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REVIEW

Curcumin as a Cancer Chemotherapy Sensitizing Agent

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Abstract The development of cancer chemotherapy made a significant progress in cancer treatment. However, most chemotherapeutic drugs are challenged by drug resistance and drug-induced toxicity. Combination therapy has been suggested as an effective strategy to avoid drug resistance and reduce toxicity derived from drug, thereby enhancing clinical treatment of cancer. Many food-derived bioactive compounds have exhibited anticancer activity and can be good candidates for combination therapy with existing chemotherapeutic drugs. Curcumin is one of compounds that present anticancer activity in many types of cancer and has been extensively studied for its anticancer mechanisms including inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation. Combinational treatment of curcumin enhanced therapeutic efficacy of traditional chemotherapeutic drugs, cisplatin, doxorubicin, 5-fluorouracil, and gemcitabine. NF-κB is a major downstream effector that leads to chemoresistance of many therapeutic drugs. Down-regulation of NF-κB by curcumin is an effective mechanism to sensitize chemotherapeutic drugs and increase therapeutic efficacy. Therefore, combination use of curcumin and available anticancer drugs has great potential to enhance chemotherapy efficacy and improve clinical treatment of cancer. More studies will be required to elucidate cause effect relationship of curcumin-induced suppression of cell survival pathways and enhancement of drug efficacy by curcumin.

Keywords cisplatin · combination therapy · curcumin · doxorubicin · gemcitabine · 5-fluorouracil

Introduction

The burden of cancer is increasing worldwide. About 14.1 million new cancer cases and 8.2 million cancer deaths are estimated to have occurred based on GLOBOCAN 2012, the standard data set produced to estimate cancer incidence and mortality worldwide by the International Agency for Research on Cancer (IARC) for 2012 (Ferlay et al., 2013). In spite of continuous cancer prevention efforts, cancer incidence increases globally with the growth of the elderly population. IARC also projected that deaths from cancer will substantially increase to over 19.3 million in 2025 (Ferlay et al., 2013). Therefore, it is important to design better strategies for cancer treatment to increase the quality of life of growing cancer patients.

Although local and regional tumors can be effectively treated by surgery and radiation therapy, chemotherapy is currently used for most cancer patients, because effective treatment requires reaching every organ in the body (Chabner and Roberts, 2005; DeVita and Chu, 2008). Traditional chemotherapy is a drug treatment that uses chemicals to kill fast-growing cells such as cancer cells. The first widely used cancer drugs, nitrogen mustards and antifolate drugs, were discovered in the 1940s (Chabner and Roberts, 2005). It was decade later that the molecular actions of those drugs were identified as induction of DNA damage, leading development of many anticancer compounds that use the same principle to treat cancer cells (Chabner and Roberts, 2005; DeVita and Chu, 2008). Those compounds include cisplatin, doxorubicin, and 5-fluorouracil (5-FU), which are still used as the mainstay treatment of many types of cancer (Chabner and Roberts, 2005; DeVita and Chu, 2008).

The development of chemotherapeutic agents made a significant progress in systemic treatments - relieving cancer burden and improving quality of life of cancer patients (Widakowich et al., 2007; DeVita and Chu, 2008). However, these traditional chemotherapeutic drugs often confront the limitation in their use. A major problem is intrinsic and/or acquired resistance of cancer cells to the drug (Sreekanth et al., 2011). Another obstacle rises from their adverse effect to normal cells - particularly rapidly growing cells (i.e., the cells that line the digestive tract and bone marrow cells) (Chabner and Roberts, 2005). These limitations led to new designs for chemotherapy such as modification of

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compounds to be more specific to cancer cells and/or development of new type of therapeutic drugs that target the processes of caner development specifically at the molecular level, namely molecular targeted therapy (Chabner and Roberts, 2005). Therefore, molecular targeted therapies are expected to be more selective than traditional chemotherapy and do less harm to normal cells. Progress in knowledge of cancer biology gave rise to development of many monoclonal antibodies and small molecules that interfere with a specific molecular target involved in tumor growth and progression (Arora and Scholar, 2005). Transition from traditional chemotherapy to targeted therapy is obviously an important advance in cancer treatment. However, targeted therapy still faces the same limitation that traditional chemotherapy has - resistance to drug and drug-induced toxicity (Widakowich et al., 2007). Although these novel targeted therapies are highly selective, molecules that they target are also expressed in normal cells and potentially disrupt normal cellular function (Widakowich et al., 2007). Moreover, cancer is highly heterogeneous disease that displays diverse phenotypes and functions among cancer cells within the same tumor (Yardley, 2013). This heterogeneity of cancer makes it difficult to be treated with the single targeted therapy. Therefore, more effective treatment can be achieved by combining existing cancer therapeutic drugs (either traditional or targeted therapy) together or using them with novel compounds (Yardley, 2013). Understanding of molecular action of each compound is critical to designing combination therapy that act through synergistic or complementary mechanisms to overcome resistance to therapy and reduce toxicity derived from chemotherapy (DeVita and Chu, 2008). Many food bioactive compounds have exhibited anticancer activity (Hatcher et al., 2008). Hence, they can be good candidates for combination therapy with either traditional or targeted chemotherapy to enhance efficacy of cancer treatment and reduce drug toxicity by lowering the dose of drug. However, a major obstacle to using food-derived bioactive compounds in combination therapy might be that their anticancer mechanisms are not well-defined.

Curcumin is a polyphenolic compound that gives the strong yellow color to the spice turmeric, powdered rhizome of *Curcuma longa*. It is one of the compounds that have been extensively studied for its anticancer activity in many types of cancer (Kwon et al., 2004; Hatcher et al., 2008). In addition, it has been extensively used for flavor and color in food preparation as well as treatment of inflammatory conditions and other diseases in East Asia (Ammon and Wahl, 1991). During its long history of usage in diet, almost no toxicity of curcumin yet has been reported (Ammon and Wahl, 1991), making it a good candidate for combination therapy. Many studies also demonstrated effectiveness of combinational use of curcumin to improve efficacy of TRAIL-mediated immunotherapy (Shankar et al., 2007; Wahl et al., 2007; Park et al., 2013; Reuss et al., 2013) and radiation therapy (Qiao et al., 2013).

This article will focus on curcumin use in combination with traditional chemotherapeutic drugs. In this article, the molecular mechanisms that are involved in resistance to the drug will be introduced, and studies that have evaluated curcumin effect on the drug efficacy will be summarized, leading to discussion on potential usefulness of combinational treatment of curcumin and traditional chemotherapeutic drugs.

Cisplatin

Cisplatin or cis-diamminedichloridoplatinum(II) is the first platinum-based chemotherapeutic drug. The best understood mechanism of cisplatin action involves crosslinking of DNA base, often with guanine, and this DNA lesion triggers inhibition of DNA replication and induction of apoptosis, leading cell death upon unrepairable DNA damage (Bauer et al., 1978; Heiger-Bernays et al., 1990). Carboplatin and oxaliplatin are also platinum-based analogs that act by forming DNA crosslinks as well (Richards and Rodger, 2007).

Cisplatin was first approved by FDA in 1978 for the treatment of testicular and bladder cancers and has been widely used for a broad spectrum of cancers including testicular, bladder, ovarian, cervical, lung, and head and neck cancers (Park et al., 2012). Many tumors are initially responsive to cisplatin treatment; however, the majority of cancer patients eventually relapse as disease becomes refractory to cisplatin (Martin et al., 2008). Therefore, besides the known cytotoxicities of cisplatin in the kidney, ears, and peripheral nerves, the high incidence of developing resistance to cisplatin is the main challenge to the clinical use of cisplatin as an anticancer drug (Martin et al., 2008). Many mechanisms of cisplatin resistance have been proposed including alteration in cellular uptake and efflux of drug (cellular concentration of drug), increased metabolism of the drug (drug inactivation and/or elimination), increased DNA repair (elimination of DNA adducts), and inhibition of apoptosis (Stordal et al., 2007). Cisplatin resistance also relates with the altered activation of signaling pathways that may lead to increase cell survival (Galluzzi et al., 2012).

Curcumin was treated in combination with cisplatin to reverse the cisplatin resistance and/or to enhance the efficacy of cisplatin in different types of cancer. Many molecular mechanisms of anticancer effect of curcumin have been reported, and they were implicated with chemosensitizing mechanisms of curcumin to cisplatin. One of the well-appreciated anticancer mechanisms of curcumin involves inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation (Hatcher et al., 2008). NF-κB is a transcription factor that activates gene transcripts involving resistance to apoptosis (X-linked inhibitor of apoptosis protein, cellular inhibitor of apoptosis protein-1, *Bcl-2*, and *Bcl-xL*), and cell cycle regulators (*cyclin D1* and *c-Myc*) upon translocation to the nucleus. High activation of NF-κB is reported in many cancer types (Dolcet et al., 2005). Thus, co-treatment of curcumin with the existing chemotherapeutic drugs becomes an attractive strategy to treat tumors with high expression of NF-κB or IκB kinase (IKK) that subsequently allows translocation of NF-κB.

Hartojo et al. (2010) reported that curcumin effectively reduced NF-κB activity and increased apoptosis in esophageal adenocarcinoma cells (Hartojo et al., 2010). Curcumin (10 or 20 mM) made "an additive effect" on induction of apoptosis in esophageal adenocarcinoma cell treated in combination with cisplatin, suggesting potential complementary mechanisms of activating apoptosis pathways by two compounds (Hartojo et al., 2010). In another study, it was demonstrated that curcumin and cisplatin induced apoptosis through different mechanisms - curcumin induced apoptosis through inhibition of IKKb expression and subsequent suppression of NF-κB activation, whereas cisplatin enhanced apoptosis in p53-dependent pathway in head and squamous cell carcinoma (HNSCC) cells (Duarte et al., 2010). In agreement with *in vitro* results, co-treatment of curcumin and subtherapeutic dose of cisplatin significantly inhibited tumor growth compared to treatment of individual agent alone (Duarte et al., 2010).

Potentiation of anticancer effect of cisplatin by curcumin could be also mediated through inhibition of signal transducer and activator of transcription-3 (STAT-3) proteins, another important transcription factor that activates genes that increase cell survival. STAT family proteins are phosphorylated and activated by receptor-associated kinases in response to various cytokines and growth factors (Yu et al., 2009). Activated STAT proteins translocate to the cell nucleus, where they act as transcription activators and mediate the expression of a variety of genes. Among known seven STAT family proteins, STAT-3 is the most appreciated in the pathogenesis of cancer (Jing and Tweardy, 2005). Upon activation, STAT-3 transcriptionally activates genes that inhibit apoptosis (*Bcl-xL*, *Mcl-1*), regulate cell cycle (*cyclin D1*, *c-Myc*), and induces angiogenesis (vascular endothelial growth factor) (Jing and Tweardy, 2005). In contrast to the transient nature of STAT-3 activation in normal cells, STAT-3 is constitutively activated in many cancers and therefore making a good target for anticancer agent (Jing and Tweardy, 2005). Treatment of curcumin-derived liposomal FLLL32 at IC_{50} level (<2 μM) inhibited phosphorylation of STAT-3 in HNSCC cells (Abuzeid et al., 2011). Combinational treatment of FLLL32 and cisplatin at near IC_{50} of individual agent enhanced apoptosis compared to treatment of individual drug alone, allowing a similar or enhanced anticancer effect at lower dose of cisplatin (<5 μM) (Abuzeid et al., 2011). Curcumin analogue of HO-3867 also reversed cisplatin resistance through down-regulation of STAT-3 signaling pathway in ovarian cancer (Selvendiran et al., 2011). Interestingly, STAT-3 was highly activated in cisplatin-resistant cancer cells compared to sensitive parent lines (Selvendiran et al., 2011). Combinational treatment of cisplatin (<35 μM) and HO-3867 (<10 μM) significantly inhibited constitutive activation of STAT-3 compared to cisplatin treatment alone in ovarian tumor xenografts (Selvendiran et al., 2011).

Activation of Akt and Notch is also known to mediate tumorigenesis and resistance to therapeutic drugs including platinum-based drugs by enhancing cell survival (Wang et al., 2008). Some studies also suggested that curcumin may resensitize cisplatin-resistant cells through suppression of Akt or Notch signaling (Weir et al., 2007; Howells et al., 2011). These studies indicated that co-treatment of curcumin may potentiate the effect of cisplatin or reverse the drug resistance by modulating transcription factor activities that increase cell survival and thereby, result in enhancement of apoptosis induced by cisplatin. However, these studies did not clearly demonstrate the cause and effect relationship between curcumin-induced suppression of cell survival pathways and chemosensitization of curcumin to cisplatin. Chanvorachote et al. (2009) suggested mechanisms that curcumin directly regulates apoptosis rather than modulates activation of transcriptional factors. In their study, curcumin induced proteasomal degradation of Bcl-2, a major anti-apoptotic protein, resulting in down-regulation of Bcl-2 and sensitizing Bcl-2 overexpressing non small cell lung cancer (NSCLC) cells to cisplatin-induced apoptosis (Chanvorachote et al., 2009). This novel mechanism of apoptosis regulation by curcumin may also mediate chemosensitizing effect of curcumin.

Cisplatin-sensitizing effect of curcumin was also achieved by inhibiting DNA repair. DNA repair is an important mechanism for prevention of cancer by correcting damaged DNA in normal cells. However, high activation of DNA repair can interfere with the action of drugs that induce DNA damage. Therefore, it has been challenged to treat cancer cells with intact DNA damage response (DDR) and overexpression of DNA repair enzymes such as excision repair cross-complementary 1 (ERCC1) (Martin et al., 2008). Treatment of curcumin at the range of 5-40 μM down-regulated ERCC1 at mRNA and protein levels through inactivation of mitogen-activated protein kinase kinase1/2 (MKK1/2), extracellular signal-regulated kinase 1/2 (ERK1/2) signaling in NSCLC (Tsai et al., 2011). Ogiwara et al. (2013) reported that curcumin suppressed DDR response by inhibition of DNA damage checkpoint and DNA double-strand break repair. Therefore, curcumin can lower the dose of cisplatin with similar or enhanced cytotoxicity perhaps mainly through the ability of curcumin to suppress survival signaling pathways and cellular DNA repair, concordantly increasing apoptosis in the cisplatin-treated cells.

Doxorubicin

Doxorubicin also termed adriamycin is an anthracycline anticancer drug that has been used as first-line therapy for many types of cancer (Fornari et al., 1994). Doxorubicin acts by interacting with DNA - intercalation between two base pairs of the DNA (Fornari et al., 1994). Intercalation with DNA prevents the progression of topoisomerase II that relaxes supercoiled DNA, resulting in DNA double strand breaks (Fornari et al., 1994). In response to double strand breaks, normally DDR is activated to repair the DNA damage but failure of repair triggers apoptosis (Forrest et al., 2012). Doxorubicin-induced DNA damage more rapidly affects replicating cells such as cancer cells than normal cells as is the case with other traditional chemotherapeutic drugs. In addition,

Pang et al. (2013) demonstrated a novel mechanism of doxorubicin action. Doxorubicin induces histone eviction from chromatin that contributes to deregulation of DDR, making cancer cells more susceptible to DNA-damaging agents (Pang et al., 2013).

Doxorubicin-induced cardiotoxicity is well recognized, although its mechanism remains unclear (Latorre et al., 2012). Doxorubicin can produce fatal cardiac toxicity with increasing dose that results in dose limitation in the use of doxorubicin (Orhan, 1999). In addition, intrinsic and acquired resistance to doxorubicin is common. The most common mechanism is overexpression of P-glycoprotein, a membrane pump responsible for drug efflux, reducing drug concentration inside the cell (Slovak et al., 1988). Another member of membrane pump, breast cancer related protein, also contributes to resistance against doxorubicin (Calcagno et al., 2008). Other mechanisms involved in drug resistance are alterations in DNA damage-sensing, repair capability of cancer cells, and alteration in apoptosis signaling (Luqmani, 2005). Reduced topoisomerase II expression is another major factor that attributes to doxorubicin resistance (Burgess et al., 2008). In addition, HuR, the RNA binding protein, has been suggested to be involved in resistance to doxorubicin (Latorre et al., 2012). HuR acts as an mRNA stabilizer and/or a translational enhancer that binds to a large AU-rich element containing mRNAs (Latorre et al., 2012). Upon exposure to doxorubicin, HuR translocates into the cytoplasm, which was necessary for the doxorubicin-induced apoptosis in a breast cancer cell line, MCF-7 cells (Latorre et al., 2012). Doxorubicin-resistant cell presented lower expression of HuR and restoration of HuR expression sensitized to the drug (Latorre et al., 2012). Cancer cells often exhibit multifactorial nature in drug resistance and this was reinforced in the study of AbuHammad and Zihlif (2013). Analysis on gene expression change associated with the doxorubicin-resistant phenotype in a breast cancer cell line revealed alteration in a broad range of genes involved in drug metabolism (especially the CYP1A1 and the CYP1A2), drug efflux, topoisomerase II expression, cell cycle, apoptosis, and DNA repair (AbuHammad and Zihlif, 2013).

High activation of NF-κB was also implicated in resistance to doxorubicin although it remains controversial whether NF-κB activation is required for doxorubicin-induced apoptosis or oppositely makes resistant to the drug-induced apoptosis. However, it seems to be consistent that cells exposed to doxorubicin elevate NF-κB activation. Doxorubicin treatment induced transcriptional repression and degradation of IκBα that resulted in activation of NF-κB and increase of *Bcl-2* transcription to impart survival advantage to drug-resistant cells (Sen et al., 2011). Curcumin was evaluated for doxorubicin sensitizing potential primarily through its ability to suppress NF-κB activation. Compared to doxorubicin treatment (<4 μM) alone, pretreatment of curcumin (10 μM) effectively reduced cell viability in doxorubicin-resistant breast cancer cells (Sen et al., 2011). Curcumin inhibited NF-κB activation in drug-resistant cells and this inhibition allowed p53-depenent activation of apoptosis, thereby sensitizing doxorubicin (Sen et al., 2011). Consistently, NF-κB activation induced by doxorubicin was attenuated by curcumin co-treatment in hepatoma cell lines (Notarbartolo et al., 2005). In agreement with *in vitro* findings, curcumin and doxorubicin combinational treatment exhibited greater inhibitory effect on the growth of tumor bearing doxorubicin-resistant ovarian sarcoma cells compared to single treatment of doxorubicin (Sadzuka et al., 2012). This study also demonstrated a simultaneous decrease in drug-induced systemic toxicity by curcumin, suggesting that reduction of adverse effect by curcumin might also contribute to enhancement of doxorubicin efficacy (Sadzuka et al., 2012). Hence, previous studies suggested that curcumin may potentiate doxorubicin efficacy by altering NF-κB activation and decreasing drug toxicity. Unfortunately, these studies did not elucidate cause and effect relationship between curcumin-induced suppression of NF-κB activation and the enhancement of doxorubicin efficacy by curcumin.

5-Fluorouracil (5-FU)

Antimetabolites represent a class of anticancer drugs that mimic normal cellular molecules (i.e., purine and pyrimidine analogs) and consequently interfere with DNA replication (Murakami et al., 2000). 5-FU is a pyrimidine analog that also includes capecitabine (an oral prodrug of 5-FU), floxuridine, and gemcitabine (Sikic, 1999). The incorporation of purine and pyrimidine analogs into DNA during S-phase of cell cycle prevents proper nucleotide addition, causing DNA replication failure (Major et al., 1982). 5-FU can be incorporated into DNA or RNA in place of thymine or uracil, respectively, and prevents the addition of the next nucleotide due to a fluoride atom at the 5-carbon position on the ring, resulting in termination of chain elongation and consequently induction of apoptosis (Parker and Cheng, 1990). 5-FU also initiates apoptosis by targeting thymidylate synthase (TS), a rate-limiting enzyme in production of deoxythymidine triphosphate (Ghoshal and Jacob, 1997; Longley et al., 2003). 5-FU forms a covalent ternary complex with 5,10-methylenetetrahydrofolate and TS, resulting in inhibition of DNA synthesis (Santi et al., 1974). However, prolonged exposure to 5-FU appeared to increase the expression of TS, making free TS available for DNA synthesis (Vinod et al., 2013). Not surprisingly, several studies have demonstrated strong association between increased TS expression and development of resistance to 5-FU (Chu et al., 1993; Hu et al., 2003). Yoo et al (2009) reported that elevation of astrocyte elevated gene-1 (AEG-1) was related with 5-FU resistance in hepatocellular carcinoma through its capability of inducing LSF transcription factor that regulates *TS* transcription (Yoo et al., 2009). In addition, AEG-1 increased dihydrophyrimidine dehydrogenase that inactivates 5-FU by catalyzing conversion of 5-FU to inactive fluoro-5,6-dihyrouracil, augmenting 5-FU resistance (Yoo et al., 2009). In contrast, Wang et al. (2004) did not observe apparent increase of *TS* expression in 5-FU-resistant lines when they compared expression profiles of pairs of 5-FU resistant and drug-sensitive parental cancer cells. Cells resistant to

5-FU exhibited phenotypes of slower growth, higher proportion of G_1, and lower proportion of S phase that may allow time to repair when 5-FU is incorporated into DNA chain and protect cells from death triggered by 5-FU-induced DNA damage (Wang et al., 2004). Cells irresponsive to 5-FU consistently exhibited high expression of p65 (NF-κB subunit) at both mRNA and protein levels. Furthermore, p65 in resistant cells had high DNA binding and transcriptional activities, suggesting that high activation of NF-κB signaling pathway plays an important role in 5-FU resistance (Wang et al., 2004).

Possible combinational use of curcumin with 5-FU have been studied in different cancers. In these studies, NF-κB inhibitory effect of curcumin was implicated as a major molecular mechanism underlying chemosensitization of 5-FU by curcumin. Relatively high concentration of curcumin (50 μM) effectively suppressed the constitutively active NF-κB in esophageal squamous carcinoma cells through the inhibition of IκBα phosphorylation, subsequently down-regulating the NF-κB-regulated genes, *Bcl-2* and *cyclin D1* (Tian et al., 2012a). The same group also reported that effect of curcumin (50 μM) was comparable or superior to p65 siRNA in inhibition of p65 expression and IκBα phosphorylation, leading reduction of cell viability and enhancement of apoptosis in esophageal squamous carcinoma cells (Tian et al., 2012b). Curcumin also effectively sensitized colon cancer cells to 5-FU treatment with more physiologically achievable dose. Pretreatment of 5 μM curcumin reduced the amount of 5-FU by 5-fold compared to IC_{50} of 5-FU in order to achieve the same cytotoxicity in colon cancer cells (Shakibaei et al., 2013). This synergistic effect of curcumin and 5-FU was related with collaborative alteration of apoptosis-regulatory proteins including caspase-8, caspase-9, caspase-3, Bax, and Bcl-xL in both colon cancer cells *in vitro* and their xenografts (Shakibaei et al., 2013). Furthermore, this potentiation of anticancer effect of 5-FU in the presence of curcumin was associated with curcumin-induced suppression of NF-κB and phosphoinositide 3-kinase signaling activated by 5-FU (Shakibaei et al., 2013).

More comprehensive mechanistic study that involves curcumin-mediated chemosensitization to 5-FU was conducted by Vinod et al. (2013). Curcumin synergized cytotoxicity induced by 5-FU treatment in breast cancer cells regardless of their estrogen and progesterone receptor status (Vinod et al., 2013). This synergizing effect of curcumin involves the ability of curcumin to inhibit NF-κB activation and degradation of IκBα induced by 5-FU, subsequently enhancing 5-FU-induced apoptosis through caspase-dependent cleavage of poly ADP ribose polymerase (PARP) (Vinod et al., 2013). Interestingly, TS was upstream regulator of NF-κB activation in breast cancer cells exposed to 5-FU (Vinod et al., 2013). 5-FU treatment induced TS expression and curcumin pretreatment significantly down-regulated 5-FU-induced up-regulation of TS (Vinod et al., 2013). Therefore, enhancement of 5-FU anticancer effect was also mainly through modulating NF-κB activation.

Gemcitabine

Gemcitabine (2'-deoxy-2',2'-difluorocytidine monohydrochloride) is a fluorinated analog of deoxycytidine that can be incorporated into DNA during DNA replication, causing inhibition of DNA synthesis and apoptosis (Noble and Goa, 1997). It also inhibits ribonucleotide reductase (RNR) involved in deoxyribonucleotide synthesis required for DNA synthesis; thereby inhibiting RNR by gemcitabine induces apoptosis (Artin et al., 2009). Gemcitabine has been used as a first-line treatment for patients with advanced or metastatic pancreatic cancer; however, the disease develops resistance to the drug (Skrypek et al., 2013). Cellular mechanisms responsible for resistance to gemcitabine are less understood. High activation of ERK appeared to be implicated in gemcitabine resistance, although studies did not demonstrate definitive causality (Fryer et al., 2011). ERK was highly activated in pancreatic cancer cell lines that exhibit high degree of resistance to gemcitabine (Fryer et al., 2011). Zheng et al. (2013) also suggested that high ERK activity may protect pancreatic cancer cells from gemcitabine-induced apoptosis. Moreover, Skrypek et al. (2013) demonstrated that the MUC4 mucin mediates gemcitabine resistance in pancreatic cancer cells, and MUC4 induced gemcitabine resistance by regulating the expression of nucleoside transporters (hCNT1) and ratio of apoptosis-related proteins, Bax/Bcl-xL. Interestingly, NF-κB was shown to mediate the regulation of hCNT1 expression by MUC4. NF-κB activation down-regulated the hCNT1 expression, resulting in decreased gemcitabine uptake and efficiency (Skrypek et al., 2013). In addition, regulation of Bax/Bcl-xL ratio by MUC4 was mediated through the NF-κB (Skrypek et al., 2013). Furthermore, they reported that decreased expression of NF-κB led to increased sensitivity to gemcitabine, suggesting potential improvement of gemcitabine efficacy by targeting the NF-κB pathway with natural or chemical inhibitors.

Curcumin was tested for potential combinational use to enhance the effect of gemcitabine or overcome chemoresistance to the drug. Curcumin (10 or 50 μM) inhibited constitutive NF-κB activation in pancreatic cancer cell lines (Kunnumakkara et al., 2007). Co-treatment of curcumin (10 μM) and gemcitabine (50 nM) effectively enhanced cytotoxicity and apoptosis at the concentrations of individual compounds that were minimally effective (Kunnumakkara et al., 2007). The same study also validated potentiation of gemcitabine effect by curcumin in orthotopic pancreatic tumor model. This synergistic effect of curcumin was related with inhibition of NF-κB activation and subsequent down-regulation of NF-κB-regulated proteins including VEGF, cyclooxygenase-2, cyclin D1, c-Myc, Bcl-2, Bcl-xL, and c-IAP-1 (Kunnumakkara et al., 2007). Similarly, difluorinated curcumin (CDF), a synthetic analogue of curcumin, synergized gemcitabine effect in pancreatic cancer but with lower concentration due to greater bioavailability of CDF compared to the parent compound. Combinational treatment of CDF (4 mM) and gemcitabine (10 nM) greatly decreased cell viability in consistence

with increased apoptosis and suppression of NF-κB activation (Ali et al., 2010). They also reported that CDF either by itself or combined with gemcitabine significantly down-regulated miR-21 that is overexpressed in gemcitabine-resistant cells. Interestingly, down-regulation of miR-21 correlated with reactivation of phosphatase and tensin homolog (PTEN) that induces the cell cycle arrest. Likewise, CDF restores PTEN expression in colon cancer cells through down-regulation of miR-21 (Ali et al., 2010). Thus, curcumin increased gemcitabine efficacy by suppression of NF-κB activation and reactivation of PTEN.

Conclusions

The development of cancer chemotherapy made a significant progress in cancer treatment. However, both traditional and targeted chemotherapeutic drugs are challenged by drug-induced toxicity and resistance to drug in spite of tremendous effort to improve therapy. Combination therapy has been suggested as a strategy to avoid therapeutic drug resistance while cutting down the drug-derived toxicity by lowering the dose of each drug. Many food bioactive compounds have exhibited anticancer activity and can be good candidates for combination therapy as well. For successful combination therapy, however, it is important to identify molecular mechanisms of each compound and combine two or more agents that work together in complementary or synergistic ways. Main obstacle of using food compounds in combination therapy might be that their mechanisms of anticancer actions are less understood, making difficult to establish strategies to combine with available therapeutic drugs or other bioactive food compounds. Curcumin is one of food compounds that exert anticancer activity in many types of cancer and has been extensively studied for its mechanisms of anticancer action. In addition, there are efforts to enhance bioavailability of curcumin by modifying curcumin structure and liposomal delivery (Ali et al., 2010; Abuzeid et al., 2011). Combinational treatment of curcumin enhanced therapeutic efficacy of chemotherapeutic drugs, cisplatin, doxorubicin, 5-FU, and gemcitabine. NF-κB is a major downstream effector that leads to chemoresistance of many therapeutic drugs. Down-regulation of NF-κB by curcumin is an effective mechanism to sensitize to the drugs. Therefore, combinational use of curcumin and available anticancer drugs has great potential to enhance chemotherapy efficacy and improve clinical treatment of cancer. More studies will be required to elucidate cause effect relationship of curcumin-induced suppression of cell survival pathways and enhancement of drug efficacy by curcumin.

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