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Inflammation in Peritoneal Dialysis

Joseph C.K. Leung, Loretta Y. Y. Chan,
Kar Neng Lai and Sydney C.W. Tang

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1. Introduction

The prevalence of kidney disease has grown continuously. The loss of kidney function during acute kidney disease may occur rapidly and reversibly, and most unfortunately, may progress to end-stage renal disease (ESRD) in which renal replacement therapy (RRT) is required. Due to the short supply of donor kidneys, RRT is now dominated by dialysis. Dialysis can be applied intermittently or continuously using extracorporeal (hemodialysis or HD) or paracorporeal (peritoneal dialysis or PD) methods. Among patients with ESRD, the choice of PD or HD varies considerably from country to country and is related to non-medical factors such as finance, physician preferences, and social culture [1]. It has been suggested that PD should be offered as the first-line dialysis modality [2]. Compared with HD, PD offers better preservation of residual renal function, lower risk of infection with hepatitis B and C, better outcome after transplantation, preservation of vascular access, easy to place on home therapy, simplicity of the technique, and lower costs [3, 4]. The predominant problems associated with PD are ultrafiltration failure and peritonitis. Dialysis patients after an episode of peritonitis may still be affected by prolonged systemic chronic inflammation [5]. Likewise, PD maintains a state of intraperitoneal micro-inflammation that affects the structure and function of the peritoneal membrane, and impairs ultrafiltration efficiency. An understanding of the mechanism in peritoneal inflammation will provide new insight to better preserve the function of the peritoneum membrane, with a goal to improve the quality of life in patients under PD.

2. Inflammatory response during peritoneal dialysis

Inflammation is the body's natural defense involving cascades of immediate immunological responses towards various stimuli, including pathogens, necrotic cells, injury, or irritants.

Acute inflammation is a protective machinery by which the injurious stimuli will be removed and the healing process initiated. On the other hand, chronic inflammation develops if the conditions causing acute inflammation is not resolved over a period of time. Intriguingly, chronic inflammation may be due to excessive physiological responses, such as the wound repairing process, which are intrinsically essential for maintaining normal life. Certain stimuli may directly provoke chronic rather than acute inflammation. Peritoneal inflammation of the microenvironment in the peritoneal cavity during PD generally presents in two major forms: (i) acute inflammation triggered by microbial infection, and (ii) low-grade inflammation or "para-inflammation" under various exogenous or endogenous stimulations during PD. These two forms of inflammation affects the membrane structure and function, and is associated with increased mortality.

2.1. Acute inflammation in PD

The most common form of acute inflammation of peritoneum in PD is peritonitis, which is a serious and the most frequent complication leading to hospitalization and catheter loss [6, 7]. Peritonitis causes a high infection-related mortality in PD patients [8, 9]. The leading cause of PD-associated peritonitis is contamination, predominately with the microorganisms from skin and environment, which is most commonly occur during the dialysis procedure such as PD exchange [10]. Exit site infection (ESI) in which transmigration of microorganisms from the exit site along the PD catheter into the peritoneal cavity, may cause tunnel infections and peritonitis [11, 12]. Enteric peritonitis is a less common cause but important, due to the severity of the inflammation process [13]. Fungal peritonitis accounts for about 4–6% of episodes of the total incidence of the peritonitis, and is with high mortality [14]. Rapidly resolving the infection is the primary approach to treat peritonitis, even if this involve the need for prompt removal of the peritoneal catheter. Before the causative microorganism is identified, initial therapy with broad spectrum antibiotic which is active against the most commonly occurring organisms, will be given according to the guideline from the International Society for Peritoneal Dialysis (ISPD) [9]. It is recommended that in addition to the standard initial protocol, specific regime tailored to the geographic and cultural characteristics, the relevant organisms and their antibiotic resistance pattern should be considered [15]. Detailed examination of the causality of infection-related peritonitis is important for the management. The molecular pathways of inflammation induced by different microbial pathogens are somehow redundant, yet also complex and diverse [16, 17].

2.2. Chronic inflammation in PD

An inherent immune dysfunction in PD patients and the continuous non-specific immune cell stimulation by dialysis procedure contribute to the chronic inflammatory state of patients under the long-term dialysis [18]. Patients on maintenance PD have increased intra-peritoneal levels of hyaluronan and cytokines including interleukin (IL)-1 β , IL-6 and transforming growth factor- β (TGF- β) [19, 20]. Chronic inflammation remains an important cause of morbidity in patients with ESRD. During continuous ambulatory peritoneal dialysis (CAPD), peritoneal cells are repeatedly exposed to non-physiologic dialysis fluid (PDF) with low pH

and high glucose [21]. PDF also contains toxic substance like glucose degradation products (GDP) generated during the sterilization process and the advanced glycation end products (AGE), which can be formed by amadori reaction between sugar and protein during long-term PD [22]. Dialysis patients are likely to gain fat mass following absorption of glucose from the peritoneal dialysate [23]. Adipocyte in adipose tissue is the major source of adipokines such as leptin, adiponectin and other inflammatory mediators. Adipose tissue is also an important contributor to the peritoneal and systemic inflammation [24, 25]. Exposure of peritoneal cells to the non-physiological dialysate during CAPD leads to "para-inflammation" [26], which is a protective mechanism helping the peritoneum to adapt to the noxious conditions during PD and to restore peritoneum functionality. Regrettably, after repeated exposure to various insults in PDF, dysregulated para-inflammation may eventually develop chronically to inflammatory states associated with ultrafiltration failure. A key feature of chronic inflammation is peritoneal fibrosis [27, 28], in which fibroblasts proliferate or are recruited to the inflamed peritoneum with the activation of cascades of inflammatory or fibrotic cytokines [29, 30].

3. The Mechanisms and pathways of inflammation in PD

The inflammatory pathway of PD consists of modulators, mediators and effectors. A simplified schema for PD-related inflammation is illustrated in Figure 1. The complex interaction among the components involved and the related machinery will determine the outcome of the immune response induced by PD.

3.1. Modulators:

Modulators of PD-related inflammation can be exogenous or endogenous. It should be noted that exogenous modulators may promote or amplify the effects of the endogenous modulators during the process of PD-related inflammation. Intriguingly, the interaction between modulators and the ongoing inflammatory events may form a vicious cycle to amplify the inflammatory process.

3.1.1. Exogenous modulators

The innate immune system recognized catheters used for PD as the foreign bodies. Severe biofilm formation on the catheters have been observed in PD patients without detectable infection [31]. Histologic and functional evidences obtained from rodent model have shown that the catheter insertion may have induced a classic inflammatory reaction characterized by formation of fibrin clots in the peritoneum [32]. Mechanical stress during PD is related to the infiltration of large volume of PDF, especially for achieving specific target of small solute clearance. Volume stress during PD are associated with significant increments in endothelin (ET)-1, a vasoactive peptide that may induce peritoneal fibrosis and indirectly contribute to technique failure in CAPD [33]. ET-1 induces the release of proinflammatory cytokines and increases the deposition of extracellular matrix (ECM) by regulating production and turnover of matrix components. In addition, high fill volumes increase circulating norepinephrine levels

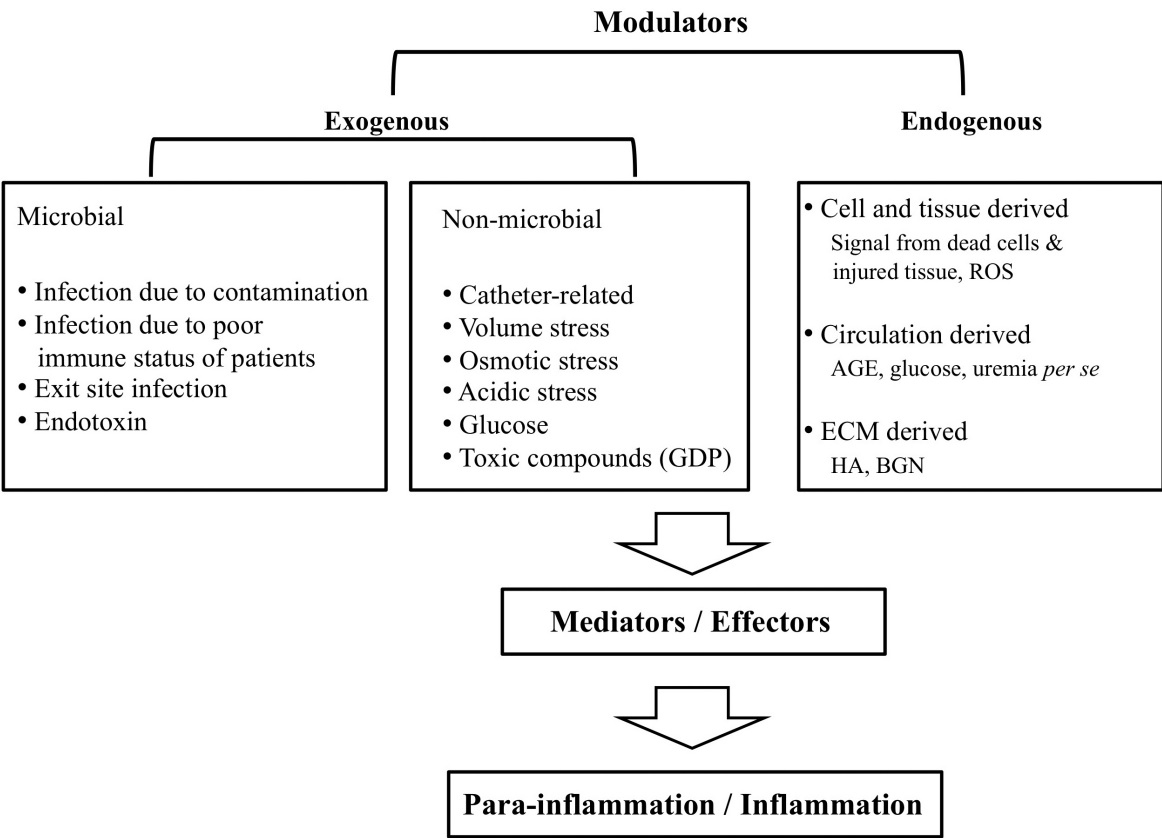


Figure 1. Pathway of the development of PD-related inflammation

[34], blood pressure, intraperitoneal pressure [35], and elicit proinflammatory effects by increasing peritoneal IL-6 and tumor necrosis factor- α (TNF- α) concentration [36]. During PD, cells lining the peritoneal cavity are exposed from time to time to the hyperosmotic environment, and this osmotic stress induces apoptosis of the peritoneal cells [37, 38]. Local acidosis occurs artificially during PD due to the non-physiological properties of PDF which has an acidic pH value. Exposure of macrophages to an acidic environment leads to the increased production of TNF- α through the up-regulation of inducible nitric oxide synthase (iNOS) activity and the activation of nuclear factor- κ B (NF- κ B) [39]. On the contrary, low pH PDF lead to rapid intracellular acidification and suppression of host defense activity [40, 41]. The acidic PDF induces stress on the endoplasmic reticulum (ER) and suppresses the induction of monocyte chemotactic protein-1 (MCP-1) in the peritoneum through de-activation of NF- κ B pathway [42, 43], and this may impair the peritoneal defense mechanisms by interfering with migration of phagocytic cells. Obviously, further study is needed to clarify the role of acidic-stress on PD-related inflammation. High glucose content in PDF induces immunological, structural and functional abnormalities in peritoneal cells during CAPD [44, 45]. High glucose induces vascular inflammatory processes through up-regulation of endothelial cell adhesion molecules, reduction of nitric oxide (NO) release, activation of reactive oxygen species (ROS) and NF- κ B [46, 47]. Storage or heat sterilization of PDF generates the toxic substances GDP. Dialysis with GDP-containing PDF is associated with increased vascular endothelial growth

factor (VEGF) production and peritoneal vascularization [48]. GDP decrease the expression of tight junction associated protein, zonula occludens protein 1 (ZO-1), in human peritoneal mesothelial cells (HPMC) *via* the VEGF [49]. Glucose or GDP in PDF may cause AGE formation, which further provoke additional inflammatory stimuli on the peritoneal environment under PD [22, 50, 51]. Contamination and the inherent poor immune status of the PD patients contribute to the microbial stress during PD. Microbial contamination or ESI during PD may evolve to peritonitis, which elicits a virulent acute inflammatory response and is an important cause of hospitalization, catheter loss, and technique failure. The most common contaminated micro-organisms are coagulase-negative *Staphylococcus*, *S. aureus*, *Streptococcus*, and Gram-negative bacteria. Much less common are mycobacterium and fungal peritonitis. Skin organisms contamination including *Staphylococcus*, *Corynebacterium*, and *Bacillus* species cause mild inflammatory responses. Exit site infection with *Staphylococcus epidermidis* or *Pseudomonas aeruginosa* is difficult to treat, with frequent progression to tunnel infections and peritonitis. Fungal peritonitis generally requires catheter removal. It is worth mentioned that sustained inflammation is observed in patients on PD with peritonitis even after resolution of the clinical symptoms of peritonitis [52]. The C-reactive protein (CRP) remains significantly higher than baseline by day 42 after an episode of peritonitis [5]. Release of neutrophil gelatinase-associated lipocalin (NGAL) into the peritoneal dialysate effluent (PDE) by HPMC is induced following an acute episode of CAPD-related peritonitis, and is related to the up-regulation of the IL-1 β concentration [53]. Lipopolysaccharide (LPS), a major component of Gram-negative bacterial cell walls, is a potent immuno-stimulatory product [54]. Endotoxemia is common in PD patients and circulating LPS may derived from the gastrointestinal tract during enteric peritonitis [55]. The level of circulating LPS correlates with the severity of systemic inflammation, suggesting that endotoxemia may contribute to accelerated atherosclerosis in PD patients.

3.1.2. Endogenous modulators

Uremia is associated with the immune dysfunction and is a significant risk factor for cardiovascular abnormalities and death in chronic kidney disease (CKD) patients [56], and this risk is further increased when CKD has progressed to ESRD requiring dialysis. Dialysis decreases the impact of uremia, yet does not remove it completely. In PD patients, uremia fuels the inflammatory state and introduces stress on the peritoneum due to the formation of carbonyl products. It accelerates the formation of advanced oxidation protein products (AOPP) and AGE, that induces an upregulation of the receptors of advanced glycation end products (RAGE) [57]. Binding of AGE to RAGE alone [58], or in combination with the Toll-like receptor (TLR)s, elicits the inflammatory activity [59]. It has been suggested that the high-mobility group box 1 protein (HMGB1) may play a central role in mediating inflammation, and interactions involving the HMGB1-TLR-RAGE axis trigger NF- κ B activation and proinflammatory cytokines induction [60]. Cytotoxic injury to mesothelial cells induces ROS, depletes ATP, and triggers the extracellular release of HMGB1, which initiates a chronic inflammatory response [61]. Serum adipokine levels are significantly elevated in uremic patients with CKD [62], and elevated plasma concentrations of adiponectin and leptin have been reported [63, 64]. Leptin activates immune system and serves as a mediator of inflammation [65]. Glucose-

based PDF induces a higher leptin secretion by a murine adipocyte cell line 3T3-L1 compared to dialysate with physiological glucose concentration *via* the hexosamine pathway [66]. We have demonstrated that the full-length isoform of leptin receptor, Ob-Rb, is expressed in HPMC and its expression is up-regulated following exposure to glucose [67]. Glucose increases leptin synthesis by peritoneal adipocytes and the adipocyte-derived leptin can induce TGF- β production by HPMC through the Ob-Rb [67]. Adiponectin exerts protective functions on innate and adaptive immunity, including the reduction of phagocytic activity, IL-6 and TNF- α production by macrophage, T-cell response, and the induction of anti-inflammatory cytokines by monocytes, macrophages and dendritic cells [68]. In a recent study using rat PD model, glucose-based PDF down-regulates adiponectin synthesis by adipocytes through an increased ROS generation [69].

In uremic patients under PD, chronic inflammatory processes induce the oxidative stress, generating excess ROS, reactive nitrogen species (RNS), and DNA-reactive aldehydes. These pro-oxidants overwhelm *in vivo* antioxidant defenses, and lead to increased oxidative damage of peritoneal structure and function [70]. The link between oxidative stress and inflammation has been demonstrated in liver injury, where oxidative stress induces the proinflammatory signaling and macrophage activation [71]. In HPMC, ROS amplifies the high glucose-induced expression of fibronectin [72], angiotensin II (AngII) and TGF- β [44].

Heat-shock proteins (HSP), a marker of the cellular stress response, is the main effector of the cellular reparative machinery. Induction of HSP expression will counteract cellular injury caused by PDF exposure. PDF induces HSP release by cultured HPMC [73, 74]. In an experimental model of PD, PDF infusion causes cellular injury but also up-regulates HSP-72 [75]. In HPMC under sublethal injury, secretion of HSP-72 correlates with the release of proinflammatory IL-8 [76].

Breakdown products of the ECM during tissue injury, may serve as the endogenous modulator of inflammation. There is growing evidence that ECM molecules may deliver proinflammatory signals [77, 78]. In the context of PD, expression and release of hyaluronan (HA) and biglycan (BGN) is well recognized. HPMC synthesize and secrete ECM proteins including BGN and HA, which are detectable in PDE [19, 79, 80]. Under physiological conditions, HA is present as an inert high-molecular-weight polymer. Upon tissue injury, HA is broken down into inflammatory low-molecular-weight fragments, which activate the TLR4 and promote either an inflammatory or a tissue-repair response [81, 82]. Other than HA, BGN also implicate in modulating the proinflammatory functions. BGN can act as a “danger” motif, a potential innate antigen analogous to pathogen-associated molecular pattern (PAMP), which signal through TLR4 and TLR2 to initiate the inflammatory cascade [83]. BGN binds with TGF- β and TNF- α to regulate the proinflammatory cytokine activity [84, 85]. Markedly elevated TNF- α and IL-1 β is found in PDE from CAPD patients with peritonitis [86]. The activity of proinflammatory master cytokine IL-1 β is regulated by sequentially synthesis and cleavage of pro-IL-1 by caspase-1 (also named as IL-1 converting enzyme) [87, 88]. The production of pro-IL-1 is signaled by TLR and the activation of caspase-1 requires the assembly and activity of a cytosolic multi-protein complex known as the inflammasome, consisting of nucleotide-binding oligomerization-like receptor family members (NLRs) [89]. NLRP3 is the best characterized NLRs

which recruits caspase-1 to the inflammasome. In macrophage, soluble BGN induces the NLRP3 inflammasome, activating caspase-1 and releasing mature IL-1 β [90]. Most notably, the pro-inflammatory events initiated by HA or BGN are also ROS dependent [91]. Figure 2 illustrates the complex interaction amongst various endogenous modulators in relation to peritoneal inflammation.

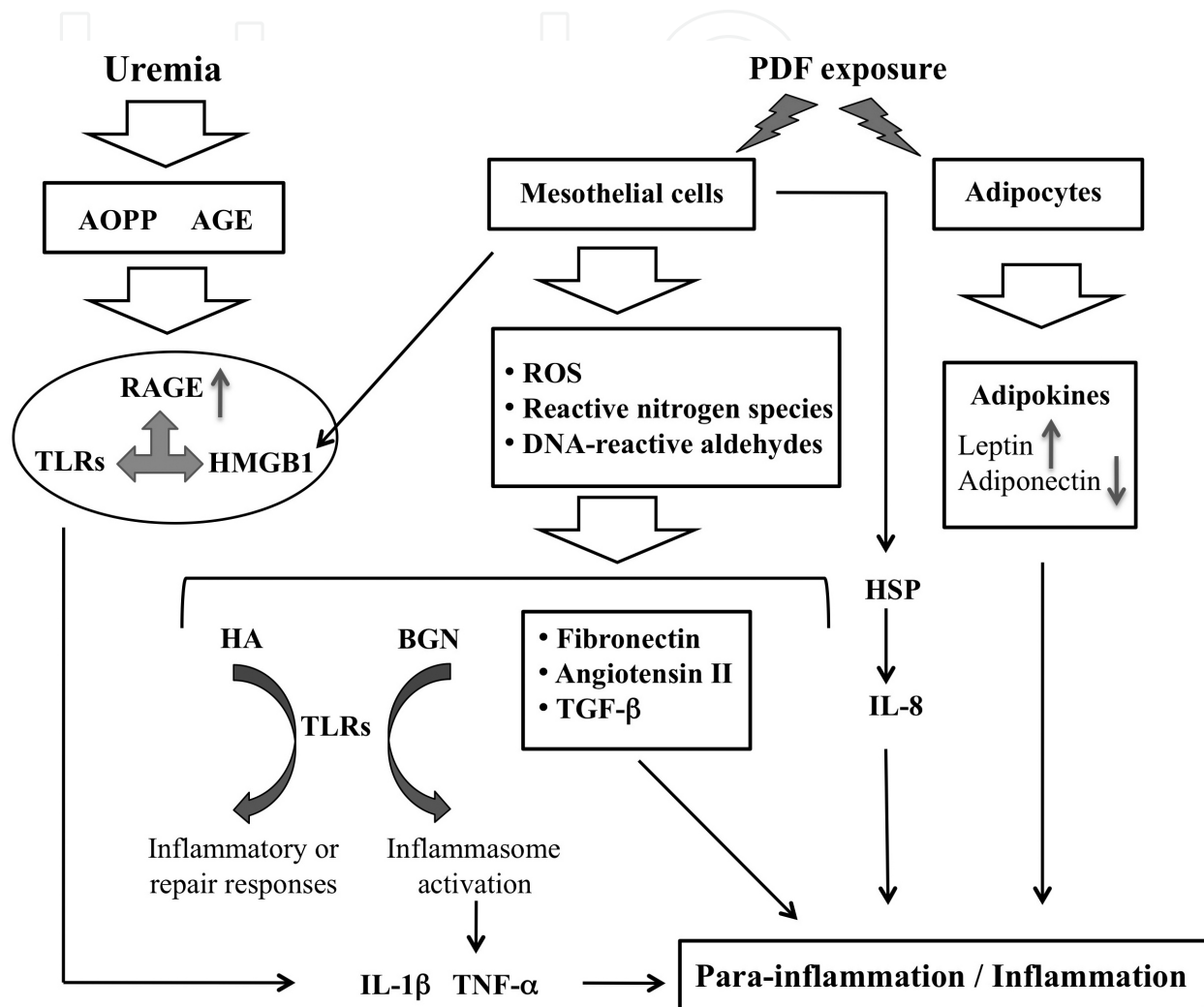


Figure 2. Endogenous modulators in the regulation of peritoneal inflammation

4. Mediators

An array of inflammatory mediators is significantly induced or up-regulated following PD, and is known to modulate the structure and function of the peritoneal membrane, as well as the function of the downstream effectors of the inflammatory pathway. Of equally important, these mediators also play a central role in the maintenance of homeostasis in peritoneum. These mediators are either derived from plasma proteins or secreted by infiltrating or resident peritoneal cells. While many of these inflammatory mediators have overlapped effects on the

vasculature and on the recruitment of leukocytes, other mediators may perform additional specific functions and are produced directly in response to particular stimulation by PD-related modulators. It should be noted that some mediators can induce the production of other inflammatory mediators and it is important to understand the logic underlying this hierarchy of mediators induction. The soluble mediators of PD-related inflammation classified according to their biochemical properties is shown in Table 1.

Acute Phase Proteins		Chemokines and Circulating Adhesion Molecules		
CRP		IL-8	sICAM-1	
NGAL		MIF	sVCAM-1	
		MCP-1	RANTES	
		SDF-1		
Complement Components		Cytokines and Adipokines		
C3	C3a	CTGF	TNF- α	Adiponectin
C4	C4a	IFN- γ	TGF- β	Apelin
C5a	Crry	IL-1	VEGF	Leptin
CD59		IL-6	RBP-4	HGF
		FGF-2		
Lipid Mediators		Vasoactive Substances		
PGE2		Histamine	PRA	
PAF		AngII	ET	
5-LOX		ANP		
Proteolytic Enzymes				
MMP-2, 3, 7, 9				
TIMP-1				
Tryptase				

There are many other members in each category, only those commonly reported are listed.

Table 1. Mediators of PD-related inflammation

4.1. Acute phase proteins

Emerging evidences have suggested that acute phase proteins generated during PD may have additional function instead of just serving as the markers of inflammation. CRP plays a

proinflammatory role in activating monocyte chemotactic protein [92]. Data from studies on endothelial cells, monocytes-macrophages and smooth muscle cells support a direct role for CRP in atherogenesis [93-95]. NGAL has been evaluated as an urinary biomarker for detecting the early onset of renal tubular cell injury [96]. In CAPD, NGAL in PDE is a marker for neutrophil-dependent bacterial peritonitis, and is also synthesized by HPMC induced specifically by IL1- β [53]. NGAL directly involves in the pathogenesis of CKD and cardiovascular abnormality [97].

Residential Effectors:	Major Soluble Factors
Adipocyte	Adiponectin, IL-6, leptin, RBP-4
Endothelial cell	MCP-1, IL-6, IL-8, sICAM-1, sVCAM-1
Fibroblast	Collagen, PGE-2, HA, IL-8
Macrophage	PGE2, IL-1, IL-6, IL-8, MCP-1, TNF- α
Mast cell	Histamine, IL-8, TNF- α , TGF- β , tryptase, VEGF
Mesothelial cell	Chemokines, HA, FGF-2, HA, TGF- β , TNF- α , VEGF
Recruited Effectors:	
Lymphocyte	TGF- β , IFN- γ
Macrophage	PGE-2, IL-1, MCP-1, TNF- α
Mast cell	Histamine, tryptase, VEGF
Polymorphonuclear cell	Soluble IL-6, TNF- α , elastase

Table 2. Effectors in PD-related Inflammation

4.2. Chemokines and circulating adhesion molecules

In response to modulators of peritoneal inflammation, chemokines are produced by peritoneal cells including HPMC [98], macrophages [43], adipocytes [99], to control leukocyte extravasation and chemotaxis towards the affected tissues. These chemokines includes IL-8 [98, 100], MCP-1 [98, 101], macrophage inhibitory factor (MIF) [102], and regulated upon activation normal T cell expressed and secreted (RANTES) [98, 101]. Strikingly, HPMC express the α -chemokine stromal derived factor-1 (SDF-1) [103]. The expression levels of SDF-1 is up-regulated by TGF- β 1 treatment, resulting in an increased migratory potential of HPMC, which is suggested to be involved in the re-epithelialization of denuded basement membrane at the

site of peritoneal injury [104]. Soluble adhesion molecules including soluble intercellular adhesion molecule-1 (sICAM-1) [105] and soluble vascular cell adhesion molecule-1 (sVCAM-1) [106] are produced by endothelial cells during PD, and their concentration correlates with atherogenesis or cardiovascular functions.

4.3. Complement components

Complement activation during PD plays key roles in the maintenance of host homeostasis by eliminating infectious microorganisms and injured cells. Complement activation releases a number of biologically active products that drive peritoneal inflammation [107]. The complement fragments, C3a, C4a and C5a (also known as anaphylatoxins), are produced by several pathways of complement activation. These complement components promote the recruitment of granulocytes and monocytes, and induce mast-cell degranulation, thereby affecting the vasculature of the peritoneum in PD. The synthesis of C3 and C4 by HPMC are regulated by PDF [108]. In rodent model, blocking C5a reduces influx of neutrophils and improve ultrafiltration [109]. Inhibiting the complement activation by complement regulators (CRegs), Crry and CD59, may protect the peritoneal membrane from long-term PD injury [110].

4.4. Cytokines and adipokines

Numerous cytokines are produced by peritoneal cells, infiltrating macrophages or mast cells (Table 1). These cytokines play pluripotent pleiotropic roles in the peritoneal inflammation, participate in the host defense mechanisms and the induction of the acute-phase response. During peritonitis, there is increased release of IL-1 β , IL-6, TGF- β and TNF- α by HPMC [52]. These cytokines may autocrinally induce epithelial to mesenchymal transition (EMT) in HPMC, and this further promotes peritoneal inflammation and fibrosis [29, 111, 112]. In the uremic pre-dialysis and PD patients, there is increased peritoneal expression of the fibroblast growth factor-2 (FGF-2) and VEGF [113]. Compared to patients dialysed with low-GDP containing PDF, patients dialysed with less-biocompatible PDF have increased concentration of TNF- α , hepatocyte growth factor (HGF), and IL-6 in the dialysate [102]. AGE and GDP in PDF differentially regulate the synthesis of connective tissue growth factor (CTGF) by peritoneal resident cells. The CTGF synthesis by HPMC can be further amplified by TGF- β released from peritoneal fibroblast or endothelial cells [114]. Crosstalk among peritoneal cells and their cytokines may amplify the inflammatory cascade. The differential activation of different transcriptional factors and the diverse response of HPMC towards CTGF, TGF- β and VEGF, suggest that peritoneal cytokines have an overlapping and yet distinct role on peritoneal target cells. Other than the cytokines, peritoneal adipocytes can mediate various physiological processes through the secretion of an array of adipokines including leptin, adiponectin, apelin, retinol-binding protein-4 (RBP-4) [103, 115]. These adipokines have distinct functions on peritoneum during PD. For example, leptin augments myofibroblastic conversion of HPMC [116]. The relative levels of leptin and adiponectin in dialysate from PD patients may indicate the risk of cardiovascular disease [117].

4.5. Lipid mediators

Two major classes of lipid mediators, eicosanoids and platelet-activating factors (PAF), are derived from phosphatidylcholine, a member of the phospholipid family that is present in the inner leaflet of cellular membranes. Prostaglandins E₂ (PGE₂) is generated from eicosanoids, whereas PAF is produced by the acetylation of lysophosphatidic acid. PGE₂ causes vasodilation and modulates the change of peritoneal permeability in PD after peritonitis [118]. PAF activates several processes that occur during the inflammatory response, including the recruitment of leukocytes, vascular permeability and platelet activation. Oxidative stress during PD causes unrestrained synthesis of PAF through interfering the proper function of alpha 1-proteinase inhibitor, a PAF inhibitor, [119]. Esterified eicosanoids are produced from 5-Lipoxygenase (5-LOX) by neutrophils after peritonitis, and enhance the generation of IL-8 and superoxide [120].

4.6. Proteolytic enzymes

Proteolytic enzymes have diverse roles in inflammation, in part through degrading ECM and basement-membrane proteins. These proteases have important roles in many processes, including host defense, tissue remodeling and leukocyte migration. Matrix metalloproteinase (MMP) is the most important family of proteolytic enzymes in mesothelial homeostasis and wound repair. Of equal important is the endogenous tissue inhibitors of metalloproteinase (TIMP), which moderate MMP activity. The balance between MMPs and TIMPs, helps to regulate ECM turnover during tissue remodeling in PD. MMP-2 has been associated with the oxidative stress marker in PD [121]. Activation of MMP-2 causes peritoneal injury during peritoneal dialysis in rats [122]. Neutral-pH PDF improves peritoneal function and decreases MMP-2 in patients undergoing CAPD [123]. MMP-2 and TIMP-1 levels in peritoneal effluents reflect solute transport rate and are associated with peritoneal injury [124]. Regression analysis revealed that both the MMP-7 and TIMP-1, are excellent predictors of cellular stress in dialyzed patients using HSP-27 as the marker [125]. The number of mast cells is increased in PD patients [126], and mast cell tryptase is a serine protease implicated in promoting angiogenesis and fibrosis [126, 127].

4.7. Vasoactive substances

Vasoactive amines modulate the vascular permeability, vasodilation, or vasoconstriction of the peritoneal vasculature during PD, and are produced in an all-or-none manner during degranulation from mast cells and platelets. PDF induces peritoneal histamine release from mast cells [128], and this further causes calcium flux, which activates HPMC and influences cytoskeleton organization [129]. The neuropeptide substance P exaggerates the affected microvascular tone, albumin loss and reduced ultrafiltration in a rat PD model [128]. Plasma levels of atrial natriuretic peptide (ANP), pro-renin activity (PRA), and ET are increased in uremic patients on long-term CAPD, and suggesting the risk of development of myocardial function [130]. AngII activates macrophages and fibroblast to secrete proinflammatory cytokines, chemokines, and VEGF [131]. AngII plays important roles in regulating peritoneal extracellular volume and in the development of peritoneal fibrosis [132, 133].

5. Effectors

The effectors of PD inflammatory response are the residential peritoneal cells and the recruited leukocytes. Residential peritoneal effector cells are adipocytes, endothelial cells, fibroblasts, macrophages, mast cells and mesothelial cells. Recruited leukocytes include polymorphonuclear cells (PMN), T or B lymphocytes, macrophages and mast cells. Table 2 shows the cell types and their released mediators, which are of relevance to the PD-induced inflammation.

Upon PD, both the exogenous or endogenous modulators activate peritoneal adipocytes, macrophages and mesothelial cells, which produce inflammatory cytokines, adipokines and growth factors. These mediators will further promote the secretion of angiogenic factors, fibrotic cytokines and growth factors, by fibroblasts, endothelial cells and mast cells through paracrine interaction. In the meantime, residential HPMC, adipocyte and macrophage also release chemotatic mediators to recruit the exogenous inflammatory immune effectors. All these events orchestrate to amplify the inflammatory cascades and eventually lead to the loss of ultrafiltration and development of peritoneal fibrosis.

6. New PDF and immune responses

Emerging evidences suggest the beneficial effects on peritoneal function by using new PDF with decreasing acidity, reducing GDP concentration, and with non-glucose osmotic agents such as amino acids or glucose polymers. *In vitro* cell culture studies have demonstrated enhanced biocompatibility with improved survival of peritoneal cells exposed to new PDF [134-136]. Data from animal models of PD using new PDF also have shown reduced fibrosis and neoangiogenesis, improved macrophage function, and better maintained ultrafiltration [137, 138]. In humans, the use of glucose-polymer-based solution reduced the cholesterol levels with enhanced lipid oxidation and improved serum profiles of adipokines [139-141]. Despite these beneficial effects, use of glucose-polymer-based solution may increase levels of AGE and other immune mediators including IL-6, TNF- α and HA [142-144]. The use of amino-acid-based PDE improves protein malnutrition but exerts negative metabolic effects of increasing serum urea and homocysteine levels [145]. Moreover, PDE level of IL-6 is increased, reflecting the activation of inflammatory response of the peritoneal membrane [146]. The use of glucose-based neutral pH PDF achieves less activation of peritoneal membrane the best preservation of its integrity. The levels of AGE, HA, VEGF and IL-6 are not altered and the effluent-derived macrophage phagocytic function is enhanced [147-150].

7. Conclusion

The PD-related inflammation is an exceedingly complex process. Although some of the destructive events of PD-induced inflammation can be prevented, nevertheless, other long-term damage is understandably unavoidable. The incidences of peritonitis, exit site infection

and catheter malfunction may be decreased with better patient education, optimal exit site care, the use of oral prophylactic antibiotics after wet contamination, and the use of the disconnect systems. The inflammatory modulators in the conventional PDF may be reduced or removed by using novel PDF-based replacement of glucose with icodextrin and amino acids, lactate with bicarbonate at a neutral to physiological pH.

There are potential therapeutic options to minimize peritoneal inflammation in PD patients, but yet need extensive research for further confirmation [151]. Acute peritonitis may be prevented by the use of chemokine receptor blockers, mast cell stabilizers or corticosteroid to block excessive macrophage activity. Chronic PD-related inflammation may be targeted by inhibiting various signaling pathways involved in the inflammatory cascade, or by the introduction of anti-inflammatory agents including anti-RAGE antibodies, bone morphogenetic protein-7 (BMP-7) or Smad7 transgene delivery.

Desperately, if patients have not been given kidney transplant, peritoneum fibrosis will be developed eventually with long term PD. Even after kidney transplant, the restoration and repair of the already injured and thickened peritoneum are still required. Thus, the uppermost challenge is to preserve and at the best, to restore the peritoneum function. Stem cells transplantation either from bone marrow or using mesenchymal stem cells, although still in its infancy, may be an attractive intervention for the repair or replenishment of the cellular reservoir of multi-potential cells of the damaged peritoneal tissue. Further investigation along this direction is warranted.

List of abbreviations

AGE Advanced glycation end products

Ang II Angiotensin II

ANP Atrial natriuretic peptide

AOPP Advanced oxidation protein products

BGN Biglycan

BMP-7 Bone Morphogenetic Protein-7

CAPD Continuous ambulatory peritoneal dialysis

CKD Chronic kidney disease

CRegs Complement regulators

CRP C-reactive protein

GDP Glucose degradation products

ECM Extracellular matrix

EMT Epithelial to mesenchymal transition

ER Endoplasmic reticulum

ESI Exit site infection

ESRD End-stage renal disease

ET Endothelin

FGF-2 Fibroblast growth factor-2

HA Hyaluronan

HD Hemodialysis

HGF Hepatocyte growth factor

HMGB1 High-mobility group box 1 protein

HPMC Human peritoneal mesothelial cells

HSP Heat-shock proteins

iNOS Inducible nitric oxide synthase

IFN- γ Interferon- γ

IL Interleukin

ISPD International Society for Peritoneal Dialysis

5-LOX 5-Lipoxygenase

LPS Lipopolysaccharide

MCP-1 Monocyte chemotactic protein-1

MMP Metalloproteinase

NF- κ B Nuclear factor- κ B

NGAL Neutrophil gelatinase-associated lipocalin

NLRs Nucleotide-binding oligomerization-like receptor family members

PAF Platelet-activating factors

PAMP Pathogen-associated molecular patterns

PD Peritoneal dialysis

PDE Peritoneal dialysate effluent

PGE2 Prostaglandins E2

PDF Peritoneal dialysis fluid

PMN Polymorphonuclear cells

PRA Pro-renin activity

RAGE Receptors of advanced glycation end products

RANTES Regulated upon activation normal T cell expressed and secreted

RBP-4 Retinol-binding protein-4

RNS Reactive nitrogen species

ROS Reactive oxygen species

RRF Renal replacement therapy

SDF-1 Stromal derived factor-1

sICAM-1 Soluble intercellular adhesion molecule-1

sVCAM-1 Soluble vascular cell adhesion molecule-1

TGF- β Transforming growth factor- β

TIMP Tissue inhibitors of metalloproteinases

TLR Toll-like receptor

TNF- α Tumor necrosis factor- α

VEGF Vascular endothelial growth factor

ZO-1 Zonula occludens protein-1

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Author details

Joseph C.K. Leung¹, Loretta Y. Y. Chan¹, Kar Neng Lai² and Sydney C.W. Tang¹

*Address all correspondence to: jckleung@hku.hk

1 Department of Medicine, Queen Mary Hospital, University of Hong Kong, Pokfulam, Hong Kong, China

2 Nephrology Center, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong, China

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