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Review

Anticancer Activity of Novel NF-κB Inhibitor DHMEQ by Intraperitoneal Administration

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There have been great advances in the therapy of cancer and leukemia. However, there are still many neoplastic diseases that are difficult to treat. For example, it is often difficult to find effective therapies for aggressive cancer and leukemia. An NF-κB inhibitor named dehydroxymethylepoxyquinomicin (DHMEQ) was discovered in 2000. This compound was designed based on the structure of epoxyquinomicin isolated from a microorganism. It was shown to be a specific inhibitor that directly binds to and inactivates NF-κB components. Until now, DHMEQ has been used by many scientists in the world to suppress animal models of cancer and inflammation. Especially, it was shown to suppress difficult cancer models, such as hormone-insensitive breast cancer and prostate cancer, cholangiocarcinoma, and multiple myeloma. No toxicity has been reported so far. DHMEQ was administered via the intraperitoneal (IP) route in most of the animal experiments because of its simplicity. In the course of developmental studies, it was found that IP administration never increased the blood concentration of DHMEQ because of the instability of DHMEQ in the blood. It is suggested that inflammatory cells in the peritoneal cavity would be important for cancer progression, and that IP administration, itself, is important for the effectiveness and safety of DHMEQ. In the present review, we describe mechanism of action, its in vivo anticancer activity, and future clinical use of DHMEQ IP therapy.

Key words: NF-κB; Dehydroxymethylepoxyquinomicin (DHMEQ); Intraperitoneal administration; Cancer; Lymphoma

INTRODUCTION

NF-κB is the transcription factor that binds to the κB sequence in DNA[1]. NF-κB promotes the transcription of many genes encoding inflammatory cytokines, such as interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10 (often suppresses inflammation), IL-12, MCP-1, and TNF-α, and cell-adhesion molecules, such as E-selectin, ICAM-1, and VCAM-1. NF-κB also increases the expression of antiapoptosis proteins, including Bcl-xL, FLIP, Bfl-1, and survivin. It also increases the expression of metastasis-promoting proteins, such as VEGFs and matrix metalloproteases (MMPs), including MMP-9, MMP-1, MT-MMP, and MMP-2. NF-κB is important for the regulation of immunity and tissue stability under physiological conditions. On the other hand, excess NF-κB activation in inflammatory cells accelerates inflammation under pathological conditions[2]. Excess activation of NF-κB in cancer cells causes resistance against chemotherapy and radiotherapy. If NF-κB is inhibited, expression of many cytokines and cancer-promoting proteins is likely to be inhibited. Therefore, NF-κB is an attractive molecular target for anti-inflammatory and anticancer agents[3].

NF-κB is usually inactive in the cytoplasm without stimulation. It is typically activated by IL-1β, TNF-α, lipopeptide, and bacterial surface lipopolysaccharide (LPS) through their specific receptors, signaling protein TRAF6 or TRAF2, and I-κB kinase (IKK) that induces degradation of NF-κB-inhibitory protein. However, NF-κB is often constitutively activated without

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stimulation in cancer and leukemia cells. Especially, difficult cancers and leukemia, such as hormone-insensitive breast carcinoma and prostate carcinoma, pancreatic carcinoma, and multiple myeloma, are more likely to possess constitutively activated NF-κB. The microenvironment of cancer tissue is considered to be important for cancer progression. These environmental factors include macrophages and cancer-associated fibroblasts. These cells often secrete NF-κB-dependent inflammatory cytokines and MMPs as described below.

Therefore, in the field of cancer research, NF-κB should be an attractive target for chemotherapy. However, no inhibitor has been developed as an anticancer agent so far. Possibly, NF-κB inhibitors may have inevitable side effects such as bone marrow toxicity. In fact, the expression of many hemopoietic growth factors, such as GM-CSF[4] and M-CSF[5], depends on NF-κB.

Dehydroxymethylepoxyquinomicin (DHMEQ) is a low-molecular-weight inhibitor of NF-κB. Its intraperitoneal (IP) administration was found to be effective on most cancer models showing no toxicity. In the present review, novel safe and effective anticancer therapy with IP administration of DHMEQ is proposed.

DISCOVERY AND MECHANISTIC STUDY OF NF-κB INHIBITOR DHMEQ

About 20 years ago, we were screening NF-κB inhibitors of low molecular weight from microorganisms and plants. We looked for the compounds that inhibited TNF-α-induced expression of the κB-luciferase system in human T-cell leukemia Jurkat cells. One of our collaborators isolated a novel epoxyquinone compound called epoxyquinomicin (Fig. 1) as a weak antibiotic from the microorganism *Amycolatopsis*[6]. Although it was structurally related to panepoxydone[7] and cycloepoxydone[8], which were known to inhibit NF-κB, epoxyquinomicin did not inhibit NF-κB. However, after removal of the protruding hydroxymethyl moiety, the designed compound, DHMEQ (Fig. 1), did inhibit NF-κB activity[9]. It inhibited TNF-α-induced activation of NF-κB activity in Jurkat cells. We also found that DHMEQ ameliorated inflammation in collagen-induced rheumatoid arthritis in mice when administered by the IP route[9]. A regioisomer of DHMEQ was used as a negative control, and it did not inhibit either NF-κB activity or the rheumatoid model[9]. In this way, we found a new NF-κB inhibitor active in animal experiments.

Racemic DHMEQ can be synthesized from 2,5-dimethoxyaniline in five steps[10] and can be separated into each enantiomer practically by lipase[11]. Lipase reacts with racemic dihexanoyl-DHMEQ to give (−)-DHMEQ and monohexanoyl-(+)-DHMEQ that can be easily removed by the difference in solubility. (−)-DHMEQ is about 10 times more effective than (+)-DHMEQ in inhibiting NF-κB[10]. (−)-DHMEQ is mainly used for cellular experiments, while racemic DHMEQ is used for animal experiments and in the development of drugs.

Cellular NF-κB is activated by various extracellular ligands, and Figure 2 shows the signaling mechanism of NF-κB activation. For the inhibitory mechanism of DHMEQ, we first reported that it would inhibit the nuclear translocation of NF-κB[12]. However, later, we have found that DHMEQ covalently binds to the Rel family proteins to inhibit their DNA-binding activity[13]. Inhibition of NF-κB nuclear translocation is likely to be a result after the inhibition of DNA binding[14]. Typical NF-κB is a heterodimer consisting of two Rel family proteins. Rel family proteins include p65, RelB, c-Rel, p50, and p52. (−)-DHMEQ was found to bind to p65 covalently with a 1:1 stoichiometry as revealed by surface plasmon resonance (SPR) and MALDI-TOF mass spectrum (MS) analyses. MS analysis of the chymotrypsin-digested peptide suggested the binding of (−)-DHMEQ to a specific cysteine residue. In the case of p65, DHMEQ only binds to the Cys38 residue, which is located close to the DNA. The binding is specific, since it does not bind to other cysteine residues such as Cys120 in p65. Observation of the adduct of p65 and (−)-DHMEQ in MALDI-TOF MS would indicate that the (−)-DHMEQ–cysteine binding is a covalent one. The formation of DHMEQ–cysteine covalent binding in the protein was supported by chemical synthesis of the conjugate molecule[13,15] (Fig. 3). Since (−)-DHMEQ covalently binds to the cysteine residue in an NF-κB molecule, the inhibitory effect is irreversible. LPS induces

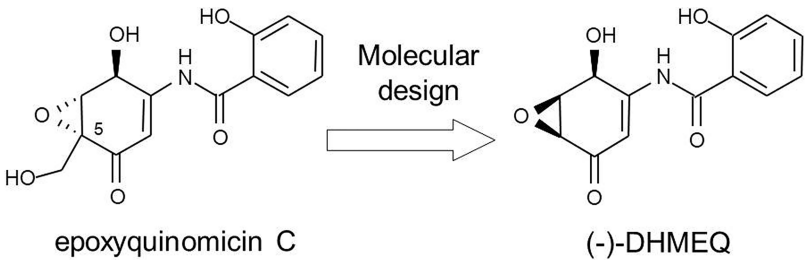

Figure 1. Molecular design of dehydroxymethylepoxyquinomicin (DHMEQ) based on the structure of epoxyquinomicin C.

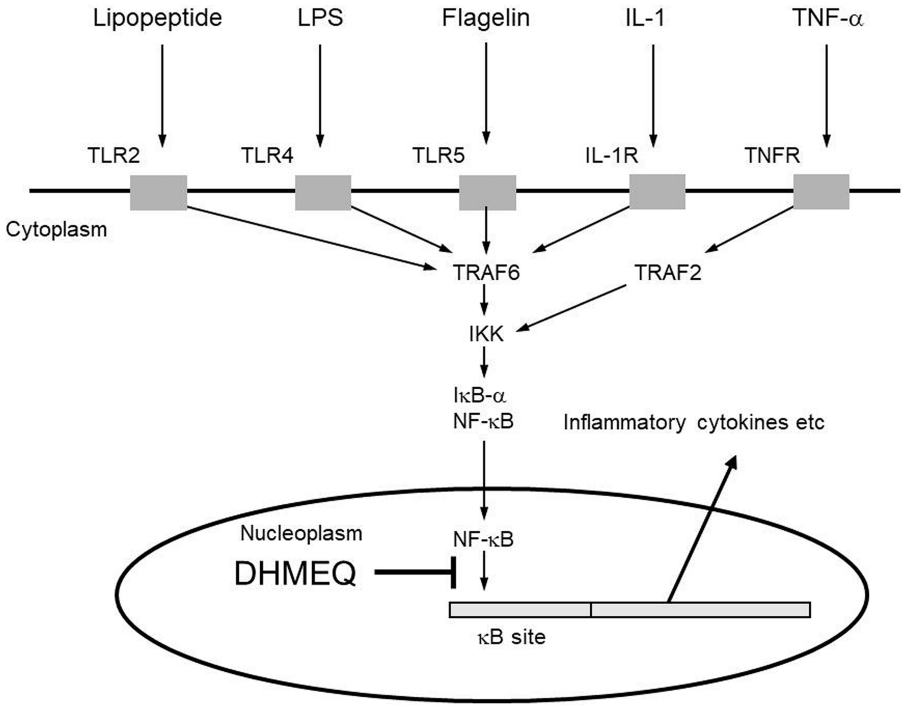

Figure 2. Main signaling pathways for NF-κB activation. DHMEQ inhibits the last step, NF-κB–DNA binding.

NF-κB activation in 30 min in macrophage-like mouse monocytic leukemia RAW264.7 cells. (−)-DHMEQ was added for only 15 min and then washed out. Even 8 h after removal, the cells were dormant, and LPS did not activate NF-κB, suggesting that NF-κB would be inhibited irreversibly[16] (Fig. 4). Although (−)-DHMEQ is considered to bind to cysteine SH, it should not bind in a nonspecific manner. It is likely that DHMEQ enters into a specific pocket in the NF-κB component protein via a key and lock mechanism to bind to the limited cysteine residue.

The signaling pathways for NF-κB are now classified into canonical and noncanonical. The former consists mainly of p65 and p50 and is important for general inflammation and cancer progression, while the latter consists of RelB and p52 and is important for B-cell generation and autoimmunity. All Rel family proteins possess specific cysteine residues essential for their DNA binding. (−)-DHMEQ binds to the cysteine residues of p65, cRel, RelB, and p50, but not of p52. In the case of RelB, (−)-DHMEQ inhibits not only DNA-binding of RelB but also its interaction with importin[17]. It also induces instability of RelB. Thus, (−)-DHMEQ specifically binds to a cysteine residue in both the canonical (p65 and p50) and the noncanonical (RelB) components, and it inhibits both the NF-κBs (Fig. 5).

Thus, DHMEQ inhibits the last step of NF-κB activation, which is the DNA binding (Fig. 2). These mechanisms may explain the highly selective NF-κB inhibition and the low toxic effects of DHMEQ in cells and in animals.

ANTICANCER ACTIVITY OF DHMEQ BY IP ADMINISTRATION IN ANIMAL EXPERIMENTS

Since DHMEQ was discovered in 2000, it has been widely used in animal experiments to suppress cancer and inflammation. Especially, DHMEQ showed potent anticancer and antileukemia activities in many animal experiments by IP administration without showing any toxicity.

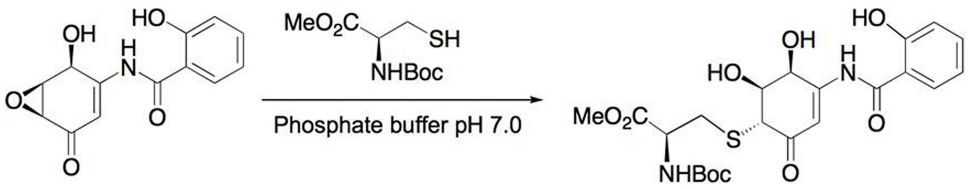

Figure 3. (−)-DHMEQ reacts with blocked L-cysteine to give a conjugate in a phosphate buffer.

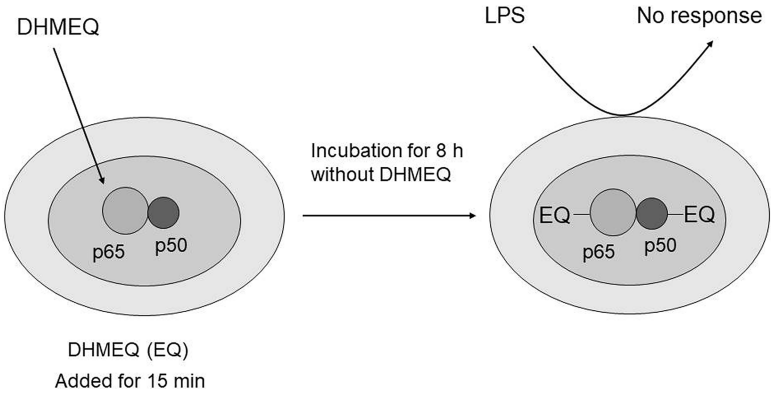

Figure 4. Inhibition of NF-κB activity is irreversible. DHMEQ was added for 15 min and washed away. After 8 h, the cells were still dormant on lipopolysaccharide (LPS)-induced NF-κB activation.

The effective concentration of DHMEQ in cultured cells is 1–10 μg/ml (3.8–38 μM), while the cytotoxic activity of DHMEQ is comparatively weak, and it can kill most cancer cells only at 30 g/ml (114 μM) or above. However, it showed potent anticancer activity in many animal experiments at 2–12 μg/kg by IP administration. Kikuchi and colleagues first reported its anticancer activity in 2003 on the mouse model of prostate carcinoma[18]. Prostate cancer cell line JCA-1 is derived from hormone-insensitive cancer and secretes multiple inflammatory cytokines and granulocyte colony-stimulating factor. IP administration of DHMEQ at 8 mg/kg daily for 2 weeks suppressed the JCA-1 subcutaneous growth of JCA-1 tumor cells in nude mice[18]. DHMEQ also enhanced the radiosensitivity of prostate carcinoma PC-3 cells in vivo[19].

The same group also reported the anticancer activity on bladder carcinoma. The cancer cell line KU-19-19 was derived from a patient with invasive bladder cancer with marked leukocytosis. Such cells secrete multiple inflammatory cytokines. DHMEQ inhibited the subcutaneous KU-19-19 tumor growth in nude mice when given by IP administration[20]. More recently, Ito and colleagues investigated the anticancer effects of DHMEQ in CDDP-resistant bladder cancer cells[21]. Invasive bladder carcinoma cell line T24 and its CDDP-resistant cell line T24PR were used. DHMEQ alone effectively inhibited the growth of T24PR cells using mouse xenograft models. Moreover, the mean volume of tumors treated with a combination of DHMEQ and paclitaxel was significantly smaller than those treated with paclitaxel alone. Thus, IP administration of DHMEQ alone showed anticancer activity, and this also increased the sensitivity to paclitaxel[21].

IP administration of DHMEQ, three times a week for 8 weeks at 12 mg/kg, strongly inhibited the tumor growth of hormone-insensitive breast carcinoma MDA-MB-231 cells in SCID mice[22]. IP administration at 4 mg/kg also inhibited the growth of hormone-sensitive MCF-7 cells, in which NF-κB was not activated[22]. No toxicity was observed during either experiment. Goto and colleagues prepared cancer stem cells from human breast cancer. These cells in the stem cell fraction showed higher tumorigenicity than non-stem cell fraction in mice. DHMEQ inhibited the growth of purely prepared breast cancer stem cells in mice[23,24].

Thyroid carcinoma would be one of the more common cancers to occur after the radiation accidents in

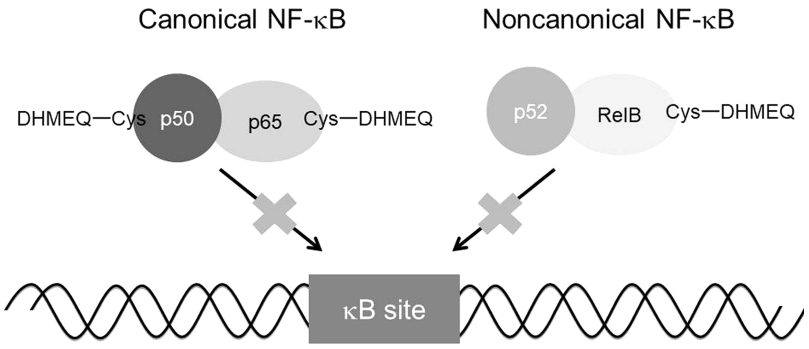

Figure 5. DHMEQ can inhibit both canonical and noncanonical NF-κBs.

Chernobyl, Ukraine, and Fukushima, Japan. It is often resistant to chemotherapy. IP administration of DHMEQ to thyroid carcinoma-bearing nude mice significantly inhibited tumor growth without side effects and increased the number of apoptotic cells in histological sections of tumors treated with DHMEQ[25]. IP administration of DHMEQ also inhibited the growth of thyroid carcinoma cells with a BRAF mutation that enhanced metastasis in mice[26]. Anaplastic thyroid carcinoma (ATC) is one of the most aggressive and refractory cancers. Mitsutake and colleagues studied the character of ATC cancer stem cells. They found that JAK/STAT3 signaling and NF-κB would be important for the stem cell character. IP administration of either a STAT inhibitor or DHMEQ inhibited the growth of ATC in mice[27].

Fluke-induced cholangiocarcinoma can be caused by eating raw fish in rivers or lakes. It is still common in Thailand, and it is one of the most difficult cancers to treat. There is currently no effective chemotherapeutic regimen for it. Seubwai and colleagues prepared cell lines from cholangiocarcinoma of patients in Thailand and reported that IP administration of DHMEQ inhibited the growth of cholangiocarcinoma in mice[28]. DHMEQ effectively reduced tumor size in cholangiocarcinoma-inoculated mice without any toxicity.

Glioblastoma multiforme (GBM) is one of the most malignant types of brain tumor. Recent studies have indicated that NF-κB, especially p65, is consistently activated in human GBM. GBM U87 cells were implanted either subcutaneously in the back of each nude mouse or intracranially to the forebrain of nude mice. IP administration of DHMEQ showed anticancer activity in vivo in both the subcutaneous and intracranial models[29]. These results suggest that the targeting of NF-κB by DHMEQ may serve as a promising treatment modality in GBM.

NF-κB in cancer cells often induces immunosuppression in patients to facilitate cancer progression. DHMEQ inhibited the NF-κB-dependent immunosuppression in ovarian carcinoma-bearing mice[30]. Although T-cell immunity is considered to be an advantageous factor of epithelial ovarian cancer patients, immunosuppressive conditions are often found to lower the antitumor immune responses. In the epithelial ovarian cancer patients, an increase in plasma IL-6 and IL-8 was observed. IP administration of DHMEQ to nude mice implanted with human epithelial ovarian cancer cells resulted in the restoration of T-cell stimulatory activity of murine dendritic cells along with the reduction in tumor accumulation. IP administration of DHMEQ to tumor-bearing mice also enhanced the antitumor effects of transferred murine naive T cells. Thus, NF-κB is involved in immunosuppression induced by human epithelial ovarian cancer cells, and its inhibitor, such as DHMEQ, may restore anticancer immune responses. IP administration of DHMEQ, as described below, should lower the blood level of inflammatory cytokines.

IP administration shows antimetastasis activity in vivo. Tumors in the pancreas often metastasize to the liver. Suzuki and colleagues studied the effects of DHMEQ on the inhibition of liver metastasis of human pancreatic cancer in a mouse model[31]. Human pancreatic adenocarcinoma AsPC-1 cells were injected into the portal vein of mice. These cells metastasized to the liver forming the foci. Mice were treated with DHMEQ and gemcitabine, alone or in combination. DHMEQ alone inhibited the metastasis. The combination of gemcitabine and DHMEQ showed a stronger antitumor effect than either monotherapy alone. Apoptosis induction in the metastatic foci was most prominent in the DHMEQ and gemcitabine group. Angiogenesis was also inhibited in the DHMEQ and/or gemcitabine groups. On the other hand, the growth of cultured cells was not inhibited synergistically, although each monotherapy had individual cytotoxic effects. For the mechanism, DHMEQ alone markedly downregulated the expression of MMP-9 and IL-8 in metastatic foci. These results demonstrate that DHMEQ can exert anticancer effects by inhibiting angiogenesis and tumor cell invasion.

DHMEQ is also effective to ameliorate leukemia in animal models. Adult T-cell leukemia (ATL) is caused by human T-cell leukemia virus type I (HTLV-1). It is mainly found in the southern islands of Japan, including Kyushu, and is extremely resistant to chemotherapy. Constitutive activation of NF-κB is found in most ATL patient cells. It is due to the Tax protein of HTLV-1, although Tax is not found in the ATL patient cells. IP administration of DHMEQ shows anticancer activity against Tax-positive ATL tumors in mice[32,33]. IP administration of DHMEQ also inhibits the growth of Tax-deficient ATL tumors transplanted subcutaneously or in the peritoneal cavity[34].

Primary effusion lymphoma is another virus-induced lymphoma. This lymphoma is caused by human herpes virus 8. IP administration of DHMEQ inhibited the growth of primary effusion lymphoma in mice[35].

DHMEQ also inhibited the growth of multiple myeloma cells in mice by IP administration[36]. Proteasome inhibitor PS-341 is clinically used for the treatment of multiple myeloma[37]. This compound inhibits the degradation of I-κBα, which results in inhibition of NF-κB. Tatetsu and colleagues employed multiple myeloma cell line 12PE, in which I-κBα is deficient. Therefore, this myeloma should be resistant to PS-341. DHMEQ also inhibited the growth of this tumor in mice when given by IP administration[38].

IP administration of DHMEQ also inhibited the growth of Hodgkin lymphoma in mice. Hodgkin/Reed–Sternberg cells were employed, and the antitumor effects were observed by IP administration of 12 mg/kg of DHMEQ three times a week for 1 month[39].

Table 1. Carcinoma and Leukemia Models Suppressed by Intraperitoneal (IP) Administration of Dehydroxymethylepoxy quinomicin (DHMEQ) in Animal Experiments

Cancer or Leukemia	Reference(s)
Prostate carcinoma	18,19
Bladder carcinoma	20,21
Breast carcinoma	22
Breast stem cell cancer	23,24
Thyroid carcinoma	25–27
Cholangiocarcinoma	28
Glioblastoma	29
Ovarian carcinoma	30
Liver metastasis	31
Adult T-cell leukemia	32–34
Primary effusion lymphoma	35
Multiple myeloma	36–38
Hodgkin lymphoma	39

Thus, IP administration of DHMEQ ameliorated various human solid cancer and leukemia models in animals (Table 1). No toxicity was reported in any of the animal experiments.

MECHANISM FOR ANTICANCER ACTIVITY OF DHMEQ BY IP ADMINISTRATION

DHMEQ showed anticancer activity on various animal models by IP administration. IP administration is often used in rodent experiments because of the technical simplicity. When a chemical is injected into the peritoneal cavity, it is usually absorbed by the capillaries to systemically circulate in the blood vessels. In the case of DHMEQ, however, no DHMEQ was found in the blood after IP administration[40]. It was also found that DHMEQ was easily degraded in the presence of blood cells[41]. Therefore, it is likely that DHMEQ would act only in the peritoneal cavity (Fig. 6). Concentrations of DHMEQ after injection were found to be high enough to inhibit NF-κB in peritoneal cells even after 1 h[40], which should inhibit NF-κB of the inflammatory cells there. Although DHMEQ can reach only the peritoneal cavity, its IP administration can inhibit solid cancer localized mostly subcutaneously on the back of mice. Moreover, it was effective to suppress the intracranial model of glioblastoma[29].

The next question is how DHMEQ in the peritoneal cavity is effective to suppress peripheral cancer and leukemia. The tumor microenvironment is the environment around a tumor, including the blood vessels, leukocytes, tumor-associated macrophages (TAM)[42,43], cancer-associated fibroblasts (CAF)[44], inflammatory cytokines, and the extracellular matrix. This environment often activates the growth of tumors. Especially, inflammatory cytokines produced by cancer cells or environmental cells often promote cancer growth[45,46]. Bearing of cancer often increases the concentration of inflammatory cytokines in the blood, a condition which is called cachexia. IP administration of DHMEQ ameliorated cachexia by lowering the blood level of IL-6 in prostate cancer-bearing mice[47]. It is likely that IP administration can reduce the blood level of various inflammatory cytokines in cancer-bearing mice (Fig. 7).

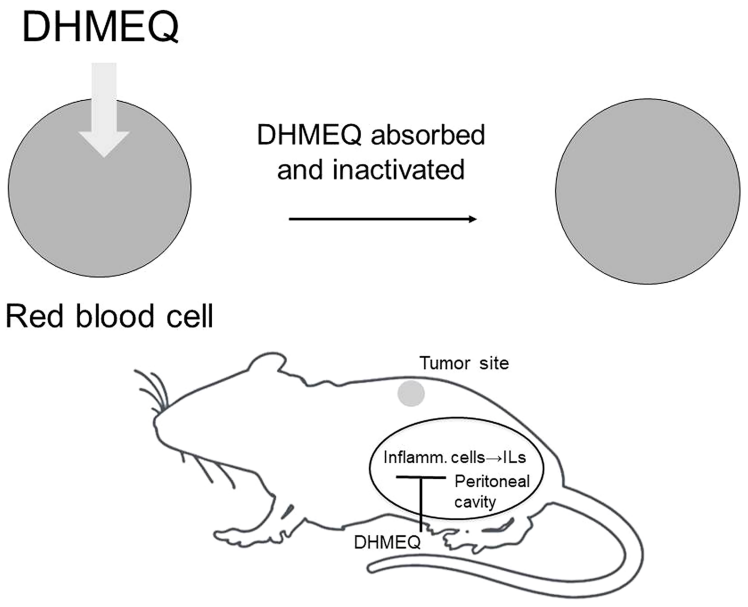

Figure 6. DHMEQ does not appear in the blood after intraperitoneal administration. This is because DHMEQ is quickly absorbed and inactivated by blood cells such as erythrocytes.

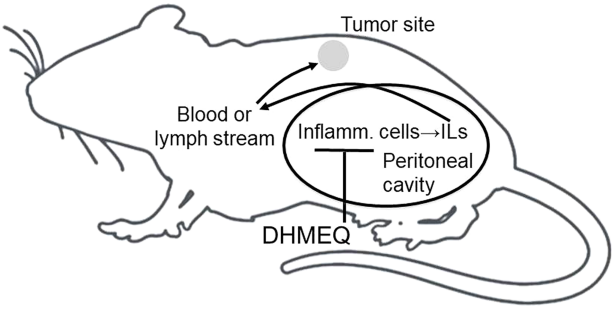

Figure 7. Inhibition of NF-κB by DHMEQ in the peritoneal cells is likely to lower the blood level of inflammatory cytokines, thereby changing the cancer microenvironment.

Almost 50 years ago Vernon-Roberts elucidated the traffic of macrophages in the body using radioactively labeled macrophages in mice. The peritoneal cavity was found to be an important space for macrophages[48]. Macrophages reside in the peritoneal cavity and move to areas of inflammation. NF-κB activates chemokine and chemokine receptors[49], and DHMEQ inhibited the expression of those proteins[50]. Therefore, it is likely that the migration of macrophages from the peritoneal cavity to adjacent regions would be inhibited by DHMEQ.

Previously, we reported that DHMEQ inhibited LPS-induced secretions of various inflammatory cytokines in a mouse macrophage-like leukemia cell line[51] and in primary cultured mouse macrophages[52]. More recently, we reported that DHMEQ inhibited primary cultured human peritoneal cells[53,54]. We studied the effects of DHMEQ on the inflammatory behavior of human peritoneal mesothelial cells (HPMCs). DHMEQ was not toxic at 10 μg/ml (38 μM) to HPMC. DHMEQ at 10 μg/ml lowered IL-6, MCP-1, and hyaluronan production in unstimulated or IL-1-stimulated peritoneal cells (Fig. 8). These effects likely occur due to the suppression of gene expression responsible for the synthesis of these molecules. DHMEQ also modified the effects of the effluent dialysates from continuous ambulatory peritoneal dialysis patients on the function of HPMC. In the presence of dialysate, DHMEQ inhibited the collagen synthesis by HPMC. These results show that DHMEQ effectively reduces the inflammatory response in HPMC and prevents dialysate-induced proliferation and collagen synthesis in these cells. These results show that DHMEQ would be useful for the prevention of progressive dialysis-induced damage to the peritoneum. In addition, DHMEQ was demonstrated to be active in inhibiting inflammatory responses in human peritoneal cells.

Thus, as the mechanism of DHMEQ IP therapy on cancer, the drug acts only in the peritoneal cavity. This mechanism can explain all the characters of DHMEQ. DHMEQ is not cytotoxic in cultured cells, and the effective concentration to inhibit NF-κB is not particularly low. It is unstable in the body, but the effective dose is low in animal experiments. It shows no toxicity in animals, although NF-κB is involved in many physiological signaling pathways.

DISCUSSION

IP administration of DHMEQ has been widely used to suppress inflammatory disease models in animals[40], such as rheumatoid arthritis, kidney inflammation, and sepsis. Among its anti-inflammatory activities, IP administration of DHMEQ was shown to ameliorate organ transplantation in animal experiments. It inhibited allograft rejection and increased graft survival in heart[55] and islet[56] transplantations in mice. Furthermore, it was as effective as tacrolimus, the most popular immunosuppressive agent, and worked synergistically[55]. Therefore, IP DHMEQ therapy appears to be an immunosuppressive therapy. Cancer immunotherapy was initiated by George Mathe in France using BCG for leukemia in the middle of the 20th century[57]. In the years following, cancer immunotherapy has been considered to be occasionally effective yet often ineffective. Recently, cancer immunotherapy has been gaining popularity in regard to immune-activating antibodies. However, immune-activating therapy may not always be advantageous in curing disease.

In the case of peripheral cancers, the anticancer mechanism is considered to include a decrease in the blood concentration of inflammatory cytokines as discussed above. If the target is in the peritoneal cavity, the mechanism should be simpler. We should like to test the effects on metastatic colon cancer, metastatic ovarian cancer, and appendix cancer in animal experiments.

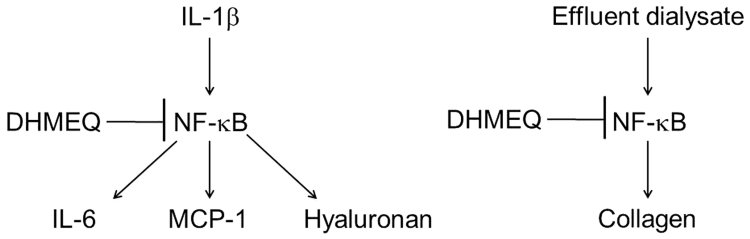

Figure 8. Inhibition of inflammatory cytokine production by DHMEQ in primary cultured human peritoneal cells.

The unstable character of DHMEQ may contribute to the fewer side effects by NF-κB inhibition. However, we are also interested in the stable analogs of this compound. The unstable character of DHMEQ should be derived from the existence of epoxide moiety. Then we designed and synthesized the epoxide-free analog (*S*)-β-salicyloylamino-α-exo-methylene-γ-butyrolactone (SEMBL)[58]. SEMBL was more stable than DHMEQ in a phosphate buffer and showed ant-inflammatory activities in cultured macrophage-like cells. Its in vivo toxicity and anticancer activity remain evaluated.

CONCLUSIONS

DHMEQ has been used in many laboratories around the world to reveal its effectiveness to various cancers and inflammation in animal experiments. There have been no toxic observations reported thus far, and such therapy should be safe because of the limited localization of DHMEQ. IP administration of DHMEQ is essentially an immunosuppressive therapy. Excessive immunity may be harmful considering cancer progression. DHMEQ IP therapy may be useful for the treatment of immunity-activated cancer and leukemia. Clinical application of DHMEQ IP therapy is being developed by PeritonTreat Ltd. in Russia.

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