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REVIEW ARTICLE

Effect of NF-κB inhibition on chemoresistance in biliary–pancreatic cancer

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Abstract Biliary cancer and pancreatic cancer are considered to be difficult diseases to cure. Although complete resection provides the only means of curing these cancers, the rate of resectability is not high. Therefore, chemotherapy is often selected in patients with advanced unresectable biliary–pancreatic cancer. Many combination chemotherapy regimens have been applied in clinical trials. However, the survival time is not satisfactory. On the other hand, most chemotherapeutic agents induce anti-apoptotic transcriptional factor nuclear factor kappa b (NF-κB) activation, and agent-induced NF-κB activation is deeply involved in the onset of chemoresistance. Recently, novel approaches to potentiating chemosensitivity in cases of biliary–pancreatic cancer using NF-κB inhibitors with cytotoxic agents have been reported, most of which comprise translational research, although some clinical trials have also been conducted. Nevertheless, to date, there is no breakthrough chemotherapy regimen for these diseases. As some reports show promising data, combination chemotherapy consisting of a NF-κB inhibitor with chemotherapeutic agents seems to improve chemosensitivity and prolong the survival time of biliary–pancreatic cancer patients.

Keywords Pancreatic cancer · Biliary tract cancer · Chemosensitivity · Chemoresistance · NF-κB

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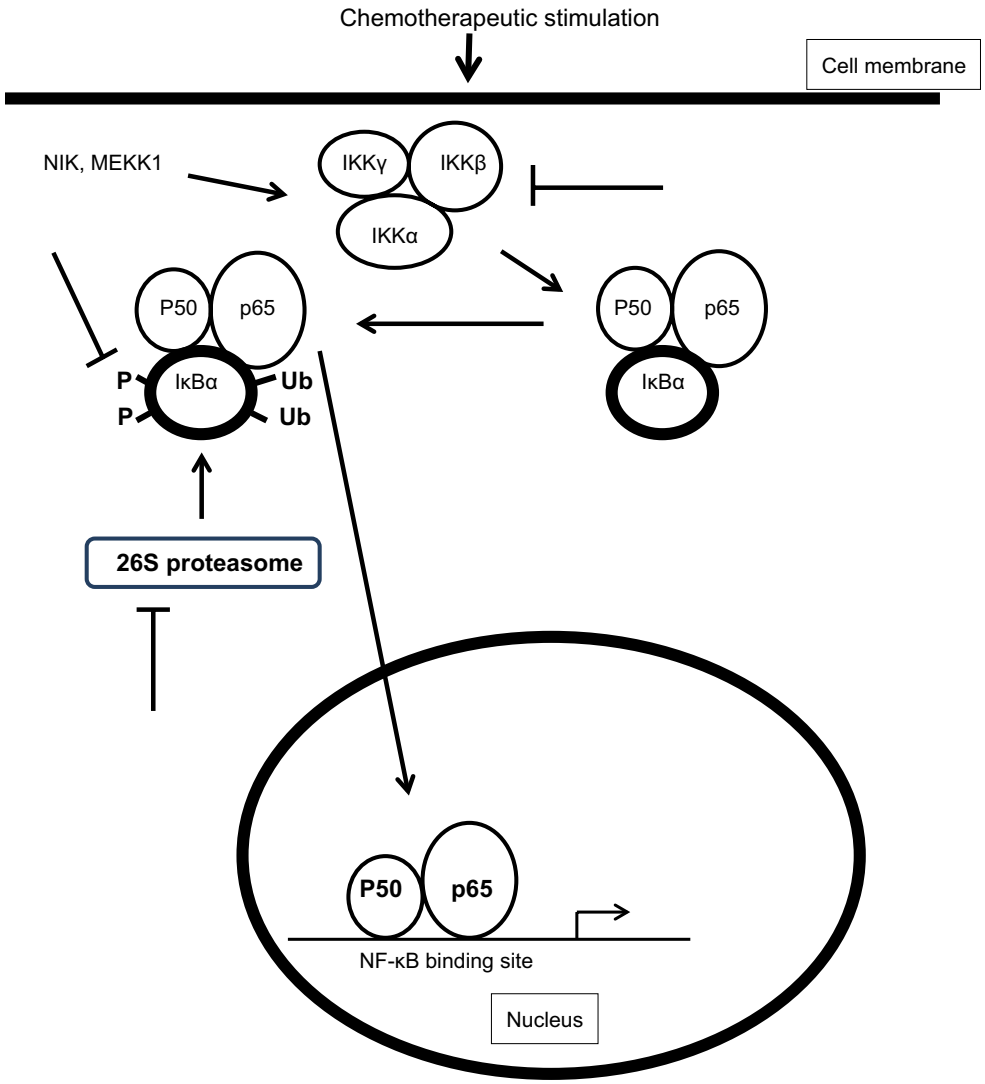
Introduction

According to Ministry of Health, Labor, and Welfare in Japan, biliary–pancreatic cancer caused approximately 45,000 deaths in 2010 [1]. The only means of curing these cancers is complete surgical resection. However, diagnosing these cancers in the early stage is difficult, and most patients fail to fulfill the criteria for surgical indications. Furthermore, even after curative surgery, the recurrence rate is very high [2, 3]. Nevertheless, chemotherapy is indispensable for treating biliary–pancreatic cancer. Although there are many different types of chemotherapeutic agents, including molecular target drugs, agents effective for biliary–pancreatic cancer are limited. In general, antimetabolic agents, such as fluoropyrimidine or gemcitabine, and platinum-containing agents, such as cisplatin or oxaliplatin, are selected as chemotherapeutic agents [4]. Resistance to chemotherapy is an obstacle to treatment, and the mechanism underlying the onset of chemoresistance has been documented in many reports within the past three decades, with NF-κB having been shown to be a key regulator. The first report of NF-κB goes back to 1986 [5], and, since then, this protein has been found to play pivotal roles in various regulatory mechanisms, including inflammation, immunity, and cell death, in many studies using dominant-negative or knockout models [6–9]. In particular, NF-κB plays a prominent role in both cell survival and cell death [10] and is oncologically involved in the proliferation and differentiation of cancer cells [11, 12] as well as chemoresistance [13, 14]. Moreover, a correlation between the NF-κB activity and the progression and prognosis of pancreatic cancer in vivo has been reported [15]. In this report, we document the potential role of NF-κB as a chemotherapeutic target for biliary–pancreatic cancer.

NF-κB and tumorigenesis

NF-κB was originally identified as a protein that binds to a sequence in the immunoglobulin κ light chain enhancer and is restricted to B cells [5]. NF-κB consists of a heterodimer of various members of the Rel family, such as p50, p52, c-Rel, v-rel, p-65(RelA), and Rel B [16]. NF-κB is inactivated in the cytoplasm by binding to the inhibitor of κB proteins, which subsequently blocks the nuclear localization sequences of NF-κB [17]. Therefore, NF-κB plays an important role in cell death [18, 19]. Furthermore, NF-κB, an anti-apoptotic transcriptional factor, is also believed to induce cell survival [20]. Once activated by various extracellular stimuli, the NF-κB present in normal cells is downregulated to maintain tissue homeostasis [21]. On the other hand, NF-κB is constitutively activated in many types of cancers [22, 23]. Because NF-κB regulates the expression of many genes implicated in cellular transformation, survival, proliferation, angiogenesis, invasion, metastasis, angiogenesis, and inflammation, constitutive NF-κB activation in cancer cells plays a pivotal role in many aspects of tumor progression [24]. In fact, many genes essential for tumor growth have binding sites for NF-κB and are targeted by NF-κB. As NF-κB activation is involved in the tumorigenesis and metastasis of pancreatic and biliary tract cancers, controlling NF-κB activation is a potential target for novel therapeutic strategies for these cancers [25, 26]. A schematic drawing of the NF-κB signaling pathway and therapeutic targets is described in Fig. 1.



NIK: NF-κB inducing kinase, MEKK1: MAP ERK Kinase Kinase 1, IKK: κB Kinase

Fig. 1 NF-κB signaling pathway. *NIK* NF-κB inducing kinase, *MEKK1* MAP ERK Kinase Kinase 1, *IKK* IκB Kinase

Mechanism of chemotherapy resistance

In order to enhance the effectiveness of cytotoxicity of chemotherapeutic agents for cancer cells, reducing the onset of chemoresistance acquired via diverse anti-apoptotic activities is indispensable. Chemoresistance is classified into two types, natural resistance and acquired resistance. Although normalizing both the types of resistance is important, controlling acquired chemoresistance directly contributes to a prolonged survival. Various studies of the mechanisms of chemoresistance have been conducted. In particular, mitochondria have been found to play critical roles in apoptotic processes, and mitochondrial permeability transition pore complex (PTPC) regulates mitochondrial membrane permeabilization, which is important for chemotherapy-induced apoptosis [27]. Hence, disorders of these systems cause chemoresistance. Chemotherapy induces somatic mutations, deletions, and the hypermethylation of genes that play pivotal roles in cell survival/death and DNA repair. These genes mutations are also crucially involved in chemosensitivity [28]. Chemotherapeutic agents primarily induce cancer cell death. Concomitantly, many chemotherapeutic agents induce NF-kκB activation in cancer cells. As a result, their cytotoxic potential is suppressed and chemoresistance develops [29]. Key drugs for biliary–pancreatic cancer, such as fluoropyrimidine, gemcitabine, and oxaliplatin, stimulate NF-κB activation. Camp et al. [30] demonstrated that the inhibition of 5-fluorouracil-induced NF-κB activation via the adenoviral delivery of an IkBα suppressor enhances the growth inhibition promoted by 5-fluorouracil alone in gastric cancer cells. Furthermore, gemcitabine and oxaliplatin induce NF-κB activation in pancreatic cancer cells [31, 32].

Translational research targeting NF-κB activation for biliary–pancreatic cancer

Many types of agents targeting NF-κB activation in various cancers have been reported. As it is difficult to classify NF-κB inhibitors precisely, any agent that inhibits NF-κB signal transduction is defined as a NF-κB inhibitor. Treatments involving NF-κB inhibitors for biliary–pancreatic cancer are listed in Table 1. Previous reports have documented that the inhibition of activated NF-κB is effective in suppressing tumor growth. The mechanism of NF-κB inhibition induced by each agent is different. As to monotherapy for pancreatic cancer, the availability of PS-341 (bortezomib) was first reported [33]. PS-341 is a potent inhibitor

Table 1 Pre-clinical research targeting NF-kB for biliary–pancreatic cancer

Cancer type	Agents	References
Pancreatic		
Monotherapy	Fisetin	Murtaza et al. [34]
	DCB-3503	Shiah et al. [33]
	PS-341	Nawrocki et al. [32]
	Quinoxaline urea analog	Radhakrishnan et al. [35]
Combination	Bortezomib/Gemcitabine	Bold et al. [37]
	Bortezomib/Irinotecan	Shah et al. [38]
	Bortezomib/Paclitaxel	Dong et al. [39]
	Nafamostat Mesilate/Gemcitabine	Uwagawa et al. [30]
	Nafamostat Mesilate/Oxaliplatin	Gocho et al. [31]
	MG132 or Sulfasalazine/Gemcitabine	Arlt A et al. [40]
	Gliotoxin or MG132 or Sulfasalazine/VP16 or Doxorubicin	Arlt A et al. [41]
	Curcumin/Gemcitabine	Kunnumakkara AB [42]
	Tocotrienol/Gemcitabine	Husain et al. [43]
	Honokiol/Gemcitabine	Arora et al. [44]
	Pristimerin/Gemcitabine	Wang et al. [45]
	Isoflavone/docetaxel or CDDP	Li et al. [49]
Biliary		
Monotherapy	Diethyldithiocarbamate	Srikoon et al.[36]
	Curcumin	Prakobwong et al.[46]
	Cepharanthine	Seubwai et al. [47]
	MG132	Ustundag et al. [48]
Combination	Nafamostat mesilate/Gemcitabine	Iwase et al. [49]
	Guggulsterone/Gemcitabine	Yang et al. [50]
	Icariin/Gemcitabine	Zhang et al. [51]

of proteasomes and inhibits NF-κB activation by blocking the degradation of ubiquitinated phospho-IκBα. The inhibition of NF-κB by DBC-3503, a tylophorine analog, is dependent on the downregulation of nuclear phosphorylated p65, a component of the active form of the NF-κB complex [34]. Fisetin (3,7,3′,4′-tetrahydroxyflavone), a natural flavonoid, inhibits NF-κB activation via the upregulation of IκBα and downregulation of pIkBα [35]. In addition, quinoxaline urea analog, an IKK2 inhibitor, inhibits NF-κB activation by suppressing IκBα phosphorylation [36], and diethyldithiocarbamate inhibits NF-κB translocation by blocking the cellular proteasome activity in biliary tract cancer cells [37].

Combination treatments with NF-κB inhibitors for biliary–pancreatic cancer are also listed in Table 1. The purpose of these combination therapies is to improve chemosensitivity by inhibiting chemotherapeutic agent-induced NF-κB activation. Chemosensitization to gemcitabine, irinotecan, and paclitaxel among pancreatic cancer cells by PS-341, a 26S proteasome inhibitor, was first reported in the same period [38–40]. In pancreatic cancer cells, the inhibition of gemcitabine-induced NF-κB activation by nafamostat mesilate has been approved as an effective therapeutic agent for pancreatitis, disseminated intravascular coagulation, and/or systemic response syndrome in Japan for more than two decades and potentiates chemosensitivity to gemcitabine by suppressing IκBα phosphorylation [31]. Moreover, nafamostat mesilate induces synergistic cytotoxicity with oxaliplatin in pancreatic cancer cells via the inhibition of oxaliplatin-induced NF-κB activation [32]. The proteasome inhibitor MG132 and IκB kinase inhibitor sulfasalazine, which block the phosphorylation of IκB, improve chemosensitivity to gemcitabine [41]. Furthermore, MG132 and sulfasalazine result in chemosensitization to VP-16 and doxorubicin by blocking agent-induced NF-κB activation [42]. Curcumin (diferuloylmethane), a derivative of the spice turmeric, potentiates the chemosensitivity of gemcitabine by inhibiting IκBα phosphorylation [43]. Meanwhile, tocotrienols, naturally occurring unsaturated vitamin E compounds, augment the antitumor activity of gemcitabine by suppressing the phosphorylation of IκBα [44]. Honokiol, a biologically active biphenolic compound isolated from *Magnolia officinalis/grandiflora*, also potentiates the cytotoxicity of gemcitabine by inducing G1-phase cell cycle arrest and suppressing IκBα phosphorylation [45]. Pristimerin, a quinone methide triterpenoid compound isolated from *Celastraceae* and *Hippocratea*, enhances chemosensitivity to gemcitabine by inducing G1-phase arrest and downregulating IκBα phosphorylation [46].

In biliary tract cancer cells, curcumin, cepharanthine, and MG132 have been investigated to determine whether monotherapy with these agents induces apoptosis. Curcumin, which potentiates the cytotoxicity of gemcitabine to pancreatic cancer cells [43], stimulates apoptosis via multiple signaling pathways, including inhibition of the NF-κB pathway [47]. Cepharanthine, a biscoclaurine alkaloid extracted from *Stephania cepharantha*, induces the apoptosis of cholangiocarcinoma cells by inhibiting NF-κB activation via an IKK-independent mechanism [48]. A proteasome inhibitor MG132, used in combination treatment with gemcitabine for pancreatic cancer, also induces apoptosis [49]. As for combination therapies with gemcitabine, several studies have investigated whether the addition of a NF-κB inhibitor to gemcitabine shows a synergic apoptotic effect. Nafamostat mesilate enhances chemosensitization to gemcitabine in biliary tract cancer cells via the same mechanism as in pancreatic cancer cells [50]. Guggulsterone, a plant polyphenol obtained from the gum resin of the Indian Ayurvedic medicinal plant, *Commiphora mukul*, augments the antitumor efficacy to gemcitabine in biliary tract cancer cells by inhibiting gemcitabine-induced NF-κB activation [51]. Icariin, a flavonoid isolated from *Epimedii herba*, potentiates the antitumor activity of gemcitabine by enhancing gemcitabine-induced G0/G1 arrest and inhibiting NF-κB activation [52]. Isoflavones, which are isolated from soybeans, sensitize cells to apoptosis induced by docetaxel or CDDP by suppressing chemotherapeutic agent-induced NF-κB activation [53].

Clinical trials targeting NF-κB activation for biliary–pancreatic cancer

To date, various clinical trials of treatments with chemotherapeutic agents and NF-κB inhibitors have been conducted. Clinical trials for biliary–pancreatic cancer are listed in Table 2. Most of these clinical trials were conducted to assess pancreatic cancer. Curcumin has been used in clinical trials for locally advanced or metastatic pancreatic cancer in both monotherapy and combination chemotherapy. The efficacy of monotherapy with curcumin was investigated in a phase II study ($n = 21$) [54]; no toxicities were observed. As the purpose of this phase II study was to evaluate the clinical biological effects of curcumin, the response to treatment was not assessed. The efficacy of combination chemotherapy was evaluated in a phase I/II study for gemcitabine-resistant locally advanced or metastatic pancreatic cancer ($n = 21$) [55]. In that study, the median survival time achieved with the combination chemotherapy in the patients with gemcitabine-resistant pancreatic cancer was 161 days (95 % confidence interval 109–223 days), and the 1-year survival rate was 19 % [55]. Chemotherapy with nafamostat mesilate and gemcitabine was administered for locally advanced or metastatic pancreatic cancer in a phase I ($n = 12$) and phase II study ($n = 35$) [56, 57]. The median survival time was 10 months

Table 2 Clinical trials targeting NF-kB for biliary–pancreatic cancer

Cancer type	Agents	Category	References
Pancreatic			
Monotherapy	Curcumin	Phase II	Dhillon et al. [53]
Combination	Nafamostat mesilate/Gemcitabine	Phase I	Uwagawa et al. [55]
	Nafamostat mesilate/Gemcitabine	Phase II	Uwagawa et al. [56]
	Isoflavones/Erlotinib/Gemcitabine	Phase II	El-Rayes et al. [57]
	Curcumin/Gemcitabine	Phase I/II	Kanai et al. [54]
	Bortezomib/Paclitaxel	Phase I	Ramaswamy et al. [58]
	Bortezomib/Irinotecan	Phase I	Ryan et al. [59]
	Bortezomib/Gemcitabine	Phase II	Alberts et al. [60]
	Thalidomide/Gemcitabine	Phase II	Maples et al. [61]
	Lenalidomide/Gemcitabine	Phase II	Infante et al. [62]
	Pomalidomide/Gemcitabine	Phase I	Infante et al. [63]
	Thalidomide/Capecitabine	Phase II	Shi et al. [64]
Biliary			
Monotherapy	Curcumin	Phase I	Kanai et al. [65]

(95 % confidence interval 9.3–13.5 months), with a 1-year survival rate of 40 % [57], while the response and disease control rates were 17.1 and 88.6 %, respectively. With regard to toxicities, five patients developed grade 3 leukopenia (14 %) or neutropenia (14 %) and one patient developed grade 4 neutropenia (3 %). The efficacy of chemotherapy consisting of isoflavones in combination with erlotinib and gemcitabine was assessed for locally advanced or metastatic pancreatic cancer in a phase II study ($n = 20$) [58]. In that trial, the median survival time was 5.2 months (95 % confidence interval: 4.6-N/A months), with a 6-month survival rate of 50 % [58]; the response was not evaluated. Three patients developed grade 3 adverse events, including three episodes of neutropenia (16 %), seven episodes of nausea (37 %), five episodes of fatigue (26 %), one episode of dehydration (5 %), one episodes of diarrhea (5 %), and one episode of infection (5 %), as well as grade 4 adverse events, such as one case of neutropenia (5 %) and one case of thrombocytopenia (5 %). Various trials of the use of bortezomib, a proteasome inhibitor, as a NF-κB inhibitor have also been reported. The efficacy of combination therapy with bortezomib and paclitaxel ($n = 45$) or irinotecan ($n = 41$) for advanced solid tumors, including pancreatic cancer, was investigated in a phase I study [59, 60], and combination therapy with gemcitabine for metastatic pancreatic cancer was assessed in a randomized phase II study ($n = 81$) [61]. This phase II study of bortezomib and gemcitabine yielded a median survival time of 4.8 months (95 % confidence interval: 2.4–7.4 months) and a 6-month survival rate of 41 % [61]. The response rate was 10 %, and the evaluable patients (26 %) experienced at least one grade 4 + AE, while one patient had grade 5 hypotension. Furthermore, clinical studies of immunomodulatory compounds, such as thalidomide, lenalidomide, and pomalidomide, in combination with chemotherapeutic agents for advanced pancreatic cancer have been reported [62–64]. In particular, treatment consisting of pomalidomide and gemcitabine was applied in a phase I study for metastatic pancreatic cancer ($n = 72$) [64]. A phase II study of the combination of thalidomide and gemcitabine for metastatic and locally advanced pancreatic cancer yielded a median survival of 183 days ($n = 27$) [62], with response and disease control rates of 14.3 and 76.2 %, respectively. Grade 3 or higher adverse events were as follows: sepsis (8.7 %), pneumonia (4.3 %), syncope (8.7 %), GI bleeding (4.3 %), DVT (8.7 %), neutropenia (47.8 %), thrombocytopenia (4.3 %), peripheral neuropathy (4.3 %), stroke (4.3 %), and a depressed level of consciousness (17.4 %). A phase II study of lenalidomide and gemcitabine for metastatic pancreatic cancer reported a median survival of 4.7 months (95 % confidence interval: 3.4–5.7 months) and a 6-month survival rate of 37 % ($n = 72$) [63], with response and disease control rates of 11 and 47.2 %, respectively. Adverse events were as follows: grade 3: thrombocytopenia (18 %), anemia (6 %), neutropenia (17 %), leukopenia (11 %), fatigue (7 %), DVT (18 %), rash (4 %), diarrhea (3 %), and dehydration (11 %); grade 4: thrombocytopenia (3 %), anemia (1 %), neutropenia (3 %), leukopenia (1 %), and DVT (3 %). The median survival in a phase II study with thalidomide and capecitabine for locally advanced or metastatic pancreatic cancer was 6.1 months (95 % confidence interval: 5.3–6.9 months) ($n = 31$) [65]. The response and disease control rates were 6 and 41.9 %, respectively, and the only grade 3 or higher adverse event was diarrhea (9.7 %).

For biliary tract cancer, we found only one phase I study. The safety of repeated-dose administration of

Theracurmin® containing 200 mg of curcumin under combination treatment with gemcitabine-based chemotherapy was assessed for standard chemotherapy-resistant pancreatic or biliary tract cancer ($n = 16$) [66].

Discussion

Gemcitabine remains the standard chemotherapy agent for advanced pancreatic cancer due to its prolonged survival time [67]. Many trials have been conducted using gemcitabine alone as the standard arm in randomized controlled studies. However, no new regimens may improve the survival time achieved with gemcitabine for up to a decade. Although combination therapy with gemcitabine and erlotinib has been shown to prolong the survival of gemcitabine, the difference was only 0.33 months [68]. Thereafter, two regimens achieved a longer survival time than treatment with gemcitabine. The median overall survival of 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) and that of nab-paclitaxel in combination with gemcitabine for metastatic pancreatic cancer is 11.1 and 8.5 months, respectively [69, 70]. To date, there are no regimens that achieve a survival time of more than 12 months. Although locoregional chemotherapy with gemcitabine has been applied, the survival remains unknown [71]. As for advanced unresectable biliary tract cancer, there are currently no established standard chemotherapy regimens. However, gemcitabine is generally used for this disease. As therapy with gemcitabine plus cisplatin may have a significant survival advantage, without additional toxicity, compared with gemcitabine alone, this combination is currently the standard regimen [72]. However, the survival time of advanced biliary–pancreatic cancer is not satisfactory, and it is not easy to rapidly develop novel effective agents. On the other hand, most agents used in the standard chemotherapy regimen for biliary–pancreatic cancer induce NF-κB activation. Therefore, the combination of a NF-κB inhibitor with these agents has the potential to improve the survival time. Simultaneously, it is important to assess whether individual NF-κB inhibitors can be used at adequate concentrations to inhibit NF-κB activation in cancer cells in vivo. Kanai et al. [66] assessed whether NF-κB activation is inhibited with a clinical dose of Theracurmin® in peripheral blood mononuclear cells using immunocytochemistry in a phase I study. However, the clinical dose of Theracurmin® did not inhibit NF-κB activation in these cells. We applied nafamostat mesilate a NF-κB inhibitor in our phase I and phase II studies. As the concentration of nafamostat mesilate under conditions of continuous intravenous infusion was insufficient to inhibit NF-κB activation, regional arterial infusion using a port-catheter system was selected [56]. Although the development of novel drugs for biliary–pancreatic cancer is needed, physicians currently have no choice but to use existing agents. Almost all existing cytotoxic agents induce NF-κB activation, which causes chemoresistance. Hence, the application of combination chemotherapy with existing agents and a NF-κB inhibitor that works under the clinical dose in vivo is reasonable and may be a potential treatment strategy for biliary–pancreatic cancer.

Conclusion

We herein described a novel potential approach targeting chemotherapeutic agent-induced NF-κB activation for advanced biliary–pancreatic cancer. The addition of a NF-κB inhibitor to chemotherapeutic agents used in standard chemotherapy regimens for biliary–pancreatic cancer appears to potentiate chemosensitivity.

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