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NF-kappaB: a potential target for cancer chemoprevention and therapy

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1. ABSTRACT

Nuclear factor-kappaB pathway plays important roles in the control of cell proliferation, differentiation, apoptosis, inflammation, stress response, cell signaling transduction, and other physiological processes. Because the disorder of these physiological processes has been linked with the onset of cancers, NF-kappaB has been described as a major culprit in cancer. Experimental *in vitro* and *in vivo* studies have shown that down-regulation of NF-kappaB activity by natural and synthetic NF-kappaB inhibitors suppresses the development of carcinogen-induced tumors, inhibits the growth of cancer cells, and induces apoptosis with alternation of gene expression which is critical for the control of carcinogenesis and cancer cell survival. Moreover, recent studies indicate that the effects of conventional cancer therapeutics could be enhanced by natural and synthetic NF-kappaB inhibitors, suggesting that down-regulation of NF-kappaB could sensitize cancer cells to conventional therapeutics. Therefore, targeting NF-kappaB is a novel preventive and therapeutic strategy against human cancers. In this brief review article, we will summarize the state of our knowledge for the role of NF-kappaB in relation to cancer prevention and therapy.

2. INTRODUCTION

The nuclear factor-kappaB (NF-kappaB) pathway is one of the most important cellular signaling transduction pathways involved in both physiological processes and disease conditions. It plays important roles in the control of immune function, differentiation, inflammation, stress response, apoptosis, and cell survival (1, 2). Moreover, NF-kappaB is critically involved in the processes of development and progression of cancers, raising its importance in cancer research (3, 4).

The NF-kappaB family is composed of five proteins: RelA (p65), RelB, c-Rel, NF-kappaB1(p50), and NF-kappaB2(p52), each of which may form homo- or heterodimers. In human cells without specific extracellular signal, NF-kappaB is sequestered in the cytoplasm through tight association with its inhibitors: IkappaBalpha which acts as a NF-kappaB inhibitor and p100 proteins which serves as both an inhibitor and precursor of NF-kappaB DNA-binding subunits. NF-kappaB can be activated by many types of stimuli including TNF-alpha, UV radiation, free radicals, etc. The activation of NF-kappaB occurs through site-specific phosphorylation of IkappaBalpha by IKKbeta and/or phosphorylation of p100 by IKKalpha,

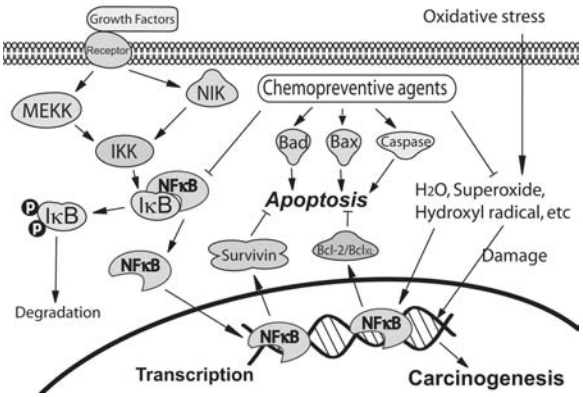

Figure 1. NF-kappaB as a target of chemopreventive agents in cancer prevention.

leading to degradation of IkappaBalpha by the 26S proteasome and/or the processing of p100 into smaller forms (p52). This process allows two forms of NF-kappaB (p50-p65 and p52-RelB) to become free, resulting in the translocation of active NF-kappaB into the nucleus for binding to NF-kappaB-specific DNA-binding sites and, in turn, regulating the transcription of target genes (5, 6). In this way, NF-kappaB controls the expression of its target genes that are involved in cellular physiological processes including cell proliferation, differentiation, apoptosis, inflammation, stress response, etc. The disorder of these physiological processes has been linked with the onset of cancers; therefore, NF-kappaB has been described as a major culprit in cancer.

3. NF-kappaB AND CANCERS

3.1. Oxidative stress and NF-kappaB activation

NF-kappaB is critically involved in the processes of oxidative stress response. Oxidative stress is defined as an increase in intracellular reactive oxygen species (ROS) such as H_2O_2, superoxide, hydroxyl radical, etc. Direct addition of H_2O_2 to cell culture medium could activate NF-kappaB in several types of cell lines (7). ROS in cells are increased in response to agents that also activate NF-kappaB. These findings suggest that oxidative stress activates NF-kappaB activity in the cells (8).

When ROS are formed intracellularly, they have the capacity to induce DNA damage and alter cellular signal transduction pathways, among which NF-kappaB signaling is the most important (Figure 1). Since DNA damage plays a central role in carcinogenesis, it is conceivable that oxidative stress could be carcinogenic (9). Hence, DNA repair is an important process in preventing mutagenesis. However, under oxidative stress, the repair of DNA damage can be inhibited by several redox-dependent metals, resulting in carcinogenesis. Moreover, the activation of NF-kappaB by ROS under oxidative stress has been known as a key event in carcinogenesis (3, 4). Therefore, it has been believed that the inhibition of NF-kappaB could suppress carcinogenesis. In addition, inhibition of ROS-stimulated NF-kappaB activation is widely recognized as a strategy to combat inflammatory disease. Evidence from many studies suggests that inhibition of NF-kappaB activity is not only beneficial for the treatment of inflammation but also for cancer therapy (6, 10). Examination of the inflammatory microenvironment in neoplastic tissues has supported the hypothesis that inflammation is a cofactor in oncogenesis for a variety of cancers. Many anti-inflammation drugs and antioxidants are known to inhibit NF-kappaB activity and induce apoptosis; therefore, they could also be used in the prevention and treatment of cancers.

3.2. NF-kappaB activation in cancers

NF-kappaB have shown its proliferative and anti-apoptotic effects in normal and malignant cells. Studies have shown that NF-kappaB is over-expressed and activated in various cancers, especially in the poorly differentiated cancers (3). It has been reported that NF-kappaB is constitutively activated in Hodgkin's tumor cells whereas inhibition of NF-kappaB blocks the tumor cell growth (11). Studies have also demonstrated that NF-kappaB regulates growth and survival of multiple myeloma, and that NF-kappaB is a novel therapeutics target in multiple myeloma (12). NF-kappaB is constitutively activated in most human pancreatic cancer tissues and cell lines but not in normal pancreatic tissues and immortalized pancreatic ductal epithelial cells, suggesting that the activation of NF-kappaB is involved in the carcinogenesis of pancreatic cancers (13, 14). The activation of NF-kappaB is also frequently observed in breast and prostate cancer cells (15, 16). Recent reports have shown that NF-kappaB is activated in gastric carcinomas and squamous cell carcinoma of the head and neck (17, 18). Therefore, it is becoming obvious that inhibition of NF-kappaB activity is highly desirable in the prevention and treatment of cancer and, as such, the chemopreventive agents that are known to down-regulate the activity of NF-kappaB could potentially inhibit the development and progression of cancers (Figure 1).

4. NF-kappaB AS A TARGET OF CHEMOPREVENTION

Experimental studies have shown that natural antioxidant compounds including isoflavones, I3C, DIM, curcumin, EGCG, etc, inhibit the activity of NF-kappaB and the growth of cancer cells, and also induce apoptosis in cancer cells (19-23), suggesting that NF-kappaB could be a target for cancer prevention. Moreover, synthetic antioxidants or NF-kappaB inhibitors also suppress tumor growth through inhibition of NF-kappaB activity. Thus, natural or synthetic antioxidants that inactivate NF-kappaB activity could serve as molecularly targeting agents against cancers (Figure 1).

4.1. Isoflavones

Isoflavones are a subclass of flavonoids and much more readily found in soybeans. Genistein, daidzein, and glycitein are three main isoflavones found in soybeans. Evidences from epidemiologic and *in vivo* studies have shown a decreased risk of cancer with soy consumption (24-26). Soy isoflavone genistein has been believed to be responsible for the decreased risk of cancer; however, some

controversies exist in the field. Experimental studies have revealed that isoflavones, particularly genistein, exert antioxidant effects on various human cells. It has been found that genistein protects cells against ROS by scavenging free radicals and reducing the expression of stress-response related genes (27, 28). Isoflavones also stimulate antioxidant protein gene expression in Caco-2 cells (29). Isoflavone supplementation has been found to reduce hydrogen peroxide-induced DNA damage in sperm, suggesting the antioxidant effects of isoflavone (30). Moreover, it has been demonstrated that genistein inhibits tumor promoter, 12-O-tetradecanoylphorbol-13-acetate induced hydrogen peroxide production in polymorphonuclear leukocytes and HL-60 cells (31), suggesting the inhibitory effect of genistein on carcinogenesis through antioxidant mechanism.

We have investigated whether genistein treatment could modulate NF-kappaB DNA binding activity in prostate, breast, and pancreatic cancer cells. We found that 50 μM genistein treatment for 24-72 hours significantly inhibited NF-kappaB DNA-binding activity in all cell lines we tested (22, 32-34). We also found that genistein significantly inhibited cancer cell growth and induced apoptotic cell death through the down-regulation of NF-kappaB (22, 32-34). Other investigators also demonstrated a similar effect of genistein on NF-kappaB in different types of cells. Baxa *et al.* showed that genistein reduced NF-kappaB in T lymphoma cells via a caspase-mediated cleavage of IkappaBalpha (35). Tabary *et al.* also found that genistein inhibited constitutive and inducible NF-kappaB activation and decreased IL-8 production in human cystic fibrosis bronchial gland cells (36). These results suggested that genistein functions as an antioxidant, which could be a potent agent for the inhibition of oxidative stress and the prevention of cancers.

Using *in vivo* studies, we found that isoflavone supplementation inhibited NF-kappaB DNA binding activity by 56% and abrogated TNF-alpha induced NF-kappaB activity by 50% in lymphocytes harvested from human subjects receiving soy isoflavone supplements (37). We also measured the levels of oxidative DNA damage in the blood of the subjects before and after supplementation with isoflavone. We found that isoflavone is very effective in reducing the level of 5-OhmdU, a modified DNA base that represents the endogenous status of cellular oxidative stress (37). These results demonstrated that isoflavone inhibits NF-kappaB activation and decreases oxidative damage, suggesting that soy isoflavone is a potent antioxidant and could be used for cancer prevention.

4.2. Indole-3-carbinol and 3,3'-diindolylmethane

Indole-3-carbinol (I3C) is produced from cruciferous vegetables. Under the acidic conditions of the stomach, I3C undergoes rapid self-condensation reactions to form several derivatives. 3,3'-diindolylmethane (DIM) is the major derivative and condensation product of I3C. Epidemiological and dietary studies have shown an association between high dietary intake of cruciferous vegetables and a decreased risk of cancer (38). The formation of DIM from I3C has been believed to be a likely prerequisite for I3C-induced anti-carcinogenesis. I3C and DIM have shown their ability to reduce oxidative stress and stimulate antioxidant response element-driven gene expression as antioxidants (39, 40). We and other investigators have found that I3C and DIM inhibit oncogenesis and cancer cell growth, and induce apoptosis in various cancer cells (21, 23, 41, 42), suggesting that I3C and DIM may serve as potent agents for the prevention of cancers. We have also found that I3C and DIM significantly inhibited NF-kappaB DNA binding activity in prostate and breast cancer cells, corresponding with the inhibition of cell proliferation and the induction of apoptosis by I3C and DIM (21, 23). These results suggest that inhibition of NF-kappaB activity by I3C and DIM may reduce the oxidative stress induced by ROS or TNF-alpha and that I3C and DIM could be used for cancer prevention and treatment.

4.3. Curcumin

Curcumin is a compound from *Curcuma longa* (tumeric). Curcumin has received much attention due to its pronounced anti-inflammatory, anti-oxidative, immunomodulating, anti-atherogenic, and anti-carcinogenic activities (43, 44). It has been reported that curcumin is a potent scavenger of oxygen free radicals such as hydroxyl radical and nitrogen dioxide radical (45). Curcumin inhibits lipid peroxidation in rat brain, liver, and lens, suggesting its antioxidant properties (46-48). Chuang *et al.* have shown that curcumin inhibits diethylnitrosamine-induced liver inflammation and activation of NF-kappaB in rats (49). It has been reported that curcumin inhibited IKK, suppressed both constitutive and inducible NF-kappaB activation, and potentiated TNF-alpha induced apoptosis (20). Curcumin also showed strong antioxidant and anticancer properties mediated through the regulation of the expression of genes that require the activation of activator protein 1 (AP1) and NF-kappaB (50). Moreover, curcumin inhibits the growth of cancer cells, induces apoptosis, inactivates Akt, and regulates the expression of genes related to anti-invasion (51, 52), suggesting its role in cancer prevention and treatment.

4.4. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is the most potent catechins from green tea. Epidemiologic evidence has shown that consumption of green tea significantly decreased overall cancer incidence (53). EGCG has shown its strong antioxidant activity. It has been reported that EGCG treatment resulted in a significant inhibition of NF-kappaB activation and translocation to the nucleus by suppressing the degradation of IkappaBalpha in the cytoplasm (19, 54). EGCG also inhibited the activation of IKK and phosphorylation of IkappaBalpha (55, 56), corresponding with the inhibition of NF-kappaB activation. Growing evidence shows that EGCG inhibits the proliferation of various cancer cells and induces apoptotic processes in cancer cells through inhibition of NF-kappaB (53, 57). It has also been found that EGCG had a concurrent effect on two important transcription factors, p53 (stabilization of p53) and NF-kappaB (negative regulation of NF-kappaB activity) (58). Moreover, EGCG has been found to reduce the levels of matrix

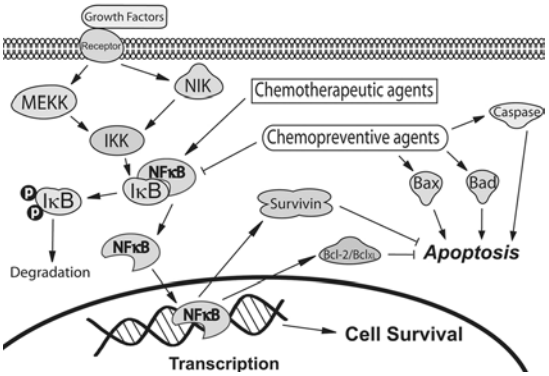

Figure 2. Targeting NF-kappaB in the combination treatment with chemopreventive agents and chemotherapeutics.

metalloproteinases, suppress angiogenesis, and inhibit invasion and metastasis (59, 60). These findings suggest that EGCG is a potent antioxidant which is likely to be useful for cancer prevention and treatment.

4.5. Resveratrol

Resveratrol is present in a wide variety of plants including grapes, mulberries, and peanuts. Relatively high quantities of resveratrol are also found in grapes. Resveratrol has beneficial effects on the reduction of oxidative stress and the prevention of cancers (61, 62). It has been found that resveratrol reduces DNA damage and the formation of A2E-epoxidation, which is implicated in the degenerative disease (63). Experimental studies have shown that resveratrol inhibits the growth of various cancer cells and induces apoptotic cell death (64-66). Resveratrol also shows its inhibitory effects on the activity of NF-kappaB (67), suggesting that its role as antioxidant may contribute to the prevention of cancers.

4.6. Lycopene

Tomatoes are rich in lycopene. The consumption of tomatoes and tomato products containing lycopene has been associated with a decreased risk of cancers (68). Lycopene is a potent antioxidant. It has been found that lycopene exhibits a high physical quenching rate constant with singlet oxygen, suggesting its high activity as antioxidant (69). Lycopene also shows beneficial effects on cancer prevention. Giovannucci *et al.* have reported that frequent consumption of tomato products is associated with a lower risk of prostate cancer (70). The inverse associations between plasma lycopene and prostate cancer have also been reported (71). Experimental studies have shown that lycopene inhibits cell growth in breast, prostate and endometrial cancer cells through the regulation of cell cycle-related genes (72, 73). Lycopene also inhibits the activity of NF-kappaB (74). A clinical trial has revealed that lycopene supplementation could reduce tumor size and PSA level in localized prostate cancers (75), suggesting its promising effect on prostate cancer treatment.

4.7. Vitamins

Vitamin E is a lipid-soluble antioxidant distributed in green leaf vegetables, nuts, seeds, sunflower, and plant oils. Vitamin E exerts a potent antioxidant effect. It has been reported that vitamin E inhibits NF-kappaB activation and NF-kappaB-dependent transcription, and induces differentiation through reduction of NF-kappaB (76, 77), suggesting that vitamin E may exert its antioxidant effect through modulation of NF-kappaB. Vitamin C is a water-soluble antioxidant. Sources of vitamin C include fruits and vegetables. It has been reported that vitamin C inhibits NF-kappaB activation by the inhibition of IkappaBalpha phosphorylation or activation of p38 mitogen-activated protein kinase (78, 79). These results suggest that vitamin E and C are beneficial for cancer prevention.

4.8. COX-2 inhibitors

Recently, aspirin has been considered as a cancer prevention drug because of its ability to down-regulate COX signaling. Experimental studies have shown that aspirin inhibits constitutively activated NF-kappaB in cell culture and, in turn, decreases the expression of the NF-kappaB downstream gene, especially COX-2, in pancreatic cancer cells (80). Another COX-2 inhibitor, SC236, has been shown to suppress NF-kappaB DNA binding activity and NF-kappaB mediated gene transcription (81). This effect was regulated through a mechanism independent of cyclooxygenase activity and prostaglandin synthesis. We and others have found that celecoxib, one of the COX-2 inhibitors, significantly inhibited tumor growth and induced apoptosis through the inhibition of NF-kappaB activation and COX-2 expression (82, 83).

5. TARGETING NF-kappaB IN THE COMBINATION TREATMENT WITH NF-kappaB INHIBITOR AND CANCER THERAPEUTICS

NF-kappaB is constitutively activated in most human cancers, suggesting that the activation of NF-kappaB is involved in the processes of carcinogenesis. Current evidence has also shown that NF-κB participates in the processes of angiogenesis, invasion, and metastasis (10). Moreover, it has been known that several chemotherapeutics such as cisplatin and docetaxel can activate NF-kappaB (84-86). The activation of NF-kappaB by chemotherapeutics has been found to cause acquired resistance to chemotherapeutic agents, resulting in treatment failure in cancer therapy. Experimental studies also demonstrated that other molecules (i.e. IL-1, E3-ubiquitin ligase receptor subunit betaTRCP1, etc) could induce NF-kappaB activation and lead to chemoresistance in human cancer cell lines (87, 88), suggesting that NF-kappaB plays important roles in the development of chemoresistance in cancers. Therefore, strategies targeting the NF-kappaB pathway could be a novel approach for improved cancer cell killing. Recently, more natural chemopreventive agents with anti-NF-kappaB activity and synthetic NF-kappaB inhibitors have been used in combination treatment with chemotherapeutics. Chemotherapy combined with these NF-kappaB inhibitors have shown enhanced anti-tumor activity through synergistic action, reduced chemoresistance, or compensation of inverse properties (Figure 2).

5.1. Genistein

The *in vitro* and *in vivo* studies from our laboratory and others have demonstrated that the anti-tumor effects of chemotherapeutic agents could be enhanced by combination treatment with genistein through inhibition of NF-kappaB. We have reported that genistein *in vitro* and *in vivo* potentiated growth inhibition and apoptotic cell death caused by cisplatin, docetaxel, doxorubicin, gemcitabine, and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in lymphoma and cancers of the prostate, breast, pancreas, and lung (32, 89-91). By *in vitro* and *in vivo* studies, we also found that NF-kappaB activity was significantly increased by cisplatin, docetaxel, doxorubicin, and gemcitabine treatment and that the NF-kappaB inducing activity of these agents was completely abrogated by genistein pre-treatment (32, 89-91), suggesting that genistein pre-treatment inactivates NF-kappaB and leads to increased growth inhibition and apoptosis induced by these agents. Recently, we found that anti-tumor and anti-metastatic activities of docetaxel could be enhanced by genistein through the regulation of osteoprotegerin/receptor activator of NF-kappaB (RANK)/RANK ligand/MMP-9 signaling *in vitro* and *in vivo* (92). These results suggest that genistein could potentiate the anti-tumor activities of chemotherapeutic agents *in vitro* and *in vivo*, resulting in more cancer cell killing and apoptotic cell death through regulation of NF-kappaB pathways in various cancers.

5.2. I3C and DIM

We and other investigators have found that I3C and DIM inhibit oncogenesis and cancer cell growth, and induce apoptosis through the inhibition of NF-kappaB activity in various cancer cells. Moreover, we and others have also found that combinations of I3C and cisplatin or tamoxifen cooperate to inhibit the growth of PC-3 prostate and MCF-7 breast cancer cells more effectively than either agent alone (42, 93). These results suggest that inhibition of NF-kappaB activity by I3C and DIM may contribute to the enhanced anti-tumor activity of chemotherapeutic agents.

5.3. Curcumin

It has been known that curcumin could enhance cancer therapeutic efficacy by inhibition of NF-kappaB. Curcumin has been found to significantly inhibit doxorubicin and paclitaxel induced NF-kappaB activation (85, 94), suggesting that curcumin could reduce drug resistance and sensitize cancer cell to chemotherapeutic agents. Curcumin and celecoxib also synergistically inhibited cell growth and induced apoptosis though the inhibition of NF-kappaB activity and the down-regulation of the expression of NF-kappaB-regulated gene products including COX-2, prostaglandin E2, and IL-8 in pancreatic cancers (13, 95). Curcumin also enhanced the anti-tumor activities of cisplatin, doxorubicin, and Taxol through inhibition of NF-kappaB in different type of cancers (96-98). A recent report showed that curcumin potentiated antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and NF-kappaB-regulated gene products (99). These results suggest that curcumin is a potent agent in enhancing therapeutic efficacy of multiple chemotherapeutic agents in various cancers.

5.4. EGCG

It has been reported that EGCG and tamoxifen synergistically induced apoptosis and growth inhibition in MDA-MB-231 human breast cancer cells through inhibition of NF-kappaB (100). EGCG could also chemosensitize resistant tumor cells to doxorubicin through an increase in the accumulation of doxorubicin in the tumors of human carcinoma xenograft model (101). EGCG was also shown to inhibit activation of IKK, phosphorylation of IkappaBalpha, and activation of NF-kappaB, suggesting its novel effects on cancer therapy (54).

5.5. Resveratrol

Resveratrol shows its inhibitory effects on the activation of NF-kappaB, suggesting its role as a NF-kappaB inhibitor contributing to the chemosensitization of cancer cells to chemotherapeutic agents. It has been found that resveratrol from grapes could sensitize non-Hodgkin's lymphoma and multiple myeloma cells to paclitaxel-mediated apoptosis (102). Resveratrol could also sensitize TRAIL-induced apoptosis in pancreatic cancer cells (103). The chemotherapeutic strategy combined with resveratrol may be a novel approach to enhance the efficacy of chemotherapy for pancreatic cancers.

5.6. Dehydroxymethylepoxyquinomicin

Dehydroxymethylepoxyquinomicin (DHMEQ) is a synthetic NF-kappaB inhibitor. It has been found that DHMEQ could inhibit constitutively activated NF-kappaB and exhibit a synergistic inhibitory effect on cell growth with cisplatin in HA22T/VGH hepatic cancer cells (104). In HA22T/VGH cells, DHMEQ decreased the level of activated nuclear NF-kappaB in a dose-dependent manner and attenuated NF-kappaB activation induced by cisplatin. The combination of DHMEQ with cisplatin also decreased the levels of IL-6 and Bcl-xL mRNA, suggesting that DHMEQ could inhibit the activation of NF-kappaB and the expression of NF-kappaB downstream target genes. In another study, the combination of DHMEQ and IFN-gamma synergistically inhibited cell proliferation with a pronounced attenuation of survivin expression, which is a known NF-kappaB downstream target gene (105). The combination of DHMEQ and TNF-alpha were also evaluated. NF-kappaB was activated by TNF-alpha; however, the administration of DHMEQ abrogated NF-kappaB transcriptional activity (106). The addition of DHMEQ to TNF-alpha markedly induced apoptosis with down-regulation of anti-apoptotic c-FLIP and survivin in PK-8 cells (106). These findings suggest that DHMEQ in combination with chemotherapeutic agents may be a promising strategy for the treatment of cancers.

5.7. COX-2 inhibitors

It has been known that NF-kappaB up-regulates COX-2 which activates EGFR signaling, suggesting that the inhibition of NF-kappaB, COX-2, and EGFR could be synergistic in killing cancer cells. We and others have found that celecoxib, a COX-2 inhibitor, combined with erlotinib (EGFR blocker) or curcumin synergistically potentiate the growth inhibitory and pro-apoptotic effects in cancer cells through the inhibition of NF-kappaB (82, 95),

suggesting that celecoxib could be a potent agent for combination treatment of cancers together with inhibition of NF-kappaB and EGFR. More recently, Mukhtar *et al.* have shown that lower doses of COX-2 inhibitors (NS-398 and celecoxib) combined with EGCG resulted in the enhanced cell growth inhibition, apoptosis induction, and NF-kappaB inhibition *in vitro* and *in vivo*, suggesting their potential role in cancer treatment (107).

5.8. Parthenolide

Parthenolide is a synthesized small molecule which suppresses NF-kappaB activation and sensitizes cancer cells to TNF-alpha-induced apoptosis in human cancer cells. The combination treatment with parthenolide and NSAID sulindac synergistically inhibited cell growth, induced apoptosis, increased levels of IkappaBalpha, and decreased NF-kappaB DNA binding activity (108), suggesting that a chemotherapeutic approach including NF-kappaB inhibitors and NSAIDs could be a novel strategy for the treatment of cancer. In addition, parthenolide also enhanced ICI 182,780 (Faslodex; fulvestrant)-induced apoptosis and cell growth inhibition in antiestrogen-resistant breast cancer cells (109), which have constitutively activated NF-kappaB, suggesting the protective role of NF-kappaB in antiestrogen-resistant breast cancer cells. The effect of parthenolide on the inhibition of NF-kappaB activation leads to growth inhibition of cancer cells.

5.9. Sulfasalazine

Sulfasalazine is commonly used as an anti inflammatory agent and is known as a potent inhibitor of NF-kappaB. Muerkoster *et al.* have investigated whether blockade of NF-kappaB activity with sulfasalazine could overcome NF-kappaB-induced chemoresistance *in vivo* in a mouse model of pancreatic cancer (110). They found that treatment with the chemotherapeutic agent etoposide alone moderately reduced tumor size (32-35% reduction), as compared to untreated tumors. Sulfasalazine alone only temporarily decreased the tumor size. However, sulfasalazine in combination with etoposide significantly reduced tumor size (80% reduction) in all experiments. TUNEL-staining showed higher numbers of apoptotic cells in tumors from the combination group. Immunohistochemical staining of the activated p65 subunit showed that sulfasalazine treatment abolished the basal NF-kappaB activity in tumor xenografts, suggesting that the anti-inflammatory drug sulfasalazine sensitizes cancer cells to chemotherapeutic agents by inhibition of NF-kappaB (110).

5.10. Proteasome inhibitor

Proteasome inhibitors PS-341 and MG-132 have been found to block intracellular degradation of IkappaBalpha proteins and, in turn, inhibit activation of NF-kappaB. It has been reported that PS-341 sensitized cancer cells to apoptosis induced by Taxol (111). Sensitization of cancer cells to Taxol could be mediated through the inhibition of IkappaBalpha degradation by PS-341. MG-132 has also been found to sensitize cancer cells to Fas-mediated apoptosis and radiation therapy (112, 113). These findings suggest that combination treatment with proteasome inhibitors could enhance the efficacy of cancer therapy.

6. SUMMARY AND PERSPECTIVE

The *in vitro* and *in vivo* studies reviewed above all suggest that NF-kappaB is an important target for cancer prevention and treatment. The strategies to reduce the activity of NF-κB by natural or synthetic NF-κB inhibitors could become a novel and potent approach for enhancing the therapeutic efficacy of conventional chemotherapeutic agents in the treatment of human cancers. However, further in-depth mechanistic studies, *in vivo* animal experiments, and clinical trials are needed for investigating the effects of NF-kappaB inhibitors in combination with conventional cancer therapeutics.

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