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Peritonitis-induced peritoneal injury models for research in peritoneal dialysis review of infectious and non-infectious models

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Abstract

Peritonitis is an important complication of peritoneal dialysis. Several animal peritonitis models have been described, including bacterial and fungal models that are useful for studying inflammation in peritonitis. However, these models have limitations for investigating peritoneal fibrosis induced by acute inflammation and present difficulties in handling the infected animals. Animal models of peritonitis which induced peritoneal fibrosis are important for establishing new therapies to improve peritoneal damage induced by peritonitis. Here, we present an overview of representative animal models of peritoneal dialysis-associated infectious and non-infectious peritonitis, including our novel animal models (scraping and zymosan models) that mimic peritoneal injury associated with fibrosis and neoangiogenesis caused by bacterial or fungal peritonitis.

Keywords: Peritonitis, Non-infectious peritonitis model, Scraping model, Zymosan model

Background

There are several reasons why peritonitis is important in peritoneal dialysis (PD) treatment. First, peritonitis remains an important cause of death in PD patients. The mortality rate for peritonitis is approximately 3% [1, 2], and peritonitis is a contributing cause of death in more than 10% of PD patients [3]. Second, peritonitis remains an important factor in withdrawal from PD. In the PD registry of the Nagoya group from both 2005 to 2007 [4] and 2010 to 2012 [5], the most common reasons for withdrawal from PD have been PD-related peritonitis, followed by dialysis failure/ultrafiltration failure and social problems such as lack of family support. PD peritonitis is primarily caused by gram-positive organisms that typically result from touch contamination. The mean incidence of peritonitis as reported twice from a study over a 3-year period was one episode every 42.8 [4] and 47.3 [5] patient-months. Third, peritonitis presents a risk for the development of encapsulating peritoneal sclerosis (EPS) [6]. The duration of peritonitis is independently associated with EPS [7]. In particular, fungal and *Pseudomonas* infections put patients at a higher risk for the development of EPS [8]. Fourth, peritonitis is one of the risks for a decrease in residual renal function. The number of peritonitis episodes has been reported to be an independent predictor of the development of anuria [9]. Fifth, peritonitis is an important cause of peritoneal membrane injury, which leads to peritoneal fibrosis, neoangiogenesis, and peritoneal dysfunction [10].

The characteristic features of chronic peritoneal damage in PD treatment are the loss of ultrafiltration capacity associated with morphological submesothelial fibrosis with extracellular matrix accumulation, and neoangiogenesis. The pathogenesis of peritoneal fibrosis is attributed to a combination of bioincompatible factors in PD fluid (PDF) and peritonitis, especially repeated episodes of peritonitis [11]. We have reported that uremia is associated with inflammation of the peritoneal membrane [12]. Histologically, acute peritonitis can cause morphological damage to the peritoneum [10, 13]. Detachment and disintegration of mesothelial cells is observed, along with the appearance of fibrin exudation and numerous infiltrating cells, ultimately resulting in internal structures becoming unrecognizable [6]. Therefore, peritonitis plays a crucial role in the

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development of peritoneal damage leading to peritoneal membrane failure.

Animal models of peritonitis-induced peritoneal fibrosis are important for establishing new therapies to improve peritoneal damage induced by peritonitis.

Peritonitis models induced by bacteria or fungus

There are several reports of animal models of peritonitis induced by bacteria or fungi (Table 1). The pathogenic microorganisms used to induce peritonitis include *Staphylococcus aureus* [14–18], *Staphylococcus epidermidis* [19, 20], *Pseudomonas aeruginosa* [21], and *Candida albicans* [22]. These models of infectious peritonitis have been mainly used to elucidate the mechanism of inflammation in the membrane and the mechanism of acute peritoneal membrane failure. However, the acute peritonitis model is not typically used to study peritoneal fibrosis.

A catheter-induced model of gram-positive bacterial peritonitis has been developed, which is an acute bacterial peritonitis model with bacteria originating from skin flora due to lack of aseptic precautions [23–25]. In subsequent studies, these researchers used a model of lipopolysaccharide (LPS)-induced peritonitis instead of the gram-positive bacteria-induced peritonitis model [26, 27]. They investigated the role of nitric oxide (NO) released by endothelial NO synthase (eNOS) in the gram-positive bacterial peritonitis model [23] and the LPS-induced peritonitis model [27] and suggested that the selective inhibition of eNOS might ameliorate the poor peritoneal function caused by acute peritonitis. They reported that mice injected with LPS developed a cloudy dialysate with increased white blood cell counts and NO metabolite levels and inflammatory cell infiltration in the peritoneum. These observations are similar to those of the gram-positive peritonitis model.

The mechanisms of inflammation were studied in the bacterial and fungal peritonitis models; however, these models were not used to investigate the long-term complications such as fibrosis and neoangiogenesis.

Table 1 Summary of representative rodent models used to study peritoneal dialysis and its associated complications

Representative animal models		Methods	Species	Experimental period	Peritoneal dysfunction	Neoangiogenesis	Fibrosis	EPS	References
Peritonitis model									
Infectious model	Bacteria	*Staphylococcus aureus*	Mouse	2 days	No report	No report	No report	–	[14]
			Rat	2 weeks	No report	No report	±	–	[15–18]
		Staphylococcus epidermidis	Mouse	2 weeks	No report	No report	No report	–	[20]
		Pseudomonas aeruginosa	Rat	1 week	No report	No report	No report	–	[21]
	Fungus	*Candida albicans*	Mouse	1 day	No report	No report	No report	–	[22]
	Performance without aseptic precautions		Mouse	1 week	+	+	No report	–	[23]
			Rat	1 week	+	+	No report	–	[23–25]
Non-infectious model		LPS	Mouse	1 day	+	No report	No report	–	[26, 27]
			Rat	1 day	+	No report	No report	–	[28, 29]
		PDF with LPS	Rat	3–6 weeks	+	+	+	–	[29–36]
		SES	Mouse	2 days	No report	No report	No report	–	[11, 37]
		Scraping	Rat	2 weeks	+	+	+	–	[38, 39]
		Zymosan with scraping	Rat	5 weeks	No report	+	+	±	[64, 67]
		PDF	Mouse	4–5 weeks	+	+	+	–	[78–83]
			Rat	1–20 weeks	+	+	+	–	[69–77]
		Chlorhexidine	Mouse	1–8 weeks	+	+	+	+	[97–108]
			Rat	1–8 weeks	+	+	+	+	[84–96]
		Methylglyoxal	Mouse	3–7 weeks	+	+	+	+	[113, 114]
			Rat	3 weeks	+	+	+	+	[109–112]
		TGF-β1	Mouse	1–10 weeks	No report	+	+	+	[115–118]
			Rat	1–4 weeks	+	+	+	–	[119, 120]

LPS lipopolysaccharide, *PDF* peritoneal dialysis fluid, *SES* a lyophilized cell-free supernatant, *TGF-β1* transforming growth factor-β1, *EPS* encapsulating peritoneal sclerosis

Non-infectious peritonitis models

Currently, the number of reports in which investigators use the non-infectious peritonitis model is increasing. The non-infectious model is convenient and useful for handling animals and performing experiments. We suggest that a model of peritoneal fibrosis induced in a peritonitis model will help identify new strategies for preventing peritoneal fibrosis. Many studies have used the LPS-induced peritoneal injury model [26–36]. LPS derived from *Escherichia coli* (Sigma, St. Louis, MO) is frequently used [26–30, 33, 35]. A method involving a single LPS dose was used to study peritoneal inflammation and dysfunction [26–29]. Rat peritoneal inflammation and significant changes in neoangiogenesis were caused by daily administration of PDF over 3 weeks following an initial exposure to LPS [29–35].

Another non-infectious peritonitis model induced by administration of lyophilized cell-free supernatants from *Staphylococcus epidermidis* has been used to study the regulation of inflammation and leukocyte trafficking [11, 37]. Hurst et al. showed that interleukin-6 (IL-6)/soluble IL-6 receptor trans-signaling, which involves signal transducer and activator of transcription 3 (STAT3) activation, regulates chemokine secretion and polymorphonuclear neutrophil apoptosis in the peritoneal cavity. These mechanisms of inflammation and leukocyte trafficking have been clearly shown in the non-infectious model.

Here, we introduce a model of peritoneal fibrosis that we generated in rats and mice that is induced by acute inflammation with mechanical scraping, the so-called "scraping model."

Scraping model

We first reported the scraping model as a non-infectious, peritonitis-induced peritoneal fibrosis model [38]. After opening the rat abdomen under anesthesia, the right parietal peritoneum received hand-driven scratching for 1 min using the edge of a 15-ml centrifuge tube (Fig. 1). Rats freely consumed food with or without NaCl loading after surgery [38–40]. Similarly, in mice, the right parietal

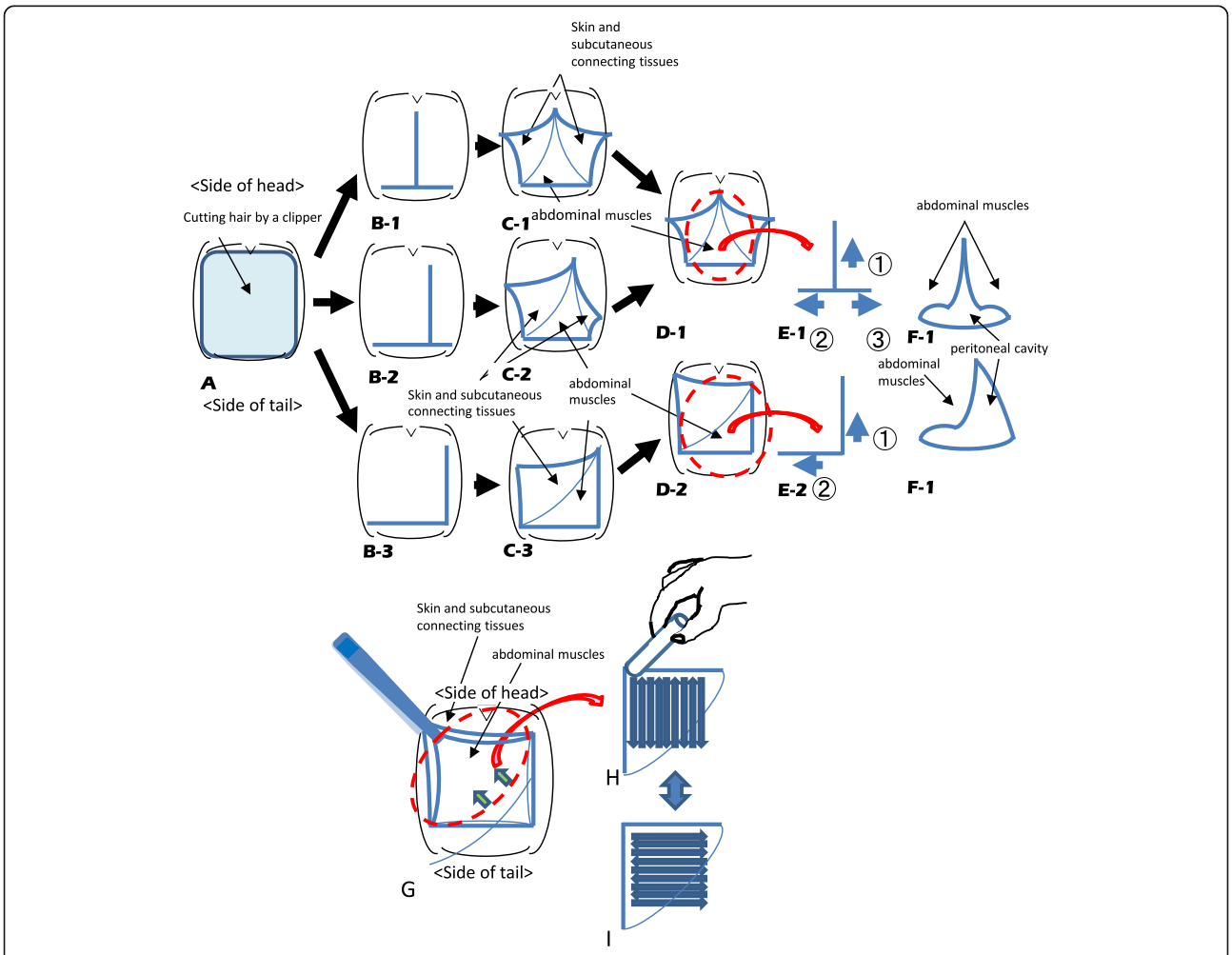

Fig. 1 Procedures to generate scraping model. Used by permission from *Methods Mol Biol* [40]

peritoneum was scraped for 90 s with the cap of an injection needle.

In this model (Fig. 2), neutrophil infiltration with fibrin exudation from the scraped peritoneum was demonstrated in 6 to 24 h after surgery. The predominant infiltrating cells switched to a mononuclear population on day 3, and inflammation gradually decreased thereafter. From days 7 to 14, the peritoneum became markedly thickened with the accumulation of alpha-smooth muscle actin (α-SMA)-positive fibroblasts and type III collagen. Mesothelial cells were not detected in 6 to 24 h after scraping, while approximately 30 and 70% of the total peritoneal length was covered with mesothelial cells on days 3 and 14, respectively. Increased CD31-positive blood vessel density was observed, which peaked at day 14. Transforming growth factor-β (TGF-β) and plasminogen activator inhibitor-1 (PAI-1), mainly expressed in the submesothelial compact zone, increased rapidly starting on day 3 and peaked at day 14. TGF-β and PAI-1 messenger RNA (mRNA) expression was upregulated from day 3 and peaked at day 7. In contrast, monocyte chemotactic protein-1 (MCP-1) mRNA rapidly increased and peaked at day 3. The pathology of this model in the early stage is characterized by strong infiltration of neutrophils and macrophages. The latter stage of this model is characterized by fibrosis and neoangiogenesis. In addition, peritoneal membrane permeability increased in rats that underwent bilateral scraping [38]. The pathological features and time course of this model are summarized in Figs. 2 and 3a.

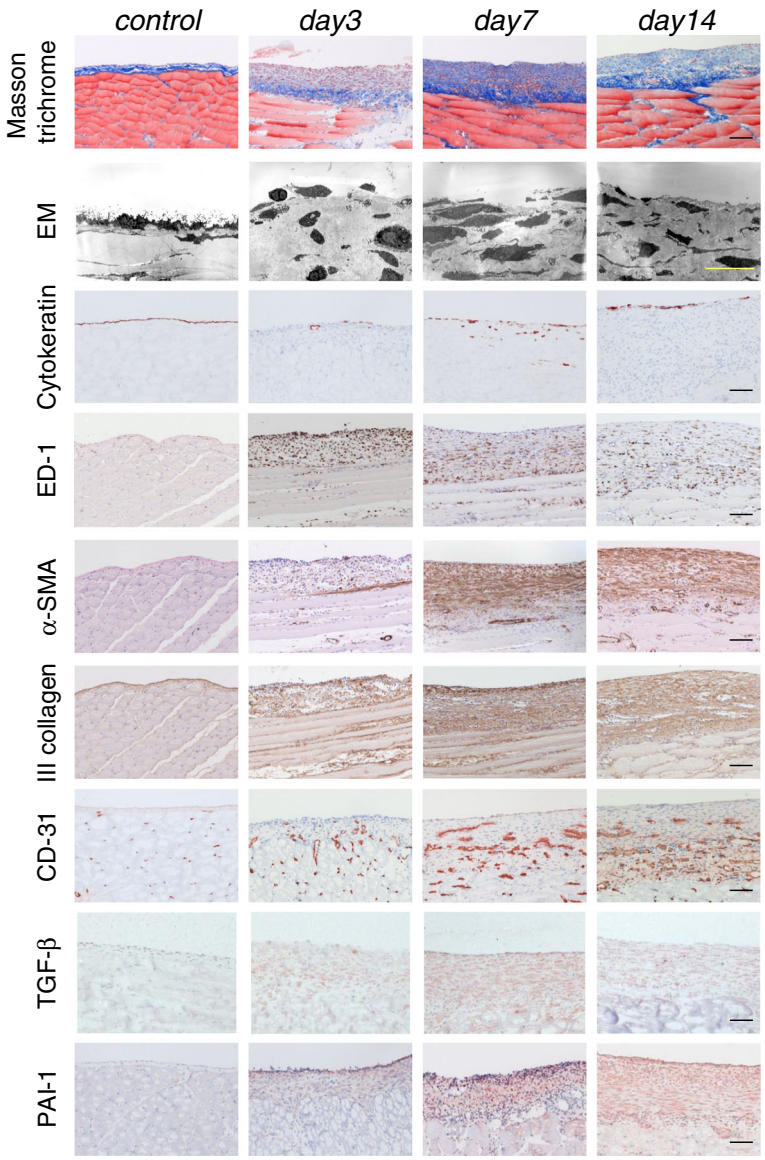

Fig. 2 Pathological findings of rat scraping model. Used by permission from *Am J Physiology* [38]

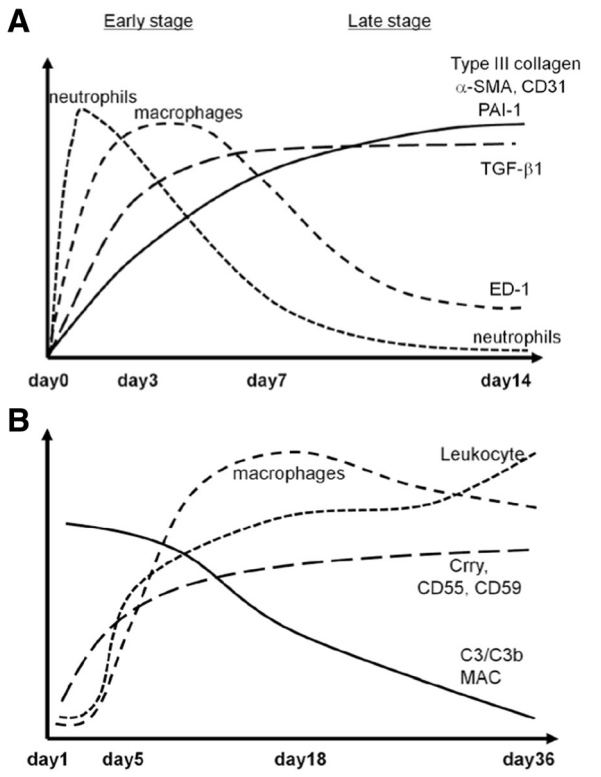

Fig. 3 Time course of rat scrape model (**a**) and zymosan-induced fungal peritonitis model (**b**)

Using this model, we investigated the effects of mineralocorticoid receptor (MR) blockade with salt loading [38]. The local renin-angiotensin-aldosterone system (RAAS) is thought to play a role in peritoneal injury in PD patients [41]. Peritoneal mesothelial cells have been observed to express angiotensinogen, angiotensin-converting enzyme (ACE), and angiotensin II type 1 receptors (AT1R) [42, 43]. We found that MRs were expressed by rat fibroblasts and scraped peritoneum. Treatment with spironolactone suppressed macrophage infiltration, neoangiogenesis, and fibrosis, which is associated with the suppression of TGF-β and PAI-1 expression, thereby resulting in improvement of peritoneal dysfunction, including ultrafiltration, glucose transport, and albumin leakage [38]. The effects of spironolactone have also been shown in the LPS-induced peritoneal injury model [36].

In addition, we demonstrated the effects of atrial natriuretic peptide (ANP) in this model [39]. ANP has been used as a diuretic and vasodilator in clinical settings. ANP has been shown to play an important function in the inhibition of RAAS [44, 45]. ANP and brain natriuretic peptide (BNP) have been reported to prevent cardiac fibrosis [44, 46] and renal fibrosis [47–49], and to reduce infarct size in acute myocardial infarction [50]. We demonstrated that AT1R, ACE, and atrial natriuretic peptide receptor (NPR-A) mRNA expression were increased and peaked at days 14, 7, and 7, respectively. ANP administration resulted in a significant reduction in macrophage infiltration, fibrosis, and neoangiogenesis [39]. In this model, the salt loading progression of peritoneal fibrosis is likely to be involved in local RAAS activation. Administration of an MR blocker or ANP with antibiotics may prevent peritoneal membrane dysfunction associated with fibrosis and neoangiogenesis in human bacterial peritonitis. In a small study, 25 mg/day of spironolactone for 6 months was shown to reduce CD20 and collagen IV levels in the human peritoneal membrane [51]. Recently, the scraping model was used to study the effectiveness of cell therapy using the mesothelial cells to prevent peritoneal damage in PD patients [52].

Zymosan-induced fungal peritonitis model

By modifying the scraping model, we established the zymosan-induced fungal peritonitis model. Although fungal peritonitis is not common, yeast infection with the most common *Candida* species results in a poor outcome with high mortality [53–55]. The 2016 International Society for Peritoneal Dialysis guidelines recommends removal of the PD catheter in fungal peritonitis [56]. Several clinical observations have suggested that EPS could be induced by a single occurrence of fungal peritonitis [56–60]. The cell walls of many types of yeast activate various signaling reactions, including the complement system [61]. Complement maintains host homeostasis by eliminating microorganisms and irregular cells and also regulates cellular immunity. The complement system in the peritoneum is continuously active at low levels, and complement regulators (CRegs) regulate complement activation. Irregular activation of complement leads to tissue damage in many diseases [62, 63].

We demonstrated the expression of CRegs, Crry, CD55, and CD59 in rat peritoneum, especially along the mesothelial cell layer [64]. In rat peritoneum, combined blockade of Crry and CD59 induced severe focal inflammation with edema [65]. We examined the state of complement activation in the aforementioned rat scraping model, and C3 and C3b were transiently present in the inflammatory stage at day 3 [64]. Zymosan is abundant in the cell walls of fungi and activates the complement system through the alternative pathway [66].

We demonstrated that administration of zymosan after scraping promoted severe peritoneal injury that is pathologically similar to human fungal peritonitis. Zymosan (5 mg/rat/day, 2 mg/mouse/day) mixed with PDF was intraperitoneally injected into the rat or mouse abdominal cavity for up to 5 days after scraping the rat or mouse peritoneum [40, 64, 67]. Macroscopic findings in the zymosan rats showed the presence of a few white plaques at day 3, and yellow-white plaques at day 5, while no plaques were found in the control scraping model.

Plaque fusion resulted in the formation of a yellow-white sheet covering the peritoneum with numerous small vessels running into the plaques, which suggests the occurrence of peritoneal neovascularization in the zymosan model at day 5. Peritoneal thickening associated with severe infiltration of inflammatory cells continued and remained present in the zymosan model at day 36, while the peritoneum was of normal appearance in the control scraping rats.

In recent experiments, we found that disease severity was affected by the lots of the zymosan (Sigma-Aldrich, St. Louis, MO). Expression of CRegs, Crry, CD55, and CD59 transiently decreased in the control scraping model at day 5. In contrast, CRegs expression was further decreased in the zymosan model at day 5 and continued decreasing up to day 18. Complement activation products, C3b and membrane attack complex (MAC), were clearly found in the zymosan model from days 1 to 5, and small amounts of these products remained at days 18 and 36. The time course of this model is summarized in Fig. 3b.

Systemic complement depletion by cobra venom factor or local suppression of complement activation by Crry-immunoglobulin or soluble complement receptor 1 dramatically reduced complement activation, peritoneal thickening, and inflammation. These findings clearly indicated that the zymosan model is a complement-dependent model of severe proliferative peritonitis [64]. Fungal peritonitis is known to be one of the causes of EPS. Subsequently, we successfully demonstrated that further enhancement of complement activation by inhibiting CRegs and enhancing systemic activation with cobra venom factor in the zymosan model induced fibrin exudation, which is the initial event of EPS [68].

Other models of non-infectious peritoneal injury associated with inflammation and fibrosis

Administration of PDF into the abdominal cavity of rats and mice by repeated intraperitoneal injection or implanting a catheter is a method used to study the pathophysiological changes of the peritoneum associated with PD [69–83], but a non-peritonitis model. Daily intraperitoneal injection of 4.25% glucose dialysate into the rat abdominal cavity for 1 week induced an increased peritoneal membrane transport rate and the absence of the peritoneal surface layer, as observed by electron microscopy [69, 70]. Daily injection of PDF (100 ml/kg, once or twice daily) was performed for up to 8 or 12 weeks to obtain morphological changes in the rat peritoneum [71–73]. Implantation of a silicon catheter into the rat abdomen was reported to amplify peritoneal inflammation from PDF through a foreign body reaction [74]. However, the peritoneum of rats that received only a puncture without infusion of any solution showed no functional or pathological changes [73, 75].

A model of renal insufficiency, such as 5/6 nephrectomy, was used in combination with PDF infusion to closely model the clinical situation of peritoneal dialysis patients and to understand the influence of PD on residual renal function [76, 77]. Daily intraperitoneal exposure of 1.5–3.0 ml of 4.25% glucose PDF for 4 or 5 weeks, with or without implanting a catheter, produced peritoneal dysfunction and morphological changes, such as fibrosis and neoangiogenesis, in mice [78–83].

Chronic intraperitoneal exposure to chemical irritation (chlorhexidine gluconate (CG)) is used as an experimental model of peritoneal fibrosis with inflammation and EPS. Suga et al. developed a CG-induced peritoneal fibrosis model in rats [84]. Daily injection of 0.1% CG in 15% ethanol, dissolved in 2–3 ml saline per 200 g body weight, was administered in the rat peritoneal cavity [85–87]. At day 7, the peritoneal tissue was partially thickened with edema and showed initial accumulation of connective tissues and modest cell migration. At day 14, significant alterations were found, including peritoneal thickening with edema, cell infiltration, and neoangiogenesis. At days 21 to 28, the peritoneal tissue was markedly thickened and showed remarkable proliferation of collagen fibers. The number of macrophages gradually increased in the thickened areas and reached a maximum at day 21. At day 28, neoangiogenesis had decreased, whereas collagen fibrils had accumulated. At day 35, fibrillary elements with cell infiltration occupied the submesothelial zone. Peritoneal resting for 3 weeks after 3 weeks of CG exposure ameliorated some functional parameters in the peritoneum; however, elevated peritoneal thickness and fibrosis continued during the resting period [88–91]. Placing an infusion pump in the rat abdominal cavity was reported as an alternative administration route for CG [92–94].

A lower dosage of CG is an option for producing mild peritoneal injury [95, 96]. Mice were given daily intraperitoneal administration of 0.3 ml or 10 ml saline/kg body weight containing 0.1% CG in 15% ethanol [97, 98]. Peritoneal fibrosis and increased infiltration of mononuclear cells were observed over time. Peritoneal fibrosis reached the chronic inflammatory stage, and macroscopic evidence of EPS was observed by 8 weeks. Lower doses of CG or shorter time courses produced milder and more infrequent development of peritoneal fibrosis [99, 100]. Recent studies showed that a standard peritoneal fibrosis model could be produced in mice following treatment with 0.1% CG every other day or three times a week for 1–3 weeks [101–108].

Glucose degradation products contained in PDF contribute to the biocompatibility of conventional PDF and are risk factors for EPS. Methylglyoxal (MGO) is an extremely toxic glucose degradation product, and administration of PDF containing MGO can be used as an animal peritoneal fibrosis model. Rats were given intraperitoneal

injections of 100 ml/kg of 2.5% glucose PDF (pH 5.0) containing 20 mM MGO every day for 3 weeks [109–111]. Peritoneal function decreased significantly, and fibrous peritoneal thickening with proliferation of mesenchymal-like mesothelial cells and abdominal cocoon was induced. The combination of low doses of MGO and adenine-induced renal failure accelerated the progression of fibrous peritoneal thickening, whereas both MGO and renal failure alone did not [112]. Intraperitoneal injection of PDF (100 ml/kg) containing 20 or 40 mM MGO for five consecutive days per week for 3 weeks induced peritoneal injury in mice [113, 114]. We clearly showed the presence of severe lymphangiogenesis in the diaphragm of both CG and MGO models [96, 114]. TGF-β is a central mediator of peritoneal fibrosis. Overexpression of TGF-β1 driven by intraperitoneal adenovirus administration induced peritoneal fibrosis through epithelial mesenchymal transition, neoangiogenesis, and poor peritoneal function in mice [115–118] and rats [119, 120]. Other chemical irritants, such as deoxycholate [121], household bleach [122] and acidic solutions [123], were also reported to produce peritoneal inflammation, fibrosis, and abdominal cocoon in rats.

Conclusions

Non-infectious peritonitis models are convenient and useful for animal handling and performing experiments. The peritoneum in the scraping model showed signs of peritonitis initially and fibrosis at a later stage. These pathological changes, along with alterations in solute transport, mimic those observed in bacterial peritonitis. This model is useful for exploring strategies for the treatment and prevention of peritoneal fibrosis and membrane failure. The zymosan model is useful for studying the mechanisms of fungal peritonitis and the drugs used to reduce peritoneal damage induced by fungal peritonitis. Anti-complement therapy might be useful as a therapeutic in human fungal peritonitis and related peritoneal damage. Other non-infectious models, such as CG and MGO models, are also useful for investigating the pathophysiology of fibrosis with inflammation, angiogenesis, and lymphangiogenesis.

Abbreviations

ACE: Angiotensin-converting enzyme; ANP: Atrial natriuretic peptide; AT1R: Angiotensin II type 1 receptors; BNP: Brain natriuretic peptide; CG: Chlorhexidine gluconate; CRegs: Complement regulators; eNOS: Endothelial NO synthase; IL-6: Interleukin-6; LPS: Lipopolysaccharide; MAC: Membrane attack complex; MCP-1: Monocyte chemotactic protein-1; MGO: Methylglyoxal; MR: Mineralocorticoid receptor; NO: Nitric oxide; NPR-A: Natriuretic peptide receptor; PD: Peritoneal dialysis; PDF: PD fluid; RAAS: Renin-angiotensin-aldosterone system; STAT3: Signal transducer and activator of transcription 3; TGF-β: Transforming growth factor-β; α-SMA: Alpha-smooth muscle actin

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Availability of data and materials

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Authors' contributions

YI and HK planned the study, searched and collected the literatures, and wrote the manuscript. All the authors wrote the manuscript partly. TK, YS, and MM discussed the contents of the manuscript with YI and HK. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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