects in the apoptotic machinery. Apoptosis plays a negative role in tumor progression. Most agents available in clinical trials of cancer treatment induce tumor cell apoptosis. There are two major pathways of apoptosis: the death-receptor pathway, which is mediated by the activation of death receptors, and the mitochondrial pathway, which is mediated by noxious stimuli that ultimately lead to mitochondrial injury. Liu et al. reported that U937 cells showed susceptibility to apoptosis induced by 27 μmol/L oridonin. Western blot analysis showed that the expression of Fas, FasL, and FADD was up-regulated, while procaspase-8 was downregulated. Furthermore, the activation of the Fas/FasL pathway resulted in a significant phosphorylation of extracellular regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) and release of cytochrome C. Together, these results showed that Fas/FasL signaling pathway-mediated ERK activation sensitized U937 cells to mitochondrial pathway-mediated apoptosis induced by oridonin (Fig. 2) (Liu et al., 2006). Oridonin induced L929 cell apoptosis in a time- and dose-dependent manner. Moreover, oridonin increased the ratio of Bax/Bcl-2 protein expression, whereas it had no effect on the expression of Bcl-xL. These results indicated that oridonin induced L929 cell death via the mitochondrial

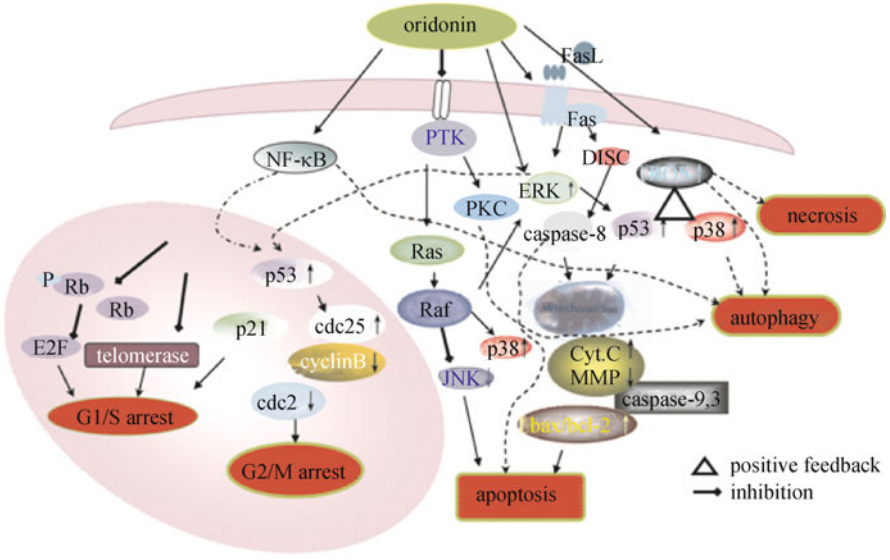

Fig. 2 The mechanisms of oridonin in anticancer activity

pathway (Zhang et al., 2004). Recent evidence has suggested that the activation of ERK and phosphorylation of p53 leads to the up-regulation of Bax protein, causes cytochrome C release, and contributes to L929 cell apoptosis (Cheng et al., 2009b). Oridonin at available concentrations inhibited growth and induced the apoptosis of t (8; 21) leukemia cells through insulting mitochondrial functions and unleashing of apoptosis machineries, down-regulating apoptosis antagonist Bcl-2, and activating apoptosis executioners including caspase-9 and -3 (Fig. 2) . Moreover, oridonin induced degradation of AML1-ETO (AE) mediated by caspase-3. Degradation of AE led to reprogramming of the expression of its target genes, such as Bcl-2 (Zhou et al., 2007).

3.2.2 Oridonin and autophagy

Autophagic cell death is an evolutionarily conserved membrane trafficking pathway and is a process by which cells recycle their own nonessential, redundant, or damaged organelles and macromolecular components. The physiological relevance of autophagy in tumor is still controversial. The cytoprotective function of autophagy in cells subjected to starvation might enhance the prolonged survival of tumor cells that are often exposed to metabolic stresses *in vivo*. Meanwhile, a tumor-suppressive function of autophagy has also been suggested. Autophagy-related cell death has been regarded as a primary mechanism for tumor suppression. Recent studies showed that oridonin induced HeLa cell autophagy. Inhibition of protein kinase C (PKC) significantly reduced oridonin-induced autophagy, whereas it markedly increased apoptosis. PKC enhanced oridonin-induced autophagy against apoptosis through regulating its downstream factors Raf-1 and Jun N-terminal kinase (JNK) in HeLa cells (Fig. 2) (Zhang et al., 2009). Cheng et al. reported that the exposure of L929 cells to oridonin led to cell apoptosis and autophagy. Moreover, oridonin-induced autophagy may block apoptosis (Cheng et al., 2009a). Several studies also pointed out that apoptosis and autophagy may be interconnected against tumor. In human MCF-7 cell line, oridonin upregulated JNK and p38 phosphorylation, while it downregulated ERK phosphorylation. 3-methyladenine (3-MA), an effective inhibitor of autophagy, reversed the effect on MCF-7 cells induced by oridonin. The results indicated that autophagy can enhance apoptosis (Cui et al., 2007). Yang et al. also found that oridonin induced apoptosis and autophagy time-dependently in HT1080 cells. The inhibition of autophagy by 3-MA decreased apoptosis induced by oridonin. Moreover, oridonin-induced apoptosis and autophagy was associated with nuclear factor κB (NF-κB) pathway (Zhang et al., 2009).

3.2.3 Oridonin and necrosis

Oridonin induced L929 cell death by affecting the balance between apoptosis and necrosis. Treatment with the caspase inhibitors (z-VAD-fmk and z-DEVD-fmk) augmented the sensitivity to oridonin-induced death. Moreover, it is well known that some necrotic cases were poly (ADP-ribose) polymerase (PARP) dependent. Blocking PARP with 20 μmol/L 3,4-dihydro-5-[4-(1-piperidinyl) butoxy]-1(2 h)-isoquinolinone (DPQ) reduced cell death

from 42.8% to 21.4% with oridonin pretreatment. Only oridonin alone caused downregulation of PARP. Oridonin induced L929 cell death mediated by PARP (Zhang et al., 2004).

Apoptosis, necrosis, and autophagy all participated in oridonin-induced tumor cell death. Different destinies of tumor cell lines, even the same response of tumor cells to oridonin, may be associated with tumor cell evolution. Further understanding the characteristics of tumor cells and interactions with different death pathways will afford us to discover novel anticancer strategies.

4 Cell signal transduction in anticancer activity of oridonin

4.1 NF-κB

NF-κB extends to transcriptional regulation in immune response, inflammation, and cell proliferation. NF-κB signaling consists of a series of positive and negative regulatory elements. Inducing stimuli triggered IκB kinase (IKK) activation, leading to the release of NF-κB from inhibitor of NF-κB (IκB)-α. Released NF-κB dimers were further activated through various posttranslational modifications and translocated to the nucleus where they were bound to specific DNA sequences and promoted transcription of target genes involved in tumor promotion, angiogenesis, and metastasis. The development of inhibitors targeting NF-κB inactivation is a promising strategy in cancer therapy. On the basis of anticancer research, oridonin can modulate NF-κB activity. Specifically, the culture of transiently transfected MT-1 cells with an NF-κB reporter construct with oridonin demonstrated that oridonin (5 μg/mL, 18 h) inhibited NF-κB transcriptional activity by 50% in MT-1 cells; additionally, it inhibited NF-κB DNA binding activity measured by luciferase reporter gene, ELISA-based, and electrophoretic mobility shift assays. Oridonin also blocked TNF-α and lipopolysaccharide (LPS)-stimulated NF-κB activity in Jurkat cells as well as RAW264.7 murine macrophages (Ikezoe et al., 2005). Further studies demonstrated that oridonin has an impact on the translocation of NF-κB from the cytoplasm to nuclei without IκB-α phosphorylation and degradation. Meanwhile, it interacted with both p65 and p50 subunits at a site other than the DNA binding site and modulated the binding affinity of different NF-κB toward DNA (Fig. 2) (Leung et al., 2005). On the contrary, the activation of NF-κB promoted oridonin-induced apoptosis and autophagy in HT1080 cells. By pretreatment with HT1080 cells at the doses of 10 and 20 μmol/L PDTC (NF-κB specific inhibitors), oridonin-induced HT1080 cell death decreased in a dose-dependent manner. Western blot demonstrated that enhanced NF-κB and p-NF-κB expression was in accordance to attenuated levels of IκBα (Zhang et al., 2009). These results suggest that NF-κB be activated by oridonin (Fig. 2) in HT1080 cells, and it promotes both apoptosis and autophagy in this circumstance.

4.2 MAPK

MAPKs are signaling components that are important in converting extracellular stimuli into a wide range of cellular responses. They are evolutionarily conserved enzymes, the activation of which requires dual phosphorylation on the Thr-X-Tyr motif. ERK1 and ERK2 MAPKs were found to be upregulated in human cancers. Two other major MAPK pathways, the JNK and p38 MAPK pathways (also called stress activated protein kinase pathways), are also often deregulated in cancers. These findings have led to the development of drug candidates targeting this pathway for cancer therapeutics. Oridonin induced L929 cell death. After treatment with L929 cell specific inhibitors, such as p38 (SB203580), JNK (SP600125) and ERK (PD98059), only PD98059 decreased oridonin-induced cell death. Western blot demonstrated that the administration of oridonin significantly and persistently enhanced the ERK phosphorylation and weakly downregulated phospho-p38, without affecting the status of JNK phosphorylation (Zhang et al., 2004). The above has mentioned that oridonin signaled to Fas/FasL pathways and activated ERK, further cleaved procaspase-8 and caused cytochrome C to release from mitochondria, finally leading to U937 cell death (Fig. 2) (Liu et al., 2006). Moreover, evidence suggested that p38 and JNK induced tumor cell death associated with reactive oxygen species (ROS) (Huang et al., 2008). The diverging roles of oridonin in the MAPKs family may associate with different tumor cells and contexts.

4.3 ROS

Most cancer cells exhibit overproduction of ROS, which is thought to provide favorable conditions for cancer cell growth, genetic instability, and survival. Increased ROS generation may also make cancer cells highly vulnerable to exogenous ROS-modulating agents through ROS-mediated mechanisms. Oridonin induced HepG2 cell apoptosis through generation of ROS. The production of ROS was mediated by p53, while the activation of ROS further led to p38 phosphorylation. In turn, phospho-p38 activated p53. The positive feedback loop contributed to cell death. ROS also caused the loss of $\Delta\psi m$, the release of cytochrome C from the mitochondria, and the activation of caspase-9/-3 (Huang et al., 2008). Oridonin induced L929 cell line apoptosis mediated by ROS production, further up-regulated p53 contributed to increased expression of Bax, and the latter caused caspase-independent cell apoptosis (Fig. 2) (Wu et al., 2008). The approach through ROS production has the therapeutic advantage of selectively targeting cancer cells while exhibiting minimal toxicity in normal cells.

4.4 PTKs

Protein tyrosine kinases (PTKs) are enzymes that catalyze the transfer of phosphate from ATP to tyrosine residues in polypeptides. PTKs are divided into two main classes. Receptor PTKs are transmembrane proteins with a ligand-binding extracellular domain and a catalytic intracellular kinase domain, whereas nonreceptor PTKs lack transmembrane domains and are found in the cytosol, the nucleus, and the inner surface of the plasma membrane. They regulate cellular proliferation, survival, differentiation, function, and motility. In many cancer cells, there exists PTK over activation. Currently, PTK antagonists offer promising potential to cancer patients. Imatinib mesylate is the first successful small-molecule PTK inhibitor. Targeting cancer cell with specific PTKs is increasingly attractive to most scientists. It has been found that oridonin could modulate the function of PTKs in several tumor types.

EGFR, epidermal growth factor receptor, is one of transmembrane PTKs participating in tumor proliferation, metastasis, and antiapoptosis. Li et al. have investigated the mechanism involved in oridonin-induced A431 cell death. A431 carcinoma cells overexpressed EGFR. The authors detected that oridonin caused the inhibition of the total tyrosine kinase activities and decreased EGFR expression or EGFR phosphorylation (Li et al., 2007a); further experiments demonstrated that expression of Grb2, Ras, and Raf-1, which are the downstream effectors of EGFR or ERK, was downregulated by oridonin (Fig. 2). Moreover, the Ras inhibitor manumycin A, Raf-1 inhibitor GW5074, or ERK inhibitor PD98059 augmented oridonin-induced apoptosis (Li et al., 2007b). Cheng et al. also reported that oridonin caused L929 cell cytotoxicity mediated by PTKs. Western blot demonstrated that the expression of Ras, Raf, or phosphor-JNK was down regulated after oridonin treatment. Pretreatment with inhibitors of PTK, PKC, Ras, Raf, or JNK has significantly increased oridonin-induced cytotoxicity in L929 cells (Cheng et al., 2009b). These results suggested that oridonin induced tumor cell apoptosis through blocking EGFR or PTKs pathways (Fig. 2). Whether oridonin as an inhibitor of PTKs can attack cancer at the root still remains to be investigated.

5 Concluding remarks

Traditional Chinese medicines are considered as a rich source in new drug discovery as a consequence of experience collected over thousands of years in Asia. It is therefore right for us to revisit and explore the possibility of learning from Traditional Chinese medicines. They may offer novel or exciting additional treatment methods for cancer and other complicated diseases. It is now a widely attractive area in the world. Oridonin, as a precious Chinese herb, has been discovered more than 30 years. However, the clinical use is unavailable, and the question of which tumor cells are most sensitive to oridonin still remains unclear. Furthermore, the endeavor to modify the structure of oridonin in order to improve its solubility and activity is ongoing. Meanwhile, exploration on the interaction of oridonin with other chemotherapeutics in cancer therapy is also promising (Ran et al., 2007). The results of ongoing investigations will undoubtedly reveal the magnitude of the potential role of oridonin in cancer therapy.

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