



REVIEW PAPERS

DOI: <https://doi.org/10.20883/jms.352>

Causes and mechanisms of peritoneal fibrosis and possible application of NF- κ B inhibitor for prevention and treatment

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ABSTRACT

Peritoneal dialysis is an established form of the renal replacement therapy in patients with end stage renal failure. Continuous Ambulatory Peritoneal Dialysis developed by Moncrief and Popovich in 1975 was a revolutionary event, and contributed much to wide application of that form of treatment in uremic patients. On the other hand, the weak point of peritoneal dialysis is relatively short viability of the peritoneum as the dialysis membrane. Two main peritoneal pathologies are observed in patients treated with that form of renal replacement therapy: neovascularization of the membrane what causes increased peritoneal permeability to osmotic solutes and ultrafiltration failure, and fibrosis which results also in ultrafiltration failure due to its decreased hydraulic conductivity and reduced permeability to uremic toxins. Meanwhile, an NF- κ B inhibitor DHMEQ was discovered in 2000 and has been successfully used to suppress various inflammatory and neoplastic disease models. NF- κ B is likely to be involved in the mechanism of peritoneal inflammation and fibrosis. We have studied whether DHMEQ would inhibit cellular model of peritoneal inflammation and fibrosis. It inhibited inflammatory cytokine and collagen productions in primary culture of human peritoneal mesothelial cells, and intraperitoneal administration of NF- κ B inhibitors would be useful to suppress peritoneal fibrosis.

Keywords: fibrosis, NF- κ B, peritoneal dialysis.

Peritoneal membrane fibrosis during dialysis: causes and mechanisms

Peritoneal dialysis is an established form of the renal replacement therapy in patients with end stage renal failure. Development in 1975 by Moncrief and Popovich technique of Continuous Ambulatory Peritoneal Dialysis was a revolutionary event which strongly contributed to wide application of that form of treatment in uremic patients [1]. Peritoneal dialysis is cheaper than hemodialysis and provides better quality of life and results in comparable to hemodialysis survival during first 5 years of treatment [2]. Additio-

nally peritoneal dialysis, better than hemodialysis, preserves residual kidney function what may result in lower amount of systemic complications [3]. Patients treated with peritoneal dialysis have lower risk, than hemodialysis patients, of complications after renal transplantation [4]. In 2008 about 200,000 and in 2012 approximately 300,000 patients were treated with peritoneal dialysis worldwide [5].

The weak point of peritoneal dialysis is relatively short viability of the peritoneum as the dialysis membrane. Approximately 50% of patients treated with chronic peritoneal dialysis for more than 6 years develop ultrafiltration failure what translates into lower efficiency of removal of

water and uremic solutes into the dialysate [6]. Two main peritoneal pathologies are observed in patients treated with that form of renal replacement therapy: neovascularization of the membrane what causes increased peritoneal permeability to osmotic solutes and ultrafiltration failure, and fibrosis which results also in ultrafiltration failure due to its decreased hydraulic conductivity and reduced permeability to uremic toxins [7]. In the extreme situations peritoneal overgrowth of the connective tissue causes encapsulating peritoneal sclerosis, which consequence is not only ultrafiltration failure but also entrapment of intestines in the fibrotic tissue leading to life threatening bowels obstruction [8]. Prevalence of that pathology in peritoneal dialysis patients is proportional to length of the renal replacement therapy and in some studies approaches 18.4% [9].

Besides length of therapy the other factors predisposing to the morphological changes in the peritoneum are diabetes mellitus and uremia, however dialysis related factors are much more important [10]. Episodes of peritonitis may accelerate progression of the dialysis induced changes in the structure and function of the peritoneum leading to ultrafiltration failure [11]. However even without episodes of peritonitis repeated infusion of the dialysis fluid into the peritoneal cavity induces chronic "sterile" inflammatory reaction which contributes both to neovascularization of the peritoneum and its fibrosis [12]. Implantation of the peritoneal catheter and intraperitoneal infusion of the sterile dialysis fluid induce inflammation, simply due to mechanical irritation of the peritoneum [13].

One of the most important factor causing intraperitoneal inflammation and fibrotic changes in the peritoneum is low biocompatibility of the fluids used during peritoneal dialysis. Biocompatibility of the dialysis solutions is related to their low pH, hyperosmolality, high concentration of glucose, presence of glucose degradation products (GDP) and lactate. Exposure of the mesothelial cells in *in vitro* culture to the acidic dialysis fluid which subsequently, to imitate the *in vivo* conditions, was diluted with the effluent dialysate from dialyzed patients resulted in their stimulation reflected by increased synthesis of interleukin 6 [14]. In rats dialyzed during 6 weeks with dialysis fluid with neutral pH and low concentration of GDP, intraperitoneal inflammation

was lower than in animals treated with standard acidic, high GDP dialysis fluid. Additionally effluent dialysate collected from the first group of animals caused weaker *in vitro* synthesis of collagen in mesothelial cells, what was reflected *in vivo* by reduced fibrosis of the peritoneum [15].

Glucose is used in the dialysis fluids in the unphysiologically high concentrations up to 235 mmol/L to create osmotic gradient between bloodstream and dialysate, necessary for induction of the transperitoneal ultrafiltration of fluid. However glucose toxic effect towards the peritoneal mesothelial cells in such scenario depends not only on hyperosmolality [16]. Oxidative stress in mesothelial cells exposed to high glucose concentration induces their senescence [17] apoptosis [18] and epithelial to mesenchymal transformation (EMT) [19]. Mesothelial senescence, apoptosis or mesenchymal transformation may lead to progression of the peritoneal fibrosis [20, 21].

Molecular mechanisms of EMT of mesothelial cells and peritoneal fibrosis are described in various recent publications, but still some details are missing. [22]. Mechanisms of these disorders are not identical in various pathological processes and therefore we should not translate directly observations from studies on various models of fibrosis to the conditions in the peritoneum during chronic peritoneal dialysis. Some mechanisms causing EMT in various experimental models have opposite effect in peritoneal mesothelium. For example, Hepatocyte Growth Factor prevents EMT in mesothelial cells, whereas has opposite effect in hepatocytes [22, 23]. Another example is the role of p38MAPK, which induces synthesis of inflammatory cytokines potentially favoring process of EMT but on the other hand it stimulates E-cadherin expression in mesothelial cells, which prevents their EMT by modulating the TAK1-NF- κ B pathway [24].

An important role in EMT of the mesothelial cells during peritoneal dialysis plays TGF- β 1, which production in these cells is enhanced in presence of high glucose concentration [25]. TGF β cytokines induce mesothelial EMT by Smad-dependent and Smad-independent pathways [26]. TGF β 1 downregulates in mesothelial cells BMP-7 signaling, which determines the maintenance of the epithelial phenotype of these cells [27]. TGF β 1 causes p38 and JNK MAPK activation pathway due to activation of TAK1, which

is an activator of NF- κ B. Inhibition of NF- κ B in mesothelial cells may slow down and even partially reverse their EMT [28]. Activation of JNK MAPK pathway via ligand binding to Toll-like receptor that has a cytoplasmic signaling homologous to IL-1, results in activation of NF- κ B and MAPK. IL-1 is a stronger inducer of NF- κ B activation in mesothelial cells than TGF β 1 but their effects are additive. Inhibition of NF- κ B in mesothelial cells from peritoneal dialysis patients prevents their EMT after treatment with TGF β and IL-1 [29]. These observations prove the role of intraperitoneal inflammation during peritoneal dialysis in progression of the peritoneal fibrosis.

Can we slow down progression of peritoneal fibrosis during chronic peritoneal dialysis?

Bioincompatible dialysis fluids and unphysiological procedure of peritoneal dialysis which result in constant induction of the intraperitoneal inflammatory response are the main causes of the peritoneal pathology in that group of patients. Despite several improvements in the composition of the dialysis fluids such as introduction of dialysis solutions with neutral pH, lower GDP concentrations, alternative to glucose osmotic solutes, problem of peritoneal damage during chronic dialysis still exists. Results from clinical studies are conflicting. In long term study performed in Netherlands, reduced incidence of peritonitis, better transperitoneal ultrafiltration were observed in patients dialyzed with low GDP and neutral pH solutions, as compared to a group treated with standard fluids with high GDP and low pH. However no differences were observed between the two studied groups in peritoneal transport characteristics, or intensity of the intraperitoneal inflammation [30]. In another study from Korea application of a new dialysis fluid with normal pH and low GDP level did not affect the peritoneal permeability to solutes and water but the authors observed reduction in the intensity of the intraperitoneal inflammation [31]. One can say that introduction of new more biocompatible dialysis fluids reduced but not eliminated the negative effect of peritoneal dialysis on the peritoneal structure and function. Problem of the peritoneal damage probable cannot be totally eliminated because pro-

cedure of peritoneal dialysis based on repeated intraperitoneal infusions of the dialysis fluid into the peritoneal cavity is not biocompatible *per se*. An interesting study, supporting that statement was done by Aoki and colleagues, who constructed *in vitro* model of peritoneal cavity lined with mesothelial and endothelial cells. Repeated infusion of physiological solutions (ie. Eagles medium) or dialysis fluids resulted in inhibition of nitric oxide synthase activity both in endothelial and mesothelial cells and EMT of mesothelial cells [32]. These results suggest that repeated infusion of any solution into the peritoneal cavity will trigger EMT of mesothelium. Therefore there is still a big interest in search for mechanisms and agents which can reduce the peritoneal injury during chronic peritoneal dialysis.

Some investigators hypothesized that high glucose induced peritoneal fibrosis is linked with angiotensin II acting via AT1Rs with subsequent activation of the intracellular signaling, such as ie. NF- κ B, leading to fibrosis [33]. Mesothelial cells exposed to high glucose concentration synthesize various elements of the renin-angiotensin system [34]. In addition to high glucose effect, low pH of the dialysis fluid may increase angiotensin receptors expression, what may result in enhancement of fibrosis [35]. In experimental model of chronic peritoneal dialysis in rats use of angiotensin inhibitors valsartan or lisinopril resulted in reduced peritoneal fibrosis caused by repeated exposure to high glucose dialysis fluid [36].

Recently various treatment leading to reduction of peritoneal fibrosis in conditions of peritoneal dialysis were proposed. The final target of these studies was defined as inhibition of the dialysis induced peritoneal fibrosis. Yang and coworkers found that during 4 months peritoneal dialysis performed with high glucose fluid in mice, intraperitoneal supplementation of 1,25(OH) $_2$ D $_3$ at weekly intervals, attenuated dialysis induced mesothelial apoptosis, EMT and fibrosis of peritoneum [37]. In another study Wu and coworkers found increased expression of TGF- β , EMT and autophagy in peritoneal mesothelial cells obtained from the effluent dialysate from patients treated with chronic peritoneal dialysis. In experiments on mesothelial cells in *in vitro* culture they demonstrated that inhibition of the cellular autophagy reduced glucose induced EMT and expression of fibrotic markers [38]. Researchers

from Italy demonstrated that extract from olive leaf blocks in *in vitro* cultured mesothelial cells their TGF- β induced EMT and expression of cellular markers of fibrosis [39]. Cheng and coworkers demonstrated that hydrogen sulfide inhibits EMT of mesothelial cells in *in vitro* culture and reduced peritoneal fibrosis in a rat model of chronic peritoneal dialysis [40]. Inhibition of heparanase blocks glucose induced EMT of the mesothelial cells and changes of their monolayers permeability studied in *in vitro* model [41]. Another approach leading to prevention of peritoneal fibrosis is use of the antioxidants. Wakabayashi and coworkers induced peritoneal fibrosis in rats with chlorhexidine gluconate and simultaneous oral supplementation with the natural antioxidant astaxanthin reduced the peritoneal expression of TGF- β , snail mRNA and type 3 collagen with decrease of the peritoneal thickness [42]. Similar observations with the another antioxidant selenium come from *in vitro* experiments on human mesothelial cells [43]. In another study on rats repeatedly infused with the dialysis fluid and endotoxin to induce peritonitis, inhibition of TAK1-NF- κ B pathway with the PPAR β/δ agonist GW501516 prevented peritoneal fibrosis. Additionally in *in vitro* cultured rat mesothelial cells inhibition of TAK1-NF- κ B pathway reduced glucose induced inflammation [44]. Kitamura and coworkers reported protective effect against the GDP induced peritoneal fibrosis in mice, of a tea polyphenol (-)-epigallocatechin gallate which inhibited NF- κ B pathway [45]. Washida and coworkers injected male rats with chlorhexidine what induced peritoneal thickening with the overgrowth of the connective tissue, macrophage infiltration and angiogenesis [46]. In animals simultaneously treated with Rho-kinase inhibitor fasudil fibrotic changes were significantly reduced and the expression of markers of tissue fibrosis, such as TGF- β , fibronectin and α -smooth muscle cell actin was reduced [46].

Presented above studies show the wide range of possible approaches aimed at inhibition of the dialysis induced peritoneal fibrosis. However most of the results come from acute studies or experiments lasting 3–4 weeks and the used doses of the tested substances sometimes were very high what potentially could induce the negative side effects [45]. Therefore further studies are required to find out/exclude the potential side effects of such a long term treatment. It seems

to be an option to test more than one substance at the same time to evaluate if due to different mechanisms of action they can have synergistic effect preventing the peritoneal fibrosis in conditions of peritoneal dialysis. After verification of these substances in further *in vitro* and *in vivo* experiments on animals, their final suitability for prevention of the peritoneal fibrosis in patients treated with chronic peritoneal dialysis requires the clinical studies.

Discovery and inhibitory mechanism of NF- κ B inhibitor DHMEQ

In the course of our search for NF- κ B inhibitors of low molecular weight, we designed and synthesized new NF- κ B inhibitors based on the structure of epoxyquinomicin C (**Figure 1**). Epoxyquinomicin C was isolated as a weak antibiotic, but it showed no toxicity in animals. Although the structurally related compounds such as panepoxydone [47] and cycloepoxydone [48] were reported to inhibit NF- κ B, epoxyquinomicin C did not inhibit NF- κ B. However, after the removal of the protruding hydroxymethyl moiety, the designed compound, dehydroxymethylepoxyquinomicin (DHMEQ, **Figure 1**), did inhibit NF- κ B activity [49]. We also found that DHMEQ ameliorated inflammation in a collagen-induced rheumatoid arthritis in mice when administered by the IP route [49]. In this way, we found a new NF- κ B inhibitor active in animal experiment.

Racemic DHMEQ can be synthesized from 2,5-dimethoxyaniline in 5 steps [50], and can be separated into each enantiomer practically by lipase [51]. Lipase reacts with racemic dihexanoyl-DHMEQ to give (-)-DHMEQ and monohexanoyl-(+)-DHMEQ that can be easily removed by difference of solubility. (-)-DHMEQ is about 10 times more effective than (+)-DHMEQ in inhibiting NF- κ B [50]. (-)-DHMEQ is mainly used for the cellular experiments, and racemic DHMEQ for the animal experiments. For the development into drugs, racemic DHMEQ is being used.

For the mechanism of DHMEQ, we have firstly reported that it inhibits the nuclear translocation of NF- κ B [52]. However, later, we have found that DHMEQ directly binds to the Rel-family proteins to inhibit their DNA-binding activity [53]. Inhibition of NF- κ B nuclear translocation is likely to be

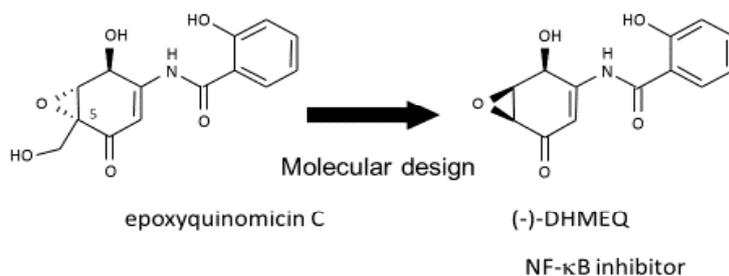


Figure 1. Molecular design of NF-κB inhibitor DHMEQ based on the structure of antibiotic epoxyquinomicin C

a result after the inhibition of DNA binding [54]. Rel family proteins are the constituents of NF-κB molecules including 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 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 [55]. Since (-)-DHMEQ covalently binds to the cysteine residue in an NF-κB molecule, the inhibitory effect is irreversible. LPS induces NF-κB activation in 30 min in a macrophage-like mouse monocytic leukemia cell line RAW264.7. In our experiment, (-)-DHMEQ was added for only 15 min and then washed out in this experimental system. Even after 8 h of the removal of (-)-DHMEQ, the cells were dormant, and LPS did not activate NF-κB, suggesting that NF-κB would be inhibited irreversibly [56].

All Rel family proteins possess specific cysteine residues essential for their DNA binding. (-)-DHMEQ binds to those cysteine residues of p65, cRel, RelB, and p50, but not of p52. In case of RelB, (-)-DHMEQ inhibits not only DNA-binding of RelB, but also its interaction to importin [57]. 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) NF-κB components [53, 57]. It is likely that DHMEQ can enter into a specific pocket via

a key and lock mechanism to bind to the limited cysteine residue.

These mechanisms may explain the highly selective NF-κB inhibition and the low toxic effect of DHMEQ in cells and in animals.

Therapeutic activity of DHMEQ in animal models of inflammation and cancer

DHMEQ has been widely used to study the mechanism of diseases, especially to study the role of NF-κB in various disease models in situ and in vivo. The most important transcription factor in osteoclastogenesis is NFATc1. DHMEQ inhibited the expression of NFATc1 in mouse primary culture macrophages to show the involvement of NF-κB in the mechanism of expression [58]. DHMEQ also inhibited the expression of NFATc1 in mouse rheumatoid arthritis model [59]. Cancer stem cell is still a popular topic in cancer research. They say it is important to suppress cancer stem cell activity to eliminate the cancer growth. DHMEQ was used to study the essential factors of cancer stem cells. Goto and coworkers demonstrated that NF-κB and Akt may be essential for the activity of breast cancer cells using DHMEQ [60, 61]. Involvement of NF-κB in the mechanism of early phase [62] and late phase [63] of metastasis was suggested by the experiments using DHMEQ, which was reviewed in [64].

Not only for the mechanistic study, DHMEQ is likely to be useful as new chemotherapeutic agent. Recently reported therapeutic activities of DHMEQ in animal experiments are shown below.

Firstly, topical application to skin of rodents ameliorated atopic dermatitis models. DHMEQ ointment showed anti-inflammatory activity in the mouse genetic atopic dermatitis model. It sho-

wed similar or stronger anti-inflammatory activities compared with betamethasone and tacrolimus ointments [65]. Accumulation of mast cells was inhibited by DHMEQ ointment in this model. Later DHMEQ was found to inhibit MMP-2 expression and cellular invasion of mouse primary culture mast cells treated with DNP antigen and IgE [66]. More recently, DHMEQ ointment was shown to suppress development of chemically induced atopic dermatitis-like lesions in mice [67, 68]. This atopic dermatitis model in BALB/c mice was chronically induced by the repetitive and alternative application of 2,4-dinitrochlorobenzene (DNCB) and oxazolone (OX) on ears, and stratum corneum of the ear skin was additionally stripped off with surgical tapes before each challenge with DNCB/OX. The lesions reaches to peak as well as DHMEQ arrives to its efficacy on day 38. The procedure using adhesive tape in preparation significantly accelerated the skin inflammation. Results showed that the drug reduced the ear thickness, epidermal thickness, mast cell infiltration, and gene expressions of interleukin (IL)-4, IL-13 and interferon (IFN)- γ in ear tissues [68]. Secondly, DHMEQ is being developed for anti-inflammatory and anticancer therapy by intraperitoneal administration, which is discussed later

Secondly, intraperitoneal (IP) administration of DHMEQ ameliorated various inflammatory and neoplastic disease models in animal

experiments. Amniotic apoptosis is essential for the onset of delivery. On the other hand, too early amniotic apoptosis causes baby loss. Activated macrophages around the amniotic epithelial cells are considered to cause amniotic apoptosis producing TNF- α and NO. The TNF- α receptor 1 is expressed in the amniotic epithelial cells. IP administration of DHMEQ inhibited TNF- α and iNOS expressions in pregnant mice to inhibit amniotic apoptosis in this model [69].

Recently, it was reported that IP administration of DHMEQ ameliorates dinitrobenzene sulfonic acid (DNBA)-induced colitis in rats [70]. IP administration of DHMEQ also inhibited dextran-sulfate-sodium-induced colitis in rats [71].

DHMEQ inhibits cancer progression in various animal models. IP administration of DHMEQ inhibited the growth of hormone-insensitive prostate carcinoma [72] and breast carcinoma [73]. It also inhibited thyroid carcinoma [74], regional model of glioma [75], and various lymphomas including adult T-cell leukemia [76], and multiple myeloma [77].

Fluke-induced cholangiocarcinoma is still common in Thailand, and it is one of the most difficult cancers to treat, and there is no effective chemotherapeutic regimen at present. Seubwai and coworkers reported that IP administration of DHMEQ inhibited the growth of cholangiocarcinoma in mice [78]. Normal bile duct epithelia rarely expressed NF- κ B subunits such as p50,

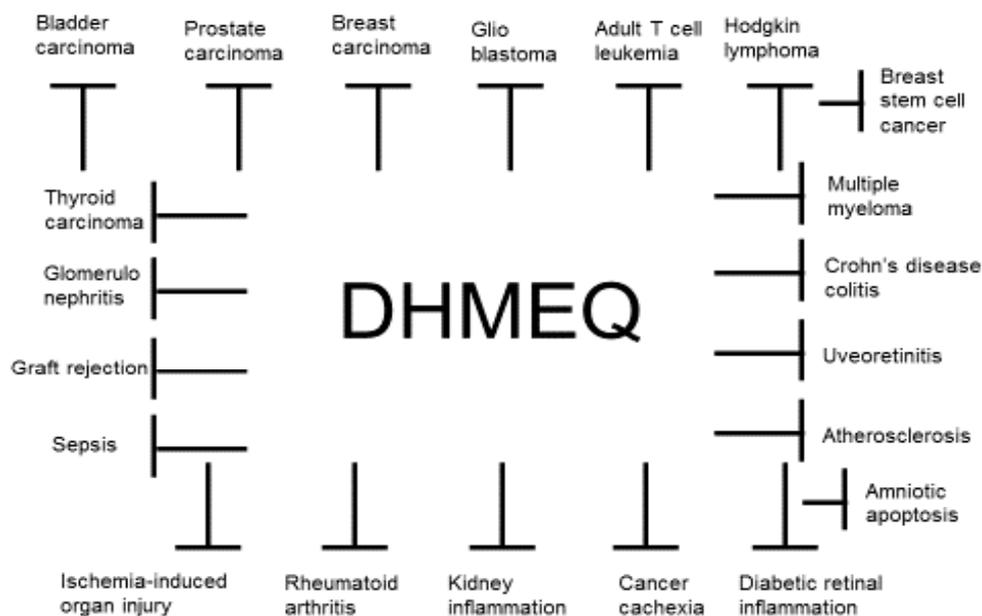


Figure 2. Anti-inflammatory and anticancer activities of DHMEQ in animal experiments. DHMEQ was all administered by intraperitoneal route

p52 and p65, whereas all cholangiocarcinoma patient tissues over-expressed these NF- κ B subunits. DHMEQ increased apoptosis by decreasing the expressions of anti-apoptotic proteins such as Bcl-2 and XIAP in cultured cholangiocarcinoma cells. Moreover, DHMEQ effectively reduced tumor size in cholangiocarcinoma-inoculated mice.

Recently, Ito and coworkers investigated the anticancer effect of DHMEQ in CDDP-resistant bladder cancer cells [79]. Invasive bladder carcinoma cell line T24 and its CDDP-resistant cell line T24PR were used. The NF- κ B activity was stronger in T24PR cells than in T24 cells. DHMEQ alone effectively lowered cell viability and induced apoptosis in T24PR cells. Moreover, using mouse xenograft models, the mean volume of tumors treated with the combination of DHMEQ and paclitaxel was significantly smaller than those treated with paclitaxel alone. Thus, IP administration of DHMEQ showed anticancer activity alone, and also increased the sensitivity to paclitaxel.

Anti-inflammatory and anticancer activities of DHMEQ in animal models are summarized in **Figure 2**, where DHMEQ was given to animals by IP injection in all cases.

Possible application of DHMEQ for the prevention and treatment of peritoneal fibrosis

Thus, IP administration of DHMEQ is quite effective to suppress various inflammatory and neoplastic disease models in animals. No toxicity has been reported so far. For the mechanism of anti-inflammatory and anticancer activity, it is likely

that DHMEQ acts only in the peritoneal cavity [80, 81], because it is easily metabolized in the blood. Because DHMEQ does not enter systemic circulation, IP administration of DHMEQ is considered to be a safe therapy.

Recently, we have demonstrated that DHMEQ inhibits primary cultured human peritoneal cells [82]. We studied the effects of DHMEQ on the functions of human peritoneal mesothelial cells (HPMC) in situ. DHMEQ was not toxic at 1–10 μ g/ml to HPMC. Synthesis of IL-6, MCP-1 and hyaluronan in unstimulated and stimulated with interleukin-1 was measured. DHMEQ at 10 μ g/ml reduced in unstimulated and stimulated HPMC synthesis of IL-6, MCP-1 and hyaluronan (**Figure 3**). The observed effects should be 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 (CAPD) 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 inflammatory response in HPMC and prevents dialysate-induced proliferation and collagen synthesis in these cells. Therefore, IP administration of DHMEQ would be useful for the prevention of progressive dialysis-induced damage to the peritoneum.

Acknowledgements

Conflict of interest statement

The authors declare no conflict of interest.

Funding sources

There are no sources of funding to declare.

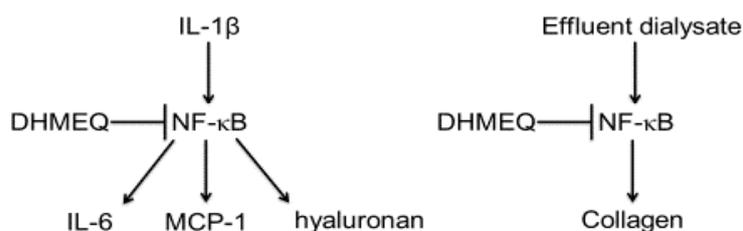


Figure 3. Inhibition of inflammatory cytokine, hyaluronan, and collagen synthesis by DHMEQ in human primary culture peritoneal cells. Human peritoneal mesothelial cells (HPMC) were supplied by the patients with continuous ambulatory peritoneal dialysis (CAPD)

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Acceptance for editing: 2019-05-09
 Acceptance for publication: 2019-06-29.

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