Advances in the Treatment of Ovarian Cancer — A Potential Role of Anti-inflammatory Phytochemicals.


Abstract:

Epithelial ovarian cancer (EOC) is the leading cause of death among gynecological malignancies worldwide. The five-year survival rates for stage IIIC and IV patients are 29% and 13%, respectively. Type-2 EOC cells have been found to be associated with this late stage disease. In contrast, women diagnosed in stage 1 disease, which mostly exhibits type-1 cells, have a high 5-year survival rate (90%). Recent progress in understanding the pathogenesis of EOC and inflammatory signaling pathways revealed that type-2 cells frequently express a deleted or mutated TP53 (60-80%), or aberrations in BRCA1 (30-60%) and BRCA2 (15-30%). The deletion or mutation of TP53 results in a dysregulated inflammatory signal network and contributes to an immunosuppressive microenvironment. Thus, to be effective, EOC therapy may be necessary to cover two areas: (1) direct cytotoxic killing of cancer cells; (2) reversion of the immunosuppressive microenvironment. Presently the first strategy is advancing rapidly while the second strategy remains behind. Isolation and characterization of cancer stem cells (CSCs) have helped to confirm the dynamic role of the tumor microenvironment in promoting cancer metastasis and recurrence. Based on widely published in vitro and mouse-model data, some anti-inflammatory phytochemicals appear to exhibit activity in modulating the tumor microenvironment. Specifically, apiegenin, baicalein, curcumin, EGCG, genistein, luteolin, oridonin, quercetin, and wogonin repress NF-kappaB (NF-κB, a proinflammatory transcription factor) and inhibit proinflammatory cytokines such as TNF-α and IL-6. Additionally, most of these phytochemicals have been shown to stabilize p53 protein, sensitize TRAIL (TNF receptor apoptosis-inducing ligand) induced apoptosis, and prevent or delay chemotherapy-resistance. Recent studies further indicate that apigenin, genistein, kaempferol, luteolin, and quercetin potently inhibit VEGF production and suppress ovarian cancer cell metastasis in vitro. Lastly, oridonin and wogonin were suggested to suppress ovarian CSCs as is reflected by down-regulation of the surface marker EpCAM. Unlike NSAIDS (non-steroid anti-inflammatory drugs), well documented clinical data for phyto-active compounds are lacking. In order to evaluate objectively the potential benefit of these compounds in the treatment of ovarian cancer, strategically designed, large scale studies are warranted.

Epithelial Ovarian Cancer Pathology and Inflammation Associated Molecular Targets

Although the incidence for epithelial ovarian cancer (EOC) is low compared to other malignancies in the U.S. (22,000 new cases in 2011) and U.K. (7,000 new cases in 2006), the mortality is ranked the highest among gynecological cancer (Jemal et al.,
The five year survival rates for stage IIIC and IV patients are about 29% and 13%, respectively. Recent studies on EOC pathology introduce two different molecular entities, type-1 and type-2 EOC cells. The type-2 cells predominately express a mutated or null cancer suppressive gene TP53 (60-80%), or aberrations in BRCA1 (30-50%) and BRCA2 (15-30%) (Kurman and Shih, 2008; Bast et al., 2009; Muggia, 2009). The majority of the detected EOC cells belong to the aggressive type-2 at diagnosis, which may be the culprit (Alvero et al., 2011).

In contrast, the slow growing type-1 cells (25-30% at diagnosis) have a high “cure” rate of 90% by the current standard therapy which includes cytoreductive surgery and combined chemotherapeutic agents, mainly, carboplatin and paclitaxel (Jemal et al., 2009).

Unlike other solid tumors, EOC cells metastasize throughout the peritoneal cavity without an anatomical barrier. Small clusters of cancer cells are shed by the ovary and implanted on the peritoneal surface by forming numerous nodules. Moreover, the accumulated ascites in the cavity often serve as an immunosuppressive microenvironment which further exacerbates tumor progression. The volume of ascitic fluid is positively correlated with the expression of vascular endothelial growth factor (VEGF). A clinical study with monoclonal antibody, bevacizumab, bound to VEGF-A, has substantially decreased ascites accumulation (Ellis and Hicklin, 2008). Recent adjuvant studies with bevacizumab showed a definite improvement in progression-free survival and for some patients also an overall survival benefit (Kristensen et al., 2011; Aghajanian et al., 2011).

It has been shown that ascitic fluid induces Akt activation via ανβ3 integrin and prevents cancer cell apoptosis induced by TRAIL (tumor necrosis factor receptor apoptosis-inducing ligand) (Kang et al., 2004; Lane et al., 2010). TRAIL is an endogenous protein and a member of tumor necrosis factor (TNF) family, which induces apoptosis in a wide variety of transformed and cancer cells but has little or no effect on normal cells. Therefore, TRAIL is considered as a selective, apoptosis-inducing cytokine in cancer treatment (Rushworth and Micheau, 2009). Ascites prevent EOC from apoptosis evoked by TRAIL.

The dynamic cytokine changes in ascites are also demonstrated in a different study (Giuntoli et al., 2009). The investigation based on 22 paired ascites and plasma samples from advanced EOC patients demonstrated a significant change in cytokines and inflammatory proteins. Up-regulation of cytokines together with related proteins (IL-6, IL-8, IL-10, IL-15, IP-10, MCP-1, MIP-1β, and VEGF) and down-regulation of IL-2, IL-5, IL-7, IL-17, PDGF-BB, and RANTES were reported (p<0.05). This study indicates an increase in interleukin-6 (IL-6) level in ascites. An elevated IL-6 concentration in ascites appears to correlate with a shorter progression-free survival (Lane et al., 2011).
Apart from ascites, a high level of IL-6 in tumor tissues has also been found to be significantly associated with poor prognosis (Coward et al., 2011). Coward et al. conducted a preclinical study on 221 advanced EOC samples, and a phase 2 clinical study in 18 patients with cis-platinum resistant EOC using IL-6 bound monoclonal antibody (siltuximab). After patients were treated with siltuximab for six months, a significant reduction in the plasma levels of IL-6 regulated chemokines, CCL2, CXCL-12, and VEGF, was detected. The study suggested that IL-6 could potentially serve as a therapeutic target in human EOC.

In addition to IL-6, a number of other inflammation-related proteins have been identified. Akt (i.e., protein kinase B), LPA (lysophosphatidyl acid), and PKC (protein kinase C) (Bast et al., 2009) are over-expressed in more than 70% ovarian cancer. Interestingly, LPA is found to up-regulate IL-6, IL-8, and VEGF via Akt/NF-κB (NF-kappaB) pathway in EOC cell lines (Chou et al., 2005; Yu et al., 2008). PKC plays a key regulatory role in a wide range of cancer signal transduction pathways. Disruption of PKC regulation is implicated in the tumorigenesis and EOC drug-resistance (Mackay and Twelves, 2007). Taken together, the proteins mentioned above are frequently activated, which partially contributes to EOC associated inflammation.

Is There a Role for Non-steroidal Anti-inflammatory Drugs (NSAIDS) in EOC Prevention?

One of the signatures of chronic inflammation is the activation of the arachidonic acid metabolism pathway followed by the production of inflammatory biochemical mediators, including prostaglandins and thromboxane (Kuehl and Egan, 1980). Inhibition to the metabolism enzyme cyclooxygenase (COX) represses the production of prostaglandins such as PGE2. These types of inhibitors are termed NSAIDS. Epidemiological studies showed that there is a positive prevention of colon cancer by intake of NSAIDS or aspirin (Lanas and Ferrandez, 2009). Because of these findings, several large scale studies were carried out to investigate the benefit of NSAIDS in the prevention of EOC. However, the results are inconsistent among these studies.

The first meta-analysis of six case-control and four cohort studies, published between 1998 and 2004, was released in 2005 (Bonovas et al., 2005). The analysis concluded that there is no evidence of an association between aspirin use and ovarian cancer risk either assuming a random-effects model (RR=0.92, 95%, CI=0.80, 1.06), or a fixed-effects model (RR=0.93, 95%, CI=0.81, 1.06). Similarly, in two large prospective cohorts in 2009, the authors found no compelling evidence to support an association between regular use of aspirin, NSAIDs, or acetaminophen and ovarian cancer incidence (Pinheiro et al., 2009). The third study conducted in 2010 investigated associations between the use of NSAIDs and incidence of ovarian and endometrial cancers in a prospective cohort of about 20,000 women with ages from 58 to 76 years in 1992. Over 15 years, 311 endometrial and 167 ovarian cancers were identified. EOC patients who reported having no use of aspirin were compared with those who had used aspirin <2, 2 to 5 times, and ≥6 times per week for the relative risk of EOC
(Prizment et al., 2010). The authors concluded that they did not observe any association between non-aspirin NSAIDs use and ovarian cancer risk.

On the contrary, one study in 2008 reported a positive protective effect of NSAIDS on EOC risk (Wernli et al., 2008). In a population-based case-control study conducted in Wisconsin and Massachusetts, the authors examined the association between non-NSAID use and ovarian cancer by including any potential effect modifiers, parity and oral contraceptive use. The analysis included a total of 487 invasive ovarian cancer cases and 2,653 control women aged 20-74 years. After adjustment for age, state of residence and other variances, the authors found women who used NSAIDs but never used oral contraceptives had a lower risk of ovarian cancer [odds ratio (OR)=0.58, 95% CI=0.42-0.80]. However, women who had used both NSAIDS and oral contraceptives did not have the protective benefit of NSAIDS (OR=0.98, 95% CI=0.71-1.35) (p=0.03). Interestingly this study not only indicated the protective effects of NSAIDS in non-birth control pill users but also implied a possible interaction between oral contraceptive drugs and NSAIDS in women.

Further studies evaluating the effect of combining contraceptives and NSAIDS would provide additional insight into the potential interaction.

**Anti-inflammatory Phytochemicals**

Anti-inflammatory phytochemicals are natural compounds derived from fruits, vegetables, and medicinal plants, which exhibit inhibitory activity in arachidonic acid pathway (Chen, 2011). They have been widely investigated for anti-cancer activities due to their general low toxicity and availability. Results from these studies demonstrate the positive role of anti-inflammatory compounds in intervening EOC progression *in vitro* and in mouse models. Below we review some of these results.

1. **Modulation of inflammatory cytokines (TNF-α and IL-6)**

Cytokines and cancer seem inseparable. Cancer cells release cytokines and growth factors that recruit endothelial cells, fibroblasts, and infiltrating inflammatory cells to the site. As a result, the recruited satellite cells interact with cancer cells by secreting more cytokines and thus create a dynamic network dictating the nature of tumor microenvironment (Kulbe et al., 2007). Moreover, recent studies show that there are different cytokine profiles in type-1 and typ-2 EOC cells (Alvero et al., 2011).

Two most studied inflammatory cytokines that play an important role in EOC cells are: tumor necrosis factor (TNF-α) and IL-6. These cytokines have been shown to be involved in EOC growth and metastasis as demonstrated in various animal models and in human ovarian cancer biopsy tissues (Kulbe et al., 2005; 2007; Szotek et al., 2006; Coward et al., 2010; Wang et al., 2010). A small quantity (picogram) of TNF-α protein has been shown to be secreted by EOC tissues in the culture, which in turn induces IL-6 synthesis. IL-6 is associated with vascularization in high grade tumors
and promotes angiogenesis (Vaughan et al., 2011). Most significantly, IL-6 has been shown to be a potential therapeutic target for EOC (Coward et al., 2011).

TNF-α is one of the most potent activators of NF-κB in cell types possessing TNF receptors (Annunziata et al., 2010; Kruppa et al., 1992). Repression of TNF-α often leads to inhibition of NF-κB (a master switch for inflammation). This is shown in certain phytochemicals which suppress TNF-α and also exhibit inhibitory activity against NF-κB activation. For example, incubation of phytochemicals of apigenin, baicalein, curcumin, EGCG, genistein, luteolin, oridonin, quercetin, and wogonin with cancer cells results in a deactivation of NF-κB pathway either by preventing NF-κB nuclear transportation or by suppressing NF-κB protein activity (Habtemarian, 2000; Gulcubuk et al., 2006; Tang et al., 2006; Ahmed et al., 2008; Xu et al., 2009; Seo et al., 2010). Since NF-κB is a central proinflammatory transcription factor, suppressors of NF-κB often not only exhibit anti-inflammatory activities but also cross-inhibit other upstream (TNF-α and IL-6) or downstream (arachidonic acid pathway) signaling proteins (Chen, 2011).

These phyto-compounds are the secondary metabolites in plants including vegetables, fruits, and medicinal plants. For examples, parsley, thyme, and celery heart contain high concentration of apigenin and luteolin which activate monoamine transporters (Holden et al., 2002; Zhao et al., 2010). As a popular antioxidant supplement, quercetin is rich in apple and onion (Holden et al., 2002). EGCG (epigallocatechin gallate) as a polyphenol and a flavonol in green tea is a potent topoisomerase inhibitor similar to some chemotherapeutic drugs such as etoposide and doxorubicin (Suzuki et al., 2001). As a known phytoestrogen and tyrosine kinase inhibitor, genestein is abundant in soybean (Markovitis et al., 1989). Baicalein and wogonin are the principal active compounds in the Chinese anti-microbial plant Scutellaria baicalensis (Chen et al., 2008; 2001). Curcumin is a broad spectrum anti-inflammatory compound from turmeric (ginger family) used in Indian Ayurvedic medicine (Aggarwal et al., 2007). As a terpenoid, oridonin is a key active compound with low toxicity in Chinese anti-cancer plant Rabdosia rubescens (Chen et al., 2005).

Among these compounds, baicalein, curcumin, oridonin, and wogonin have also been found to suppress the proinflammatory function of IL-6 either at gene transcription or at protein level (Piao et al., 2004; Xu et al., 2009; Seo et al., 2010). The example of curcumin treatment in EOC cells, which results in secretions of IL-6 and IL-8, STAT3 phosphorylation via LPA, and finally the suppression of ovarian cancer cell motility, demonstrate a definitive effect of this type of compounds in modulating cytokines in cancer cells.

2. Attenuation of therapeutic-drug resistance

Chemotherapy-resistance remains one of the key challenges in treating advanced EOC. Cancer cells acquired drug-resistance via several mechanisms. Among them, mutation or deletion of the transcription factor TP53 and loss of TRAIL-induced apoptosis in cancer cells are frequently observed.
A. Stabilization of the tumor suppressor protein p53

The tumor suppressor protein p53 is a transcription factor known to control the cell cycle and halt the cell from division when its DNA is damaged. One of the key tasks of p53 protein is to activate DNA repair and initiate apoptosis (commit suicide) if the DNA repair fails (Gudkov et al., 2011).

There is substantial evidence indicating the antagonist relationship between the two master switches, NF-κB and p53, in cancer (Ventura et al., 2007; Dey et al., 2008; Ak and Levine, 2010; Gudkov et al., 2011). A variety of experimental methods have been used to demonstrate that constitutive activation of NF-κB reduces the tumor suppressor activity of p53, thereby creating permissive conditions for dominant ontogeny-mediated transformation. The loss of functional p53 further augments NF-κB activated-inflammation without proper regulation. Therefore, stabilization of wild-type p53 is an important step to prevent EOC from progression to drug-resistance.

Several mechanisms are known to involve in the stabilization of p53: inhibition of p53 degradation via proteasome-ubiquitination system or hdm2 pathway; phosphorylation of p53 protein; or repression of the p53 negative regulator MDM2 (Issaeva et al., 2004; Townsend et al., 2004; Shi et al., 2007). Agents that could modulate any of the above processes would have the potential to stabilize p53.

The expression of p53 protein is usually low, blockage of its degradation can result in an accumulation of the protein level as detected by western blot analysis. Many in vitro studies show that baicalein, curcumin, EGCG, genistein, luteolin, quercetin, oridonin, resveratrol, and wogonin upregulated wild-type p53 protein in several cancer cell lines including ovarian (Chen et al., 2001; 2011; Shi et al., 2007; Seelinger et al., 2008; Tanigawa et al., 2008). The stabilization of p53 often accompanies a G1 phase cell cycle arrest.

B. Re-sensitization of TRAIL-induced apoptosis

Since TRAIL is considered as a cancer-selective cytokine in induction of cancer cell apoptosis, loss of TRAIL-induced apoptosis has partially contributed to the therapeutic drug resistance. Re-sensitization of TRAIL activity can thus enhance the cytotoxic killing of chemotherapeutic drugs and reduce drug-resistance.

Various studies show that baicalein, curcumin, luteolin, procyanidins, quercetin, resveratrol, sulphoraphane, and wogonin rendered TRAIL-resistance cancer cells to apoptosis (Jung et al., 2005; Maldonado-Celis et al., 2009; Mantovani et al., 2008; Lin et al., 2008; Lee et al., 2009; Rushworth and Micheau, 2009). Specifically, hispidulin was found to potentiate the TRAIL-induced apoptosis in human EOC cells and converted TRAIL-resistant cells to TRAIL-sensitive cells. The sensitization is controlled through the adenosine monophosphate (AMP)-activated protein kinase (AMPK), a central energy-sensing enzyme of the cell (Yang et al., 2010).

C. Other contributing factors to drug-resistance
These factors include activated signal pathway of Akt/mTOR (Abdollahi et al., 2010; Cai et al., 2010; Weir et al., 2007; Gilbert and Hemann, 2011). It is known that NF-κB activation is tightly associated with the Akt/mTOR pathway, which plays a major role in the induction of anti-apoptotic signals and is linked to the development of chemoresistance (Karin et al., 2005; Murtaza et al., 2009). In separate studies, the NF-κB upstream protein Toll-like receptor 4 (TLR-4) has also been found to be up-regulated in 41 advanced ovarian cancer clinical samples (Kelly et al., 2006; Wang et al., 2009; Chen et al., 2008). High expression of TLR4 is also reported to be associated with a poor prognosis and resistance to paclitaxel.

Several studies show that phytochemicals, such as curcumin, EGCG, genistein, quercetin, and reseveratrol, can reverse chemo-resistance to cisplatin and/or paclitaxel by modulating NF-κB or/and MDR (multiple-drug-resistance)-transporter proteins both in vitro and in vivo (Surh, 2003; Aggarwal et al., 2004; Weir et al., 2007). Other phyto-active compounds, such as silymarin, emodin, pipernine, oleandrin, ursolic acid, and betulinic acid, were demonstrated to sensitize tumor cells to chemotherapeutic agents (Garg et al., 2005). Interestingly, kaempferol has recently been reported to enhance the effect of cis-platinum by down-regulation of c-Myc in EOC cell line OVCAR-3 (Luo et al., 2010).

In a recent study, oridonin (a diterpene) and wogonin were shown to confer apoptosis and suppress chemo-resistant EOC cells — PTX-10 (paclitaxel-resistance cell line) and carboplatin/paclitaxel-resistant ascitic EOC cells, isolated from ascitic fluid of recurrent patients (Chen et al., 2011).

3. Inhibition of angiogenesis and metastasis via the vascular endothelial growth factor

VEGF is an important signaling protein involved in both vasculogenesis and angiogenesis (the growth of blood vessels from pre-existing vasculature). Activated VEGF signal transduction appears to be one of the primary means by which malignant ovarian cells grow and disseminate. In type 2 aggressive EOC cells, high density of vasculogenesis and expression of VEGF are observed (Kurman et al., 2008; Bast et al., 2009).

Several VEGF-targeted agents, administered either as single agents or in combination with chemotherapy, have been shown to benefit patients with advanced-stage malignancies as well as in the adjuvant setting (Ellis and Hicklin, 2008; Kristensen et al., 2011; Aghajanian et al., 2011).

The known VEGF-targeted agents include the monoclonal antibody bevacizumab and the small-molecule inhibitor aflibercept (Karihtala et al., 2010; Moroney et al., 2009).

The inhibitory activity has also been found in phytochemicals (Fang et al., 2005; Park et al., 2007; Luo et al., 2008). In the study by Luo et al., 12 different flavonoids were determined for the anti-cancer activity in ovarian cancer cell line OVCAR-3. The
result showed that 5 out of the 12 flavonoids, apigenin, luteolin, quercetin, genistein, and kaempferol, potently inhibited ovarian cancer cell growth and VEGF production in a dose-dependent manner. Interestingly, the inhibitory activity of these compounds on VEGF protein expression is shown to be more effective than cis-platinum.

In separate studies, wogonin, EGCG, and kaempferol were also found to inhibit VEGF protein expression in various cancer cells (Lin et al., 2006; Luo et al., 2010; Zhu et al., 2011). For example, treatment of EGCG in gastric cancer cells leads to an inhibition in VEGF expression and angiogenesis via the suppression of Stat3 activity.

4. Repression of cancer stem cells (CSCs) markers: CD133, EpCAM, and ALDH

Ovarian CSCs are small side-population (SP) cancer cells isolated from solid tumors or ascites of EOC patients. They exhibit the capacity to initiate and renew cancer cells. Although the phenotype of the ovarian CSCs has not been completely defined, recent studies have characterized several cell markers from isolated SP cells. The identified cell markers include: CD44, CD117, CD133, MYD88, aldehyde dehydrogenase (ALDH), and multiple drug resistance proteins of ABCG2 and BCRP1 (Sztok et al., 2006; Hu et al., 2010; Silva et al., 2011; Alvero et al., 2011). Cancer cells which express any of the above markers are found to link with a high incidence of chemoresistance and cancer recurrence (Steffensen et al., 2011; Sztok et al., 2006; Hu et al., 2010; Silva et al., 2011). CD133 is also a stem cell marker for other cancer cell types such as prostate (Miki et al., 2007). In a xenograft study with prostate cancer cell line DU-145, measurement on the global gene profile revealed that treatment of nude mice with a combined phytochemicals of baicalein, isoliquiritigen, oridonin, and wogonin results in a down-regulation of CD133 gene expression accompanied by a 75% reduction in tumor volume (Chen et al., 2011a). In ovarian cancer cells, wogonin or oridonin as single agent or in combination is able to induce apoptosis in paclitaxel-resistant EOC cell line and in EOC cells isolated from ascites of patients who were resistant to carboplatin and paclitaxel treatments (Chen et al., 2011). These isolated chemo-resistant ascitic EOC cells express high level of EpCAM (epithelial cell adhesion antigen) which is suggested to be associated with CSC-like EOC cells.

In a study with resveratrol, it was shown that resveratrol inhibits the self-renewal capacity of pancreatic CSCs derived from human primary tumors and KrasG12D mice (Shankar et al., 2011). The inhibitory activities include the suppression of pluripotency maintaining factors (Nanog, Sox-2, c-Myc, and Oct-4), drug resistance gene ABCG2, markers of epithelial-mesenchymal transition (Zeb-1, Slug, and Snail), and CSCs migration/invasion.

Moreover, sulforaphane from broccoli sprout has been recently shown to inhibit pancreatic CSCs in vitro and in vivo (Kallifatidis et al., 2009; 2011). Sulforaphane protects against DNA damage, induces apoptosis, and inhibits NF-κB activation which leads to the suppression of pancreatic CSCs. When combined with a chemotherapeutic drug, cis-platinum, gemcitabine, doxorubicin, or 5-flourouracil, sulforaphane was found to sensitize the pancreatic and prostate CSCs to the cytotoxic killing of these
chemotherapeutic drugs. The sensitization is evidenced from a decrease in ALDH-1 activity. In the same study, the xenograft model was developed by implanting pancreatic CSCs to the mice. Treatment of mice with the combined regimen eradicates CSC-tumor as well as the tumor-initiating potential. No significant side effects were reported.

5. Attenuation of immune-suppressive microenvironment via inhibition of IDO

Indoleamine 2,3-dioxygenase (IDO) is a heme-containing enzyme which catalyzes the initial rate-limiting step in the degradation of tryptophan. IDO has recently been recognized as a key enzyme in the modulation of immune tolerance to tumors (Muller et al., 2005; Robinson et al., 2006). Transcription of IDO is shown to be augmented by a synergistic action of NF-κB and TNF-α activation (Robinson et al., 2006). Secretion of IDO from cancer and surrounding satellite cells, including dendritic cells and macrophages, is partially responsible for the immunoediting consequence of cancers (Lob et al., 2009). Elevation of IDO creates an immunosuppressive microenvironment by inhibition of T lymphocyte function and by activation of Treg (regulatory T cells) at lymph nodes (Muller et al., 2005; Munn and Melor, 2007; Sharma et al., 2008).

Ovarian CSCs have the ability to polarize macrophages to a phenotype (type 2) that promotes tumor growth (Hagemann et al., 2006; Alvero et al., 2011). Concomitantly, the tumor-associated macrophage (TAM) also produces Treg and IDO which exacerbate the immunosuppressive environment.

Elevated IDO level in the ovarian cancer tissues (evaluated using GeneChip) is positively associated with paclitaxel resistance, and with impaired survival in patients with serous-type ovarian cancer (Okamoto et al., 2005). To further evaluate the role of IDO in cancer progression, several IDO inhibitors including 1-methyl tryptophan are currently under clinical investigations (Muller et al., 2005).

In our laboratory, we have found that baicalein, genistein, and wogonin are potent inhibitors to IDO protein while exhibiting null toxicity to normal stem cells (Chen et al., 2011b). Other studies with dendritic cells show that curcumin inhibits the induction of IDO gene expression and EGCG suppresses both the gene induction and IDO protein activity (Jeong et al., 2009). The phytochemical from cabbage, brassinin, was also shown to be an IDO protein inhibitor although the activity is an order of magnitude weaker than baicalein (Banerjee et al., 2007; Chen et al., 2011b).

Discussions and Conclusion

Recent research has positively correlated the chemotherapy-resistant EOC to the presence of the aggressive type-2 cancer cells in which a high frequency of non-functional p53 protein is detected. In view of the antagonistic relationship between p53 and NF-κB, the absence of a wild-type p53 has been shown to confer anti-apoptosis in chemotherapy-resistant EOC cells (Yang et al., 2011). This is a
paradoxical role of NF-κB in cancer therapy. Activated NF-κB promotes apoptosis in type-1 EOC cells, which is one of the anti-cancer mechanisms of cis-platinum (Kim et al., 2006). On the contrary, inhibition of NF-κB confers apoptosis and inhibits cell-growth in type-2 chemotherapy-resistant EOC cells (Yang et al., 2011).

Figure 1. Schematic signaling of key inflammation associated proteins in EOC cells. The protein targets are modulated by chemotherapeutic drugs or/and natural inhibitors, which exhibit anti-proliferative activity and induce apoptosis in type-1 or type-2 cells.

In parallel with the above study, anti-inflammatory phytochemicals reviewed in this article are known to exhibit inhibitory activity to NF-κB. This activity might potentially be useful in the treatment of chemotherapy-resistant EOC cells. It can either be used as a single agent or in combination with a chemotherapeutic drug as demonstrated in the examples of oridonin, resveratrol, sulforaphane, and wogonin. Resveratrol as a single agent or the combination of sulforaphane with chemotherapeutic drugs leads to the eradication of pancreatic CSC tumors in nude mice and tumor xenografts. Furthermore, curcumin, oridonin, and wogonin as NF-κB inhibitors repress cell growth in type-2 like chemotherapy-resistance EOC cells independent of wild-type p53 (Watson et al., 2010). These studies indicate the potential role of natural NF-κB inhibitors in the repression of type-2 EOC cells as illustrated in a schematic diagram shown in Figure 1.

In conclusion, results from many published studies described above indicate a definitive involvement of inflammation pathway in the progression and treatment of ovarian cancer. Some anti-inflammatory phytochemicals exhibit the activities to intervene the dysregulated inflammation pathway, and may play a beneficial role in
the treatment of advanced EOC. However, there are many questions remain to be answered. Further research in this area is urgently needed.

**References**


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