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Review Article

Triptolide: Novel Anticancer Agent for Chemoresistant Cancer Cells that are Caspase-3 Deficient

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Abstract

Cancer is a major cause of death worldwide and there are over 100 different types of cancers. The current treatment strategies for cancer patients such as surgery, chemotherapy and radiation or the combination of radiotherapy and chemotherapy may have successfully increased five-year survival rates. However, the long-term survival rates remain poor due to cancer relapse, tumor resistance and metastasis. Treatments such as chemotherapy and radiation are known to have untoward side effects on normal cells. Therefore, it is imperative to develop safer and noninvasive treatments. The use of natural products in the fight against cancer is one possible way of slowing tumor growth and may allow us to design more effective therapies. In this review, we examine the central role played by the key apoptotic executioner protease, caspase-3 and propose molecular mechanisms by which cancer cells can evade anticancer treatments by mutating this protein. Triptolide, a Chinese herb, has been used for over 200 years to treat anti-inflammatory and autoimmune disorders. A considerable body of data indicates that triptolide has potent anticancer properties. We provide supporting evidence demonstrating that caspase-3 independent cell, lysosomal-mediated death pathways induced by triptolide, a Chinese herb, may provide effective novel antitumor treatment modalities.

Keywords: Caspase-3; Chemoresistance; Triptolide; Apoptosis; Lysosomes

Abbreviations

LMP: Lysosomal Membrane Permeabilization

Introduction

Cancer is a global disease that results in a considerable health care burden. While great strides have been made in anticancer treatment modalities, there are still a significant number of treatment-resistant cancers that ultimately lead to metastatic disease. Therapies such as radiation and chemotherapy are known to have serious side effects; therefore it is imperative to develop safer treatment alternatives. The key executioner protease, caspase-3, plays a pivotal role in regulating apoptotic pathways and a considerable body of literature indicates that mutations in this protein confer a survival, chemoresistance phenotype in tumor cells. In this paper, we provide supporting data for caspase-3's effect on survival in cancer cells and propose a novel mechanism to treat resistant cancer cells using a natural product.

Triptolide

Triptolide is an extract from the Chinese herb *Tripterygium wilfordii Hook F.* Long used in traditional Chinese medicine, the herb is purported to have immunosuppressive and anti-inflammatory properties and triptolide has been identified as a major chemical component governing these properties [1, 2]. Triptolide is a diterpenoid triepoxide. It is well documented that triptolide has a broad spectrum ability to inhibit proliferation and induce apoptosis of various cancer cell lines *in vitro* and prevent tumor growth and metastases *in vivo* [3- 8]. Triptolide shows anticancer activity in cells derived from both hematological malignancies and solid tumors, such as HL-60, T cell lymphoma [9], U937, OCI-AML3 [10], Kasumi-1 and SKNO-1 cells [11], human hepatocelluar carcinoma SMMC-7721 cells and cell lines of multiple myeloma, breast, gastric, prostate, lung, oral, colon, pancreatic and cervical cancers [3, 6, 12-14], cholangiocarcinoma [15] and neuroblastoma [16, 17]. The *in vivo* experiments have also demonstrated triptolide's therapeutic efficacy in several model systems including cholangiocarcinoma in a hamster model [18] and xenografts of human melanoma, breast cancer, bladder cancer, gastric carcinoma [17], pancreatic cancer [18] and neuroblastoma in nude mice [8].

Since triptolide has epoxide moieties, it is conceivable that this compound could bind to a certain cellular protein via formation of covalent bond. In 1974, Kupchan *et al.* [19] suggested that the 14b hydroxyl along with the [9, 11] epoxide might be responsible for the observed antitumor activity. In 2007, McCallum *et al.* [20] discovered that triptolide could bind specifically and irreversibly through the epoxide moieties to a 90 kDa nuclear protein, which may be a transcriptional regulator or somehow involved in turnover of a critical transcriptional regulator, such that its covalent modification prevented a key step in transcription. Recently, Titov *et al.* [21] reported that triptolide covalently bound to a human 90 kD protein, XPB (also known as ERCC3) which is a subunit of the transcription factor TFIIH, and inhibited its DNA-dependent ATPase activity, which led to the inhibition of RNA polymerase II–mediated transcription and likely nucleotide excision repair. The identification of XPB as the target of triptolide accounts for the majority of the known biological activities of triptolide. In human gastric and prostatic epithelial cells [22, 23] and HL-60 leukemia cells [24], triptolide-caused proliferation inhibition and apoptosis induction may be primarily mediated by its modulation of p53, a nuclear phosphor protein which acts as a tumor

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Table 1: Targets of triptolide for its antitumor effects.

Target gene	Tumor/Cell Line	Reference(s)
Caspase 3, 8, and 9	Multiple myeloma cells	[39]
XIAP	Leukemic cell lines, acute myeloid leukemia	[36]
bcr-abl	K562 cells	[31]
Bax, Bcl-2	Glioma cells, HL-60	[12, 40]
p53, p21(waf1/cip1), bax	Gastric cancer cells	[12]
NFκB	Human anaplastic thyroid carcinoma cells	[4]
MKP-1, ERK-1/2, JNK-1/2, p38 MAPK	NSCLC, hippocampal cells	[41, 42]
PI3K	Human fibrosarcoma	[43]
HSP70, HSF1	Pancreatic cancer cells	[18, 44, 45]
5-LOX	Pancreatic cancer cells	[46]
ADAM10	Leukemic cell lines	[47]
RNA polymerase	Human non-small cell lung cancer cell line	[48]
Jak2, Mcl-1	Human myeloproliferative disorder cells	[49]
Histone methyltransferase	Myeloma	[50]

suppressor. Nuclear factor κB (NF-κB) is a transcription factor that can promote cell survival, stimulate growth and reduce susceptibility to apoptosis via up regulation of various targeted proteins [25-30]. However, other reports suggest that triptolide inhibits the DNA binding ability of NF-κB or cytokine-stimulated NF-κB activity [31, 32]. In multiple myeloma cells, triptolide decreases histone H3K9 and H3K27 methylation via the down-regulation of histone methyltransferases SUV39H1 and EZH2, respectively and reduces the expression of HDAC8, leading to increase of the histone H3 and H4 acetylation [33]. Triptolide also inhibits the activity of RNA polymerase, resulting in the general transcription inhibition [34].

In a cDNA array analysis, Zhao *et al.* (33) demonstrated that triptolide inhibited the expression of genes involved in cell cycle progression and cell survival, such as cyclins D1, B1 and A1, Cdc-25; Bcl-X and c-Jun. Triptolide reduced the expression of apoptosis antagonists XIAP, Bcl-2 and Mcl-1 [35]. Triptolide induced caspase-dependent apoptosis of leukemia and cervical cancer cells [6, 15, 36] and triggered caspase-independent autophagic cell death in pancreatic cancer cells [15]. Leuenroth *et al.* [37] identified calcium (Ca2+) channel polycystin-2 (PC2) as a putative direct target of triptolide in a mouse model of polycystic kidney disease (PKD). Triptolide may perturb multiple targets and interfere with multiple signaling pathways and potentiate activities of other antitumor agents such as Apo2/TRAIL, tumor necrosis factor α and other chemotherapeutic agents.

The known targets of triptolide for promoting its antitumor effects are shown in Table 1, reviewed in Liu [38]. The exact mechanisms by which triptolide regulates these molecular targets have yet to be fully elucidated. A better understanding of these processes should lay a foundation for the development of triptolide in chemotherapeutic treatments.

Triptolide and Chemoresistance

Ovarian cancer is currently the leading cause of mortality among gynecological malignant tumors, with epithelial ovarian cancer (EOC) being the most common, accounting for >85% of all cases [51]. The majority of ovarian cancers are diagnosed at an advanced stage, mostly due to a lack of effective screening strategies and difficulties in obtaining a diagnosis [52]. Despite the progress that has been made in prolonging remission by the combination of surgical resection and platinum-based chemotherapy, the overall survival of patients with advanced disease is rarely >30%. The poor prognosis in the treatment of ovarian cancer is mainly attributed to chemoresistance [53]. Tumor cells may dampen the cytotoxic effects of anticancer drugs via several mechanisms, including increased drug efflux, drug inactivation, alteration in the drug target and increased DNA repair [54, 55]. As a result, efforts have been directed towards the development of novel agents in an attempt to ameliorate the lethality of this malignancy. Recent studies on the chemoresistance of ovarian cancer have indicated that a decreased susceptibility of the cancer to apoptosis is strongly associated with drug resistance. Thus, novel strategies involving less toxic agents that are able to either enhance the antitumor effects of cisplatin or overcome chemoresistance to the drug are highly desirable.

Constitutively activated nuclear factor (NF)-κB may be critical in the development of drug resistance in ovarian cancer cells [56]. NF-κB is known to suppress apoptosis through the induction of anti-apoptotic proteins, including Bcl-2 and X-linked inhibitor of apoptosis protein (XIAP), leading to a resistance to cancer therapy and a poor prognosis [57-59]. Intriguingly, numerous anticancer drugs, including the DNA-damaging agent cisplatin are able to simultaneously stimulate NF-κB activation, as they trigger the cell death process in neoplasm cells [57, 58, 60]. Therefore, the inhibition of NF-κB may be useful in increasing the sensitivity of cells to chemotherapy-dependent apoptosis and reversing drug resistance in ovarian cancer.

Although first-line platinum-based chemotherapy following an apparent curative resection has improved survival length, severe adverse side-effects and drug resistance have emerged as the major impediments to effective ovarian cancer therapy [61]. The pleiotropic anticancer activities of triptolide have attracted a great deal of research interest. Notably, triptolide has also been identified to be effective in

the induction of apoptosis in drug-resistant multiple myeloma [62] and cervical cancer [63] cells. A recent study investigated whether triptolide treatment was able to exhibit a cytotoxic effect on platinum-resistant ovarian cancer cells [64]. The results demonstrated that triptolide reduced the growth of the platinum-resistant ovarian cancer cells by inducing apoptosis, evidenced by the externalization of membrane-bound phosphatidylserine and the cleavage of caspase 3 [64]. The results also showed that the addition of a low concentration of triptolide greatly increased the cytotoxicity of cisplatin against the SKOV3^{PT} cells, which is consistent with previous studies [62-64]. Triptolide circumvents drug resistance and enhances the antitumor effect of 5-fluorouracil [63, 65]. The understanding of the molecular mechanisms by which triptolide inhibits cancer cell growth will shed new insights for cancer therapy.

The HER2 gene, also known as *neu* (in mouse) or *erbB2*, encodes a 185-kDa transmembrane receptor tyrosine kinase and is a member of the epidermal growth factor receptor family [65]. Over expression of HER2 is found in approximately 30% of human breast cancers and in many other cancer types [66]. HER2 phosphorylates downstream substrates and activates a variety of signaling cascades, including phosphatidylinositol-3 kinase (PI3K), serine/threonine-specific protein kinase (Akt) and Ras/mitogen-activated protein kinase (MAPK) pathways. These regulatory signaling cascades promote cell survival, tumor growth, and metastasis [67, 68]. Triptolide reduces PI3K activity, which is a downstream of HER2 signaling pathway. More importantly, triptolide blocks the activity of NF-κB, which activates HER2 gene transcription [69, 70]. Thus, it is hypothesized that triptolide-induced tumor regression is attributed to its repression on HER2 activity.

The activation of anti-apoptotic effectors, such as NF-κB, can cause the resistance of cancer cells to cytotoxic therapy [71-73]. Therefore, compounds that inhibit NF-κB stimulation could overcome chemotherapy resistance. One phase I and pharmacological study of F60008, a semi-synthetic derivate of triptolide was performed in patients with advanced solid tumors [74]. In 2009, Kitzen et al. [74] enrolled 20 patients in the above study who received a total of 35 cycles. For one cycle, F60008 was given intravenously as a weekly infusion for 2 weeks every 3 weeks. The most frequent hematological side effect was mild grade 1-2 anemia. Non-hematological toxicities included constipation, fatigue, vomiting, diarrhea and nausea, which were all grades 1-2. There are few clinical trials of triptolide in solid tumors, and further clinical studies and trails are warranted to investigate its clinical applications.

Triptolide Enhances the Effects of Chemotherapy

Triptolide sensitizes several cancer cell lines to chemotherapy *in vivo* and *in vitro*. Triptolide highlights the synergistic anti-tumor effect in cells in combination with many cytotoxic drugs. The synergistic anti-tumor effect of triptolide and cisplatin or 5-FU down-regulates cancer cell viability in liver cancer cell lines *in vitro* and in nude mice and induces higher levels of apoptosis compared to single treatments [75]. Furthermore, cells treated with triptolide plus cisplatin or 5-FU exhibit a marked production of intracellular ROS and caspase-3 activity, down-regulate Bcl-2 expression and up-regulate Bax expression [76]. Previous studies showed that combined-agent-treated groups almost stopped growing and tumor weights *in vivo* were much lighter than with single-drug treatment [77]. Triptolide in combination with sorafenib is superior to single drug treatment in inducing apoptosis and down-regulating viability via decreasing NF-κB activity [78]. Tumor growth inhibition rates in combined-agent-treated groups in a nude mouse model are increased compared to single drug treatment [78]. Triptolide combined with oxaliplatin (OXA) effectively inhibits proliferation in the colon cancer cell line SW480 and induces cell apoptosis [79]. The mechanism partly involves the inhibition the expression of target genes in the cell cycle and nuclear translocation of β-catenin [79]. Moreover, combined-agent-treated groups in a nude mouse model significantly suppressed tumor growth [79]. Triptolide in combination with temozolomide significantly up-regulates the percentage of apoptotic cells in glioma-initiating cells via up-regulation of NF-κB transcriptional activity and increased expression of downstream genes [80]. Triptolide was demonstrated to synergize with CPT-11, a topoisomerase inhibitor [81], with doxorubicin (by blocking p-21–mediated growth arrest and accumulating cells in G2-M [32], and with Mylotarg [36] on leukemic cell lines. Triptolide reduced the expression of cell cycle and survival regulators in tumors, such as cyclins D1, B1, and A1, cdc-25, bcl-x, and c-jun [33]. Triptolide enhanced anthracycline toxicity *in vitro* and it cooperated with AraC to induce apoptosis on THP1 leukemic cells and primary AML blast cells [82]. Triptolide synergistically enhanced the antitumor effect of cisplatin in cisplatin-resistant human bladder cancer cells [83]. Minnelide a water-soluble pro-drug of triptolide, decreased cell viability of both platinum sensitive and resistant epithelial ovarian cancer cells *in vitro* [84].

The combination of triptolide with non-cytotoxic drugs also has synergistic effects in numerous types of cancer cells. The main mechanism of the triptolide-enhancing apoptosis effect of dexamethasone is that triptolide affects the PI3k/Akt/NF-kB pathway, mitogen-activated protein kinase signaling pathway and Bcl-2 expression [85]. The synergistic antitumor effect of triptolide and iron deficiency anemia in acute myelocytic leukemia cells is due to induction of reactive oxygen species and the inhibition of the Nrf2 and hypoxia inducible factor-1α pathways [86]. The synergistic antitumor effect of triptolide and aspirin in cervical cancer involves a reduction in cyclin E expression, up-regulation of Bax and P21 expression, the inhibition of cell proliferation and induction of cell apoptosis [87].

Caspase-3

When activated, caspase-3 can cleave the vast majority of polypeptides that undergo proteolysis in apoptotic cells [88, 89]. The activated caspase-3 acts as the critical effector in both intrinsic and extra cellular apoptotic pathways by triggering a series of downstream apoptotic cascade [90-92]. Caspase-3 is the ultimate executioner caspase that is essential for the nuclear changes associated with apoptosis, including chromatin condensation [93]. The pro-apoptotic enzyme caspase-3 is activated at a point of convergence for the intrinsic and extrinsic apoptosis induction pathways [94], so its activity should give a reliable measure of ongoing levels of apoptosis in tumor samples. Thus, apoptotic pathways depend upon activation of effector caspases, in particular caspase-3, for the final execution of apoptosis. Therefore, it might be expected that high levels of active caspase3 reflect proper functioning of one or both identified

apoptosis pathways, resulting in relatively chemotherapy-sensitive neoplastic cells and a favorable response to chemotherapy [94].

Loss of caspase-3 expression may represent an important mechanism of cell survival and chemoresistance by various cancer cells. The ability of cells to evade apoptosis is one of the essential hallmarks of cancer cells. This feature allows cancer cells to become non-responsive to anticancer therapies [95]. Normal breast parenchyma and primary breast tumor samples, obtained from patients undergoing breast surgery, lacked caspase-3 expression in the majority of breast cancer patients [96]. Low caspase-3 activity was shown to correlate with poor response to chemotherapy and clinical outcome in colon cancer patients [97]. Likewise, a significant percentage of neuroblastomas lack caspase-3 mRNA and protein [98]. Another study reported that in nasopharyngeal carcinoma patients treated with curative intent, absence of active caspase-3-positive neoplastic cells predicted rapid fatal outcome and was associated with poor response to radiotherapy and high T and N stage at time of presentation [99].

Resistance to apoptosis is a key characteristic of neoplastic cells, and response to chemotherapy is thought to be related to the capacity to restore the apoptotic program in a given tumor cell [100, 101]. Reports demonstrated that the level of caspase-3 expression decreased as gastro carcinogenesis progressed and became undetectable in the majority of malignant samples examined [102, 103]. It is therefore implicated that the down-regulated caspase-3 expression may be one of the important intrinsic factors that confer on gastric cancer and other cancer cells, an apoptosis resistant property. Caspase-3 activity is a final effector of the apoptotic program. Being a late step in the apoptotic cascade, it is likely that its variations reflect the accumulated effect of small variations in a number of genes harboring distinct functions such as DNA damage sensors, cell cycle checkpoints, DNA repair and the apoptotic cascade itself, among others [97].

Lysosomal-Mediated Cell Death

Lysosomes, discovered over fifty years ago, are the major cell digestive organelles [104, 105]. They contain a number of hydrolases that are capable of breaking down nucleic acids, proteins, carbohydrates and lipids. Today, it is clear that lysosomes and lysosomal proteases can be involved in apoptosis. Among lysosomal proteases, the role of cathepsins in cancer progression is especially well documented [105-107]. Following their release into the cytosol, they cleave Bid and degrade anti apoptotic Bcl-2 proteins, thereby triggering the mitochondrial pathway of apoptosis, with lysosomal membrane permeabilization (LMP) being the critical step in this pathway [107, 108]. How LMP is modulated by the complex Bcl-2 protein network, however, is still unclear. Various insults, including oxidative stress and DNA damage, may lead to the limited release of cathepsins that culminate in the induction of apoptosis [109-112]. Hsp70 has been implicated in playing an important role for inhibiting LMP to promote the survival of stressed cells [113]. However, blocking cathepsins by small molecule inhibitors has been shown to significantly delay cancer progression in a number of mouse cancer models as well as to sensitize tumor cells to other chemotherapeutic agents [114]. Lysosomal-mediated apoptosis is still largely under investigation and not fully understood.

LMP and Cancer

Immortalization and transformation have been shown to increase the susceptibility of mouse embryonic fibroblasts to lysosome-dependent cell death induced by anticancer agents [115]. This effect is mediated through cathepsin B over expression and increased cathepsin-dependent cell death. Lysosomal maturation, size and activity are tightly regulated by PI3K [116], an enzyme that is activated in many cancers. Inhibition of PI3K induces the translocation of cathepsin B to the cytosol and may sensitize endothelial cells to TNF-α-induced apoptosis [117, 118]. Hsp70 may promote tumorigenesis by stabilizing lysosomal membranes and by protecting cells against lysosomal membrane permeabilization (LMP) induced by hypoxia, non-inflammatory cytokines, oxidative stress, irradiation or anticancer drugs [119]. The reasons for the increased susceptibility of cancer cell lysosomes to LMP are not understood. As one possibility, relatively large lysosomes, as found in cancer cells [120], may be more fragile than normal-sized lysosomes [121]. Moreover, cancer cells exhibit higher metabolic rates and an increased turnover of iron-containing proteins, leading to the lysosomal accumulation of iron, with consequent iron-mediated sensitization to ROS-induced LMP [122]. Cancer cells often produce elevated ROS levels and the associated higher rate of spontaneous cathepsin release from lysosomes may facilitate cell death induction [123]. On theoretical grounds, all these factors render lysosomes from cancer cells particularly susceptible to the therapeutic induction of LMP. However, this speculation awaits experimental verification.

Triptolide Induces Lysosomal-Mediated Cell Death in Caspase-3 Deficient Breast Cancer Cells

Among the various in vitro cell line models available for breast cancer, the MCF-7 cell line presents distinctive properties that may help shed new light on the mechanism of action of triptolide. In particular, MCF-7 is an estrogen receptor-positive cell line that lacks caspase-3 and beclin-1 [124, 125]. Thus, it represents a cell model with compromised apoptotic machinery and low autophagic activity that might influence cellular response to anticancer drug treatment. We demonstrated that MCF-7 cells treated with triptolide undergo an atypical, apoptotic death that is dependent on LMP because they lack caspase-3 [126]. This cell death was accompanied by chromatin condensation, over expression of cleaved caspase-7 and cleaved caspase-9 proteins and up-regulation of cathepsin B in the cytosolic fractions of experimental cells [126]. To our knowledge, this was the first report in the literature of triptolide-induced lysosomal membrane permeability as an anticancer treatment.

Conclusions

Caspase-3 is a key executioner protein in both the intrinsic and extrinsic apoptotic pathways. Several studies have confirmed that this protein is a desirable target for cancer cells to mutate because the resulting phenotype promotes cell survival, and thus chemoresistance. Further studies are warranted to decipher the mechanisms by which triptolide exerts its antitumor effects via a lysosomal-mediated mechanism and a caspase-3 independent manner. We hope that triptolide will provide more benefit in the treatment of malignant tumors in the future as a prospective anticancer drug candidate.

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