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REVIEW

Strategies for preventing peritoneal fibrosis in peritoneal dialysis patients: new insights based on peritoneal inflammation and angiogenesis

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Abstract **Peritoneal dialysis (PD) is an established form of renal replacement therapy. Long-term PD leads to morphologic and functional changes to the peritoneal membrane (PM), which is defined as peritoneal fibrosis, a known cause of loss of peritoneal ultrafiltration capacity. Inflammation and angiogenesis are key events during the pathogenesis of peritoneal fibrosis. This review discusses the pathophysiology of peritoneal fibrosis and recent research progress on key fibrogenic molecular mechanisms in peritoneal inflammation and angiogenesis, including Toll-like receptor ligand-mediated, NOD-like receptor protein 3/interleukin-1β, vascular endothelial growth factor, and angiopoietin-2/Tie2 signaling pathways. Furthermore, novel strategies targeting peritoneal inflammation and angiogenesis to preserve the PM are discussed in depth.**

Keywords peritoneal dialysis; peritoneal fibrosis; inflammation; angiogenesis

Introduction

Peritoneal dialysis (PD) is an established form of renal replacement therapy for patients with end stage renal disease (ESRD). PD relies on the peritoneal membrane (PM) as a semipermeable barrier for ultrafiltration and diffusion [1]. PM consists of two layers, namely, mesothelial monolayer and submesothelial compact zone comprising connective tissue, wherein fibroblasts, immune cells such as macrophages and mast cells, peritoneal lymphatic vessels, and capillaries are found (Fig. 1) [1]. Until now, there are more than 272 000 patients receiving PD worldwide, representing approximately 11% of global dialysis patients with ESRD [2].

Long-term PD leads to morphologic and functional changes to the PM, which is defined as peritoneal fibrosis, a leading cause of peritoneal ultrafiltration failure. The most important features of peritoneal fibrosis are the loss of MCs, thickening of the submesothelial layer, and angiogenesis (Fig. 1). As differences between fibrosis, sclerosis, and encapsulation have not been clearly elucidated, defining peritoneal fibrosis is difficult [3]. It could vary from mild submesothelial thickening to the rare and fatal cases of encapsulating peritoneal sclerosis [4]. According to data from peritoneal biopsies in PD patients, the prevalence of peritoneal fibrosis is almost universal at midterm duration of PD with bioincompatible PD solutions [5]. Uremia, bioincompatible PD solutions (high glucose, low pH, glucose degradation products [GDP], and advanced glycation end products [AGEs]), and peritonitis are known contributors to peritoneal fibrosis [6–8]. Peritoneal inflammation and angiogenesis are key events during the development of peritoneal fibrosis. Inflammation is characterized by the enhanced production of proinflammatory factors, such as C-reactive protein, tumor necrosis factor-α (TNF-α), and various interleukins (ILs). Angiogenesis, on the other hand, results from increased production of vascular endothelial growth factor (VEGF) and other proangiogenic factors that stimulate the formation of new capillaries in the PM [9].

The present review will discuss the recent research progress on the pathophysiology of peritoneal fibrosis. In particular, we will focus on the individual and interactive molecule mechanisms of peritoneal inflammation and angiogenesis in the pathogenesis of peritoneal fibrosis. Meanwhile, selective strategies targeting peritoneal inflammation and angiogenesis for the preservation of the PM are introduced in detail.

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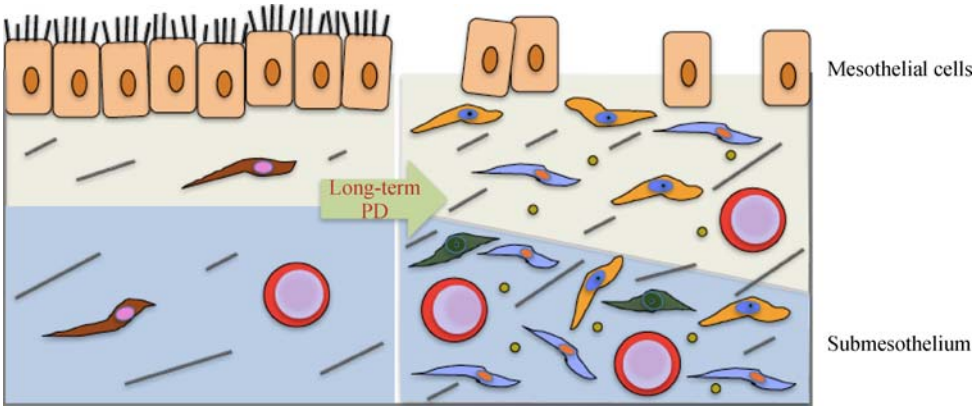

Fig. 1 Schematic diagram showing the structure of normal peritoneum and peritoneal fibrosis. The left side of the figure: The peritoneum of a healthy subject is lined with a continuous monolayer of mesothelial cells (MCs,) with multiple microvilli on the apical surface. The submesothelium is composed of connective tissue with blood vessels ( ) and few resident fibroblasts ( ). The right side of the figure: Peritoneal fibrosis is characterized by mesothelial denudation, decreased microvilli density, thickening of the submesothelium attributed to increased matrix protein deposition, infiltration of myofibroblasts, and neoangiogenesis. In this process, peritoneal inflammation and the release of inflammatory factors ( ) are observed. Myofibroblasts may originate from activated fibroblasts ( ), MCs that have undergone epithelial mesenchymal transdifferentiation (EMT) ( ), or circulating cells such as fibrocytes ( ).

Pathophysiology of peritoneal fibrosis

Peritoneal Inflammation

Peritoneal injury causes activation of macrophages, neutrophils, endothelial cells (ECs), and MCs, which are the principle sources of proinflammatory cytokines and fibrotic mediators in response to external signals [10,11]. Once activated, they are able to recognize the bacterial pathogens through Toll-like receptors (TLRs), resulting in the activation of nuclear factor-κB (NF-κB) signaling pathways and subsequent secretion of numerous inflammatory cytokines, including IL-6, IL-1β, IL-8, TNF-α, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein 2 [12–14]. Overexpression of these cytokines leads to acute inflammatory response, neutrophil accumulation, mononuclear cell recruitment, and activation of resident fibroblasts, termed "myofibroblast," which play a vital role in peritoneal fibrosis by secreting extracellular matrix [8]. Apart from resident fibroblasts, myofibroblasts are also derived from MCs and fibrocytes [15]. Peritoneal inflammation is finally followed by EMT of MCs triggered by inflammation and results in peritoneal fibrosis and angiogenesis.

A number of factors potentially trigger the inflammatory response. First of all, peritonitis remains a main complication in PD patients, leading to MC damage and fibrosis. Moreover, uremic toxins, such as asymmetric dimethylarginine, homocysteine, and modified proteins (i.e., AGE); mechanical stress of the vascular wall (as a result of hypertension); comorbidities such as advanced age and diabetes; and extra-osseous calcification all contribute to peritoneal inflammation [16]. AGEs, derived from glucose and GDPs contained in the PD solution, bind to receptors for AGEs (RAGE) and then stimulate the upregulation of NF-κB, MCP-1, and proinflammatory cytokines, such as IL-6 and TNF-α [17]. RAGE activation mediates the activation of TGF-β-Smad signaling, which is an essential signaling pathway involved in peritoneal fibrosis [18]. On the other hand, bioincompatible PD solution is also associated with production of proinflammatory and profibrotic cytokines. In a retrospective study, we showed that high peritoneal glucose exposure is associated with increased incidence of relapsing/recurrent peritonitis in PD patients, and high glucose may conduct proinflammatory and profibrotic reactions in the peritoneal cavity [19]. It can also upregulate IL-6 synthesis in Met-5A cells (immortalized human MCs derived from pleural fluids obtained from non-cancerous individuals) [20].

IL-6 is a key player in modulating peritoneal inflammation. Our previous studies indicate that intraperitoneal IL-6 and IL-6 polymorphisms were associated with increasing peritoneal solute transport rate [21,22]. IL-6 and soluble IL-6 receptor induce the synthesis and secretion of MCP-1, which attracts monocytes and lymphocytes. In addition, IL-6 also induces the formation of MCP-3 and IL-8, which are involved in the pathogenesis of peritoneal inflammation [23]. High dialysate glucose concentration resulted in proportionate increase of intraperitoneal IL-6 production [19]. Chemokines such as MCP-1/CCL2 and IL-8/CXCL8; granulocyte colony-stimulating factor, which mobilizes neutrophils from the bone marrow and promotes their survival; and CCL5, which is a strong chemoattractant for mononuclear leukocytes, can be synthesized by peritoneal fibroblasts [24,25].

Selective molecular mechanisms of peritoneal inflammation

Toll-like receptor ligand-mediated signaling pathways

TLRs can be expressed by non-classical immune cells, such as ECs and MCs. TLRs expressed by MCs play an important role in peritoneal inflammation. Human MCs express Gram-positive and Gram-negative TLRs, including TLR1, TLR2, and TRL5 but not TLR4 [26]. When binding to ligands, TLRs induce MyD88-dependent signaling pathway, which leads to the activation of downstream molecules of ERK1/2, p38 MAPKs, NF-κB, and c-Jun N-terminal kinase (JNK) and induction of proinflammatory cytokines, including TNF-α and IL-6 (Fig. 2) [27].

The activation of NF-κB typically involves phosphorylation of nuclear factor of κ light polypeptide gene enhancer in B cell inhibitor (IκB) by the inhibitor of NF-κB kinase complex. The phosphorylation of IκB leads to its ubiquitylation and subsequent degradation, which allows the release of NF-κB and its translocation to the nucleus. Furthermore, MAPKs pass the signals to p38 and JNKs to activate cAMP-responsive element and activator protein-1 transcription factors inducing the transcription of inflammatory cytokines and chemokines [28].

In MCs, inhibition of the ERK1/2 pathway attenuated EMT, which was mediated by TGF-β1 in combination with IL-1β. Moreover, blockade of ERK1/2 promoted mesenchymal-to-epithelial transition in MCs that had undergone EMT *in vivo* [29]. The p38 MAPK pathway plays a role in the control of cell differentiation and apoptosis [30]. p38 activity maintains E-cadherin expression in MCs, and the p38 MAPK pathway modulates the mesenchymal conversion of MCs by a feedback mechanism based on the downregulation of 25ERK1/2 and TAK-1/NF-κB activities [31]. NF-κB controls Snail expression and cooperates with Snail in inducing fibronectin transcription [32,33]. Inhibition of NF-κB partially reverses EMT in MCs collected from PD patients [29]. Interestingly, NF-κB nuclear translocation and transcriptional activity are enhanced by MEK-ERK1/2 pathways but inhibited by the p38 MAPK pathway [31]. Similar to ERK1/2 inhibition, JNK inhibition is also associated with E-cadherin maintenance and blockade of EMT in MCs [33,34].

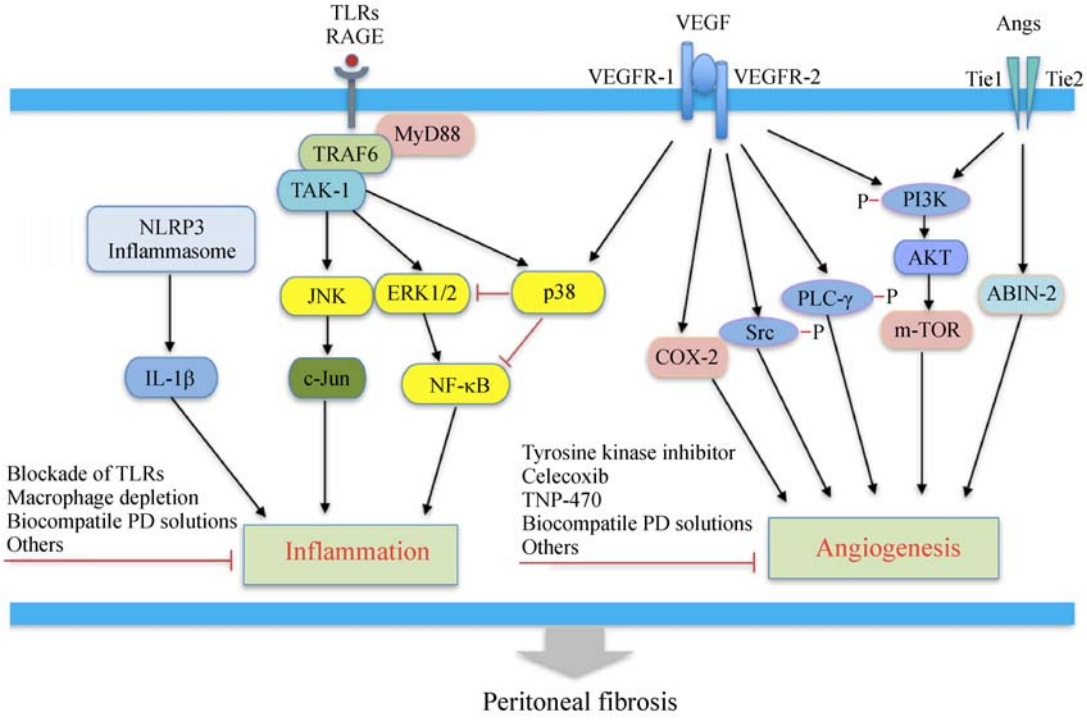

Fig. 2 Selective molecular mechanisms of peritoneal inflammation and angiogenesis and their contribution to peritoneal fibrosis. TLR ligands activate redundant pathways leading to the activation of ERK1/2, MAPKs, NF-κB, and JNK and inflammation. Activation of NLRP3 inflammasome triggers IL-1β release and inflammation. VEGF, when bound to VEGFR-2, induces the phosphorylation of phospholipase (PL) C-γ, PI3K, MAPK, and the Src family and expression of COX-2, which are involved in angiogenesis. Angiopoietin-1 and angiopoietin-2 bind to Tie1/Tie2 and activate the PI3K/Akt and ABIN-2 pathways. They play an important role in angiogenesis. NLRP3, NOD-like receptor protein 3; IL, interleukin; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor-κB; COX-2, cyclooxygenase-2; PI3K, phosphatidylinositol-3-kinase; m-TOR, mammalian target of rapamycin; Angs, angiopoietins; ABIN-2, A20 binding inhibitor of NF-κB-2; P, phosphate.

NOD-like receptor protein 3/interleukin-1β signaling

Recently, the role of inflammasomes in peritonitis has attracted the attention of researchers. We demonstrated that NOD-like receptor protein 3 (NLRP3) inflammasome mediated contrast-induced acute kidney injury through modulating the apoptotic pathway, which provided a potential therapeutic target for its treatment [35].

Hautem and colleagues demonstrated that the NLRP3 inflammasome is activated during peritonitis in patients on PD and in mouse model of peritonitis [36]. Activated NLRP3 is directly involved in PD-related inflammatory response, which leads to structural and functional impairment in the PM. An early report demonstrated that the IL-1β pathway was involved in enhancing the EMT of MCs because an additive morphologic effect of TGFβ1 in combination with IL-1β could be observed in MCs [37]. In co-treatment with TGFβ1 and IL-1β, EMT was enhanced in primary MCs [38]. NLRP3 knockout and administration of IL-1β receptor antagonist anakinra could treat peritoneal morphologic alterations and transport defects during acute peritonitis, which revealed novel therapeutic perspectives for peritonitis in PD patients [36]. When exposed to high glucose-based PD solutions, human peritoneal MCs produce increased ROS, which further triggers NLRP3 inflammasome activation and leads to increased IL-1β secretion (Fig. 2) [39]. These data provide a basis for further development of therapeutic strategy for protecting the peritoneum membrane during long-term PD.

Angiogenesis

Angiogenesis and vasculopathy are observed in the peritoneum of patients in long-term PD, and the degree of vascularization correlates with the area of fibrotic tissue, suggesting the involvement of angiogenesis in the progression of peritoneal fibrosis.

Angiogenesis is defined as the formation of new blood vessels. Catheterization, uremia, glucose, GDPs, AGEs, and peritonitis are risk factors that contribute to angiogenesis. In a uremic rat model, we demonstrated peritoneal angiogenesis and fibrosis following PD therapy, which is accompanied with increased expression of angiopoietin (Ang)-2 and reduced expression of Ang receptor Tie2 [40]. The significance of Ang-2/Tie2 signaling in peritoneal angiogenesis will be discussed in depth later. VEGF possesses a dominant role in mediating EC sprouting, migration, and network formation. Effluent VEGF concentration increases along with PD duration [41], and it decreases when patients change to glucose-free PDF, which indicates that high glucose is associated with increased production of VEGF [42]. Moreover, AGEs and IL-6 can promote the production of VEGF by MCs. The molecular mechanisms of VEGF in mediating peritoneal angiogenesis will be discussed in the following text.

Many other factors are involved in the formation of new blood vessels. Prostaglandin E2 is involved in angiogenesis by enhancing EC migration and contributing to cell survival [43]. MCP-1 has been shown to be involved in angiogenesis. Stimulating ECs with MCP-1 enhances cell migration and the induction of angiogenesis-related genes which resulted in capillary-like tube formation [44]. Overexpression of IL-1β leads to sustained angiogenesis and submesothelial thickening and fibrosis *in vivo* [45]. In addition, IL-1β increases vessel-like structures through enhancing VEGF production and downregulation of Ang-1 and augments EC proliferation [46]. IL-6 stimulates endothelial progenitor cell proliferation and migration, and IL-6 trans-signaling induces VEGF synthesis. However, IL-8 enhances EC survival, proliferation, and capillary tube formation [20,47–49]. TNF-α causes capillary-like blood vessel formation induction *in vitro* and *in vivo* [50].

Selective molecular mechanisms of angiogenesis

Vascular endothelial growth factor signaling

VEGF belongs to a gene family that includes VEGFA, placental growth factor, VEGFB, VEGFC, and VEGFD. VEGF is a key player in peritoneal angiogenesis. Bioincompatible PD solution, growth factors (epidermal growth factor and TGF-β1), and inflammatory cytokines (IL-1α, IL-6) are major inducers of VEGF production instead of release [51,52].

Even though the molecular mechanism of VEGF-inducing angiogenesis is not fully explained, inhibiting the expression of VEGF could reduce pathological angiogenesis in a wide variety of tumor models [53]. Recently, in a mice PD model, inhibiting the synthesis of VEGF reduced angiogenesis and lymphangiogenesis in the peritoneum [54]. Inhibition of VEGF expression or VEGF signaling can prevent angiogenesis in the omentum and parietal peritoneum in PD patients [43,53].

VEGFA binds two related receptor tyrosine kinases (RTKs), VEGFR-1 and VEGFR-2, which are expressed on the cell surface of vascular ECs. VEGFR-1 signaling is involved in the release of vascular-bed specific growth factors, and VEGFR-2 signaling is a major mediator of EC proliferation, migration, survival, and angiogenesis. When binding to VEGFR-2, VEGFA can induce the phosphorylation of PL C-γ, phosphatidylinositol-3-kinase (PI3K), MAPK, and the Src family, which then mediates the proliferation, migration, survival, and angiogenesis in ECs (Fig. 2) [55]. VEGFC and VEGFD bind to VEGFR-3, which is a member of the same family of RTKs, modulating angiogenesis mostly in lymphatic ECs [56].

Angiopoietin-2/Tie2 signaling

Angs belong to a family of growth factors that are critically involved in blood vessel formation during developmental and pathological angiogenesis.

Ang-1 and Ang-2 are best characterized among the Ang family [57]. They bind to Tie receptors with similar affinities and play a vital role in angiogenesis (Fig. 2). Tie receptors, including Tie1 and Tie2, were originally described as members of an orphan RTK subfamily. Tie1, as an orphan receptor, regulates the effects of Ang-1 and Ang-2 on Tie2 *in vitro* and *in vivo*, which can both negatively and positively regulate Tie2 signaling during angiogenesis, depending on the cellular context [58]. For example, in the presence of Tie1, Ang-2 becomes a Tie2 antagonist under inflammatory conditions, whereas it acts as a Tie2 agonist under pathogen-free conditions, although the precise mechanism by which Tie1 alters Ang/Tie2 signaling is still unclear [58].

Ang-1 is the first identified Tie2 ligand and responsible for baseline Tie2 activation in resting state [59]. Ang-2 was originally described as a competitive antagonist of Ang-1/Tie2 signaling. It acts as a context-dependent agonist/antagonist for Tie2 [60]. For instance, inflammation shifts the effects of Ang-2 from agonist to antagonist [60]. Activated Tie2 receptor stimulates a number of intracellular signaling pathways, including PI3K/Akt, MAPK, and ABIN-2 (A20 binding inhibitor of NF-κB-2) pathways [61]. Engagement of Tie2 by Ang-1 is responsible for receptor phosphorylation and the induction of survival signals in ECs, mediating vessel sprouting and migration. Ang-1 can stabilize the interactions between endothelial and pericytes/smooth muscle cells. In Ang-1 mutant mice, the association of ECs with support cells is evidently decreased [62,63]. Collaborating functions have been described for Ang-2. Ang-2 can be upregulated by VEGF or hypoxia, which results in vessel destabilization. Binding of Tie2 by Ang-2 antagonizes receptor phosphorylation in transgenic animals, thereby disrupting contacts between endothelial and peri-endothelial support and smooth muscle cells. This process is fundamental for the initiation of vessel sprouting or regression [43].

Our previous study investigated the relationship between Ang/Tie2 and peritoneal angiogenesis. We demonstrated increased levels of Ang-2 and Tie2 in conditions of uremia and PD therapy, which were correlated with peritoneal angiogenesis and functional deterioration [64]. Consistent with our findings, Zareie *et al.* showed an increase in the number of blood vessels in the omentum, mesentery, and parietal peritoneum upon PD treatment [65]. Furthermore, supplementation with sTie2/Fc partially inhibited tube formation and migration in human omental tissue microvascular ECs [60]. The findings were further confirmed in a rat PD model [66,67]. In addition, Ang-2 levels are associated with systemic markers/mediators of micro-inflammation, and elevated Ang-2 levels are strong predictors of long-term mortality in CKD patients, independent of arterial stiffness index or vascular calcification [67].

Preventive strategies for peritoneal fibrosis

Strategies targeting peritoneal inflammation

As peritoneal inflammation is a main mechanism involved in peritoneal fibrosis, its inhibition may be effective for preventing peritoneum damage during long-term PD (Fig. 2).

Blockade of Toll-like receptors

Given the fundamental role of TLRs in peritoneal inflammation, Raby and colleagues assessed the potential effect of blocking TLRs in PD-associated fibrosis. They found that proinflammatory genes were markedly down-regulated by soluble TLR2, a negative modulator of TLRs. Meanwhile, Gram-positive and Gram-negative bacteria-induced fibrosis *in vivo* was reduced, and fibrotic gene expressions were inhibited. These findings revealed the significance of peritoneal TLR2 and TLR4 in PD-associated fibrosis and suggested a novel therapeutic strategy against peritoneal fibrosis [68,69].

Macrophage depletion

As macrophages are major inducers of proinflammatory factors, targeting infiltrating macrophages can be a potential therapeutic intervention. When liposome-encapsulated clodronate was administrated in rat PD model to deplete macrophages, peritoneal fibrosis was attenuated significantly, with decrease in the number of cytokeratin and stained α-smooth muscle actin (α-SMA)-positive MCs, and reduced expressions of TGF-β1 and collagen types I and II [70].

Biocompatible peritoneal dialysis solutions

Biocompatible PD solutions with physiologic pH, bicarbonate–lactate buffers, and lower GDPs using non-glucose osmotic agents such as amino acid and icodextrin have been developed in recent years. Neutral pH and low GDP solution were associated with significant improvement in the effluent biomarkers of PM integrity and peritoneal UF, such as CA125, hepatocyte growth factor, and IL-6, and decreased effluent circulating AGE levels and markers of EMT in MCs from PD patients [71,72]. The

plasma and dialysate IL-6 and TGF-β1 levels were decreased in CAPD patients treated with biocompatible PD solutions. Meanwhile, inflammation and high peritoneal small-solute transport rate have also been improved [73].

Others

Alanyl-glutamine (Ala-Gln), a dipeptide with immunomodulatory effects, improved resistance of MCs to PD fluids. Supplementation of PD fluid with Ala-Gln resulted in reduced peritoneal thickness, α-SMA expression, and angiogenesis in rat and mouse PD models. The addition of Ala-Gln also attenuated IL-17 expression induced by PD, reflected by substantial reduction or normalization of peritoneal levels of IL-17, TGF-β1, and IL-6 [74].

Additionally, immunosuppressants (glucocorticoid, azathioprine, and cyclosporine) prevented peritoneal fibrosis through downregulation of cytokine production and infiltration of macrophages in rat encapsulating peritoneal sclerosis models [75]. Mycophenolate mofetil and mizoribine showed similar inhibitory effects on peritoneal fibrosis [76,77].

Strategies targeting angiogenesis

Tyrosine kinase inhibitor

Sunitinib is a tyrosine kinase inhibitor and is involved in the inhibition of VEGF signaling. Tapiawala and colleagues showed that sunitinib prevented new vessel formation in the omentum and mesentery after five weeks of PD treatment in rats [78]. Furthermore, it significantly abrogated peritoneal overexpression of TGF-β1, MCP-1, and VEGF in encapsulated peritoneal sclerosis rats [79]. Similarly, VEGF blockade and EGFR inhibitor inhibited angiogenesis and suppressed the progression of peritoneal fibrosis in rat PD model [80,81].

Celecoxib

Cyclooxygenase (COX) enzymes are involved in prostaglandin synthesis. COX-2 is known to be an angiogenesis stimulator by upregulating VEGF mRNA transcription and protein production [51]. Furthermore, it enhances the production of prostaglandin E2 [52]. Celecoxib, a COX-2 inhibitor, prevented PD-induced angiogenesis in the omentum and parietal peritoneum of PD rats. Although prostaglandin E2 levels were reduced, VEGF levels were not affected by celecoxib. Most importantly, UF was restored upon celecoxib treatment [82]. Therefore, celecoxib may be effective in the prevention of peritoneal angiogenesis in PD patients.

TNP-470

TNP-470 is a known angiogenesis inhibitor by inhibiting EC proliferation [83]. It shows effects in attenuating peritoneal fibrosis, indicated by reduction of blood vessels and VEGF-expressing cells and suppression of myofibroblast proliferation [83].

Biocompatible peritoneal dialysis solutions

Hekking *et al.* demonstrated reduced neovascularization and fibrosis in PD rats after 9–10 weeks treatment of bicarbonate/lactate-buffered PDF compared with lactate-buffered PDF [84]. Compared with conventional solution, neutral pH and low-GDP-containing PD solution was associated with higher levels of urine output and residual renal function after 12 months [85,86]. However, because it still uses glucose as osmotic agent, the density of blood capillaries was significantly increased compared with biocompatible solution.

Icodextrin improves UF compared with glucose-based solutions, resulting in better control of fluid balance [87]. However, it showed no apparent benefits in preserving residual renal function and peritoneal abilities after two years [88]. Amino acid-based solution showed better effect in the preservation of MCs [82]. However, markers of angiogenesis or predictors of morphological changes of PM were not detected in this study [89]. Peritoneal biopsies from patients receiving biocompatible PD solutions showed less hyalinizing vasculopathy and submesothelial thickness and better MC preservation compared with patients treated with conventional PD solutions [90]. After treatment with biocompatible PD solutions, the plasma and dialysate VEGF and TGF-β1 levels were significantly decreased, and peritoneal angiogenesis and high peritoneal small-solute transport rate were also improved in CAPD patients [73].

Others

Rapamycin shows antifibrotic and antiproliferative effects on blood and lymphatic vessels in the peritoneum [54]. It also inhibits EMT in MCs [91]. Fasudil, a Rho-kinase inhibitor, prevented peritoneal fibrosis and angiogenesis by downregulating the expression of TGF-β1, fibronectin, α-SMA, and VEGF [91,92]. Endostatin also demonstrated antiangiogenic and antifibrotic effects in mouse PD model [93]. Bosentan and macitentan, vasoconstrictor peptide endothelin-1 receptor antagonists, markedly attenuated PD-induced EMT, fibrosis, angiogenesis, and peritoneal functional decline [94]. Sulodexide manifested antiangiogenic effects and attenuated peritoneal fibrosis [95].

Conclusions

Peritoneal fibrosis is a major complication in long-term PD patients, which leads to high cost of health care. Peritoneal inflammation and angiogenesis are the main mechanisms involved in the pathogenesis of peritoneal fibrosis. Many attempts have been made to investigate the molecular mechanisms involved in peritoneal inflammation and angiogenesis, and a number of therapeutic strategies have been suggested to preserve the PM. However, their incidence remains high. Thus, more efforts are needed to better elucidate the molecular mechanisms in the peritoneum in response to inflammatory/proangiogenic signals during PD.

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Compliance with ethics guidelines

Zhen Zhang, Na Jiang, and Zhaohui Ni declare that they have no conflicts of interest. This manuscript is a review article and does not involve protocol requiring approval by the relevant institutional review board or ethic committee.

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