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Review

Molecular pathways in peritoneal fibrosis

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ABSTRACT

Peritoneal dialysis (PD) is a renal replacement therapy for patients with end-stage renal disease that is equivalent to hemodialysis with respect to adequacy, mortality, and other outcome parameters, yet providing superior quality-of-life measures and cost savings. However, long-term usage of the patient's peritoneal membrane as a dialyzer filter is unphysiological and leads to peritoneal fibrosis, which is a major factor of patient morbidity and PD technique failure, resulting in a transfer to hemodialysis or death. Peritoneal fibrosis pathophysiology involves chronic inflammation and the fibrotic process itself. Frequently, inflammation precedes membrane fibrosis development, although a bidirectional relationship of one inducing the other exists. This review aims at highlighting the histopathological definition of peritoneal fibrosis, outlining the interplay of fibrosis, angiogenesis and epithelial-to-mesenchymal transition (EMT), delineating important fibrogenic pathways involving Smad-dependent and Smad-independent transforming growth factor-β (TGF-β) as well as connective tissue growth factor (CTGF) signaling, and summarizing historic and recent studies of inflammatory pathways involving NOD-like receptor protein 3 (NLRP3)/interleukin (IL)-1β, IL-6, IL-17, and other cytokines.

1. Introduction

Peritoneal dialysis (PD) is a life-sustaining renal replacement therapy for around 10–15% of patients with end-stage renal disease worldwide. It is equivalent to hemodialysis with respect to adequacy, mortality and other outcome parameters [1,2], yet provides better preservation of residual renal function, superior quality-of-life measures, and cost savings [3–6]. The large surface of the peritoneum together with its dense vascularization facilitates high solute and water transport across the peritoneal membrane, which can be used to serve as a natural dialysis filter when a hypertonic, mostly glucose-based solution is introduced into the peritoneal cavity and exchanged several times per day via an intraperitoneal catheter. Hypertonicity serves as the driving osmolar force for equilibration of uremic and other solutes as well as ultrafiltration of excess water from the intravascular to the intraperitoneal space. As such a use of the peritoneum is unphysiological, a major problem of PD is its short technique survival due to functional membrane failure in a significant proportion of patients (around 50%). This functional failure finds its morphological correlate in the form of peritoneal inflammation, angiogenesis, and fibrosis [8].

It is known that these processes are triggered by a multitude of factors, such as the uremic state of end-stage renal disease, mechanical irritation by the presence of an intraabdominal catheter, and most prominently by the composition of PD solutions: Hypertonicity for the generation of crystalloid osmosis [9], glucose degradation products (GDPs) formed during heat sterilization of PD solutions [10,11], high glucose content [12] and formation of advanced glycation end products (AGEs) both in the peritoneal cavity [13,14], as well as the systemic circulation [15] are all detrimental to peritoneal integrity (Fig. 1). Over recent decades, major advances have been made towards more biocompatible solutions. In comparison to earlier solutions used, state-of-the-art PD solutions have a neutral pH, as lactate has been replaced by bicarbonate to facilitate buffering, and the introduction of double chamber bags led to considerably reduced GDP content [16]. However, increasing survival and slowing the deterioration of the peritoneal membrane continues to be a major problem in PD. [17]

It is important to note that peritoneal fibrosis development is preceded substantially by functional changes that alter water and solute permeability. Retrospectively looking at patients who would later develop EPS, Lambie et al. showed that ultrafiltration capacity was significantly worse at least 2 years before stopping PD for those patients developing EPS than in matched patients who did not develop EPS,

Abbreviations: AGE, advanced glycation end product; CAPD, continuous ambulatory peritoneal dialysis; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ESRD, end stage renal disease; GDP, glucose degradation product; PD, peritoneal dialysis

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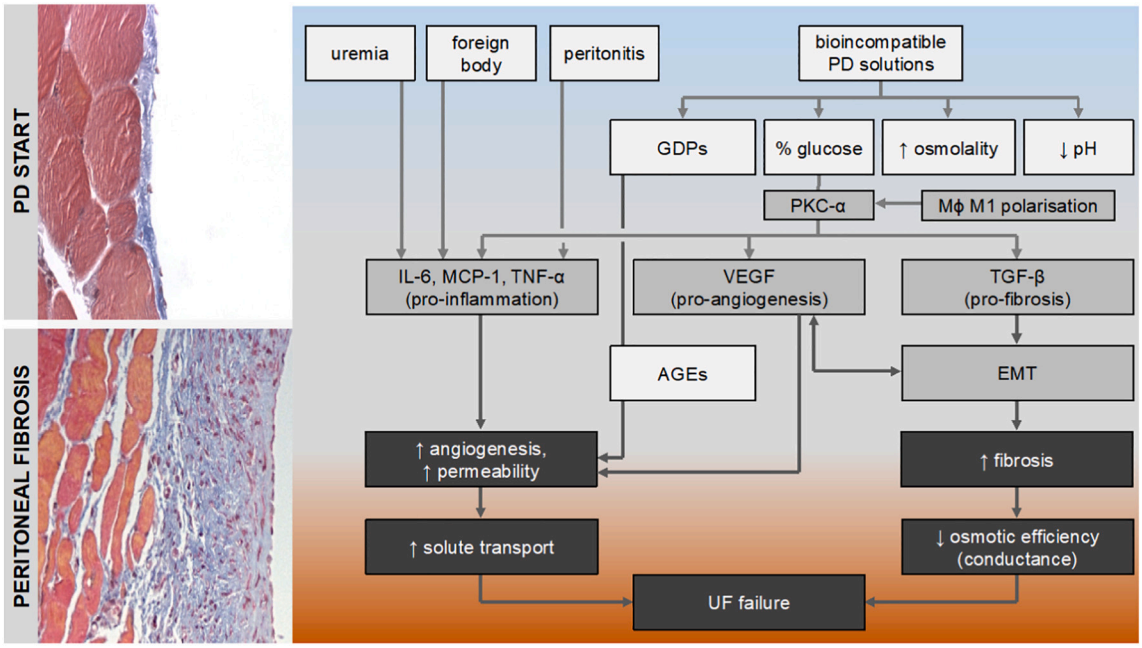

Fig. 1. Common causes and pathways of peritoneal membrane damage. AGEs = advanced glycation end products; EMT, endothelial-to-mesenchymal transition; GDPs = glucose degradation products; IL-6 = Interleukin-6; MCP-1 = monocyte chemoattractant protein-1; Mϕ = macrophage; PD = peritoneal dialysis; PKC = protein kinase C; TNF-α = Tumor necrosis factor- α; TGF-β = Transforming growth factor- β; UF = ultrafiltration; VEGF = vascular endothelial growth factor.

suggesting reduced osmotic conductance [18]. Although both groups did not have different solute transport up until PD termination, it is interesting to note that the slope of solute transport increase seemed to be steeper in those patients who would later develop EPS [18], underlining the disconnect of earlier functional vs. later structural changes at the peritoneal membrane. Similarly, as it has been demonstrated in peritoneal biopsy studies that specimens with fibrosis/vasculopathy do exist in the presence of an intact mesothelium, the authors concluded that it is likely that submesothelial changes such as vasculopathy precede mesothelial cell layer loss [19].

Technique survival remains to be an important issue for patients on PD and a substantial proportion of patients drops out of PD due to technique failure even in the absence of fibrosis. Baseline peritoneal transport status as well as detrimental changes to the peritoneal membrane secondary to inflammation and repeated peritonitis episodes are crucial aspects to focus on if we want to improve technique survival for patients on PD. Nevertheless, these early changes ultimately drive later development of peritoneal fibrosis. Unraveling the mechanisms of peritoneal fibrosis development is still at the heart of efforts to slow the peritoneal membrane function decline and improve PD outcomes. After discussing the histopathological definition of peritoneal fibrosis, this review therefore outlines the interplay of fibrosis, angiogenesis, and epithelial-to-mesenchymal transition (EMT), and delineates important fibrogenic pathways that have mainly been studied in animal studies.

2. Histological definition of peritoneal fibrosis

Features of peritoneal fibrosis in PD patients were first described in the early 1980s in ultrastructural studies of the peritoneum in patients undergoing chronic ambulatory PD (CAPD) [20]. These features were distinguished from findings in peritoneal biopsies of normal human, mouse and rat samples and encompassed mainly degenerative changes of the mesothelial cell layer. The same group later published categorized findings of the International Peritoneal Biopsy Registry (IPBR), which was a registry set up for the collection and morphological examination of specimens of peritoneal tissue obtained at surgical implantation or removal of the catheter before, during or after treatment with continuous ambulatory PD. [7] In this report, marked changes in response to uremia but prior to commencement of PD were noted systematically for the first time, such as distinctive cytoplasmic inclusions in mesothelial cells in 21 of 57 biopsies (37%). Signs of focal defoliation of mesothelium such as ruptured cell membranes lying on the surface of the peritoneum were also described [7]. Most interestingly, after comparing peritoneal biopsy specimens from uremic and PD patients, the authors concluded that the process of continued dialysis would not induce further significant pathological change in the peritoneal mesothelium, whereas progressive changes were noted in the submesothelial stroma and blood vessels. The term “peritoneal fibrosis” was then coined later in a nephrology forum report that discussed histological findings from a single patient on CAPD and already made mention of the implication of major profibrotic cytokines, such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), interleukin-1 (IL-1), interferon-ɣ (IFN-ɣ), and tumor necrosis factor-α (TNF-α) [21]. In a seminal paper, Williams et al. correlated structural changes of the parietal peritoneum of 130 PD patients with functional characteristics, noting an increase in submesothelial zone thickness and progressive vasculopathy with duration of PD as well as a higher blood vessel density in patients with membrane failure [19]. It is important to note that data on differentiating common peritoneal fibrosis, affecting more than 50% of PD patients at some point, from rare and catastrophic encapsulating peritoneal sclerosis (EPS) are conflicting: While an earlier Japanese study [22] noted no difference in submesothelial thickness, two other studies out of Italy [23] and Japan [24] demonstrated significant differences in thickness of the submesothelial compact zone. As another example, Garosi et al. noted increased vasculopathy in EPS patients [23], whereas the other two studies did not [22,24]. There is an ongoing debate whether EPS can be considered a separate disease entity with different pathophysiology or whether it is an extreme occurrence of peritoneal fibrosis along a spectrum with the same pathophysiology. For the sake of simplicity, EPS-specific pathophysiology and signaling mechanisms are disregarded for this review. Furthermore, it is important to note that the literature has not been very precise in differentiating peritoneal fibrosis from sclerosis and encapsulating fibrosis/sclerosis, respectively. This is

Table 1
Histopathological features in peritoneum under normal, uremic and PD conditions, as adapted from Dobbie et al. [7].

Normal peritoneum	Peritoneum during uremia	Peritoneum during PD
Thin mesothelial layer Intact tight junctions (basal interdigitation)	Cytoplasmic inclusions in mesothelial cells	Cytoplasmic inclusions in mesothelial cells Abnormal surface protuberances (variously shaped projections, blisters and blebs)
Mesothelium rests on a thin basement membrane	Focal defoliation of mesothelium (ruptured cell membranes, detachment from basement membrane)	Focal defoliation of mesothelium (ruptured cell membranes, detachment from basement membrane)
		Thickening and diabetiform basement membrane reduplication Occasional mesothelial denudation, especially in the presence of accompanying inflammation Failed re-mesothelialization, conversion of stroma to a 'cellular desert': pale hyalinized fibrous tissue void of any cells
Submesothelial zone with only sparse mesenchymal cells (well-spaced out fibroblasts, occasional mast cells)		Submesothelial zone thickening
Submesothelial zone with limited number of small arteries, arterioles, capillaries and venules		Submesothelial zone with increased blood vessel density
		Submesothelial zone vasculopathy (vessel calcification, obliteration, adventitial proliferation)

underscored by the fact that these terms are still used and cited interchangeably, which is also due to the fact that – as stated above – it is still unclear, whether EPS and peritoneal fibrosis are two distinct diseases with different pathophysiology or opposing ends of a continuum of fibrotic changes. Taken together, however, denudation of the mesothelial cell layer and thickening of the submesothelial cell layer along with vasculopathy are considered main features of peritoneal fibrosis (Table 1) [19,25–27].

3. Pathophysiology interplay of fibrosis, angiogenesis, and epithelial-to-mesenchymal transition (EMT)

Research over the last two decades has shown that peritoneal fibrosis is tightly associated with inflammation, angiogenesis, and epithelial-to-mesenchymal transition (EMT), and that these processes are influencing each other [28]. Along those lines, peritoneal fibrosis can be regarded as a hallmark of final destructive changes along a spectrum of different other detrimental processes that might take place in parallel or precede fibrotic changes [29]. One of the processes receiving much attention over the last years is epithelial-to-mesenchymal transition (EMT). In this process, epithelial cells undergo a transition in which they lose their cell-cell contacts, cell-matrix interaction, cell polarity, and consequently their epithelial markers and gain a mesenchymal motile phenotype [30]. EMT plays an important role both in organ development and wound healing, but also in disease, including cancer and tissue fibrosis. In the peritoneum, this has also been referred to as mesothelial-to-mesenchymal transition. During this transitional process, mesothelial cells migrate from the superficial mesothelial layer towards the submesothelium, where they produce extracellular matrix (ECM), thereby contributing to fibrosis [31]. Mesothelial cells that undergo this process lose their epithelial markers such as E-cadherin, cytokeratin, and zona occludens-1 (ZO-1) and adopt a myofibroblast-like phenotype expressing N-cadherin, vimentin, and α-smooth muscle actin (α-SMA) [32,33]. However, this hypothesis has been questioned by lineage tracing experiments in mice suggesting distinct fates of mesothelial cells and submesothelial fibroblasts after peritoneal injury by showing that type I collagen-producing submesothelial fibroblasts are progenitors of α-SMA-positive myofibroblasts during peritoneal injury [34]. Although these findings still need to be reproduced, it is very well possible that EMT is not the only source of myofibroblast-like submesothelial cells promoting fibrosis during PD. The same study also proposed platelet-derived growth factor receptor-β (PDGFR-β) as an important signaling mechanism that was successfully targeted by tyrosine kinase inhibitor imatinib. There is still an ongoing debate about the individual contribution of EMT-derived myofibroblasts to the pool of submesothelial myofibroblasts on the one hand and activated resident stromal fibroblasts on the other [35]. Just recently, single cell transcriptomics-based analysis demonstrated metabolic reprogramming towards hyperglycolysis in mesothelial cells of PD patients, a process that could be recapitulated by TGF-β in HPMCs in culture [36]. Moreover, the contribution of other processes such as endothelial-to-mesenchymal transition (EndMT) is not clear and warrants further exploration, especially as the vasculature within the submesothelial compact zone is an important determinant for successful peritoneal solute and water exchange during PD.

It has been shown that vascular endothelial growth factor (VEGF)-mediated signaling in angiogenesis is importantly implicated in increased effective vascular surface area of patients on PD, resulting in a decrease in osmotic pressure, which in turn is associated with ultrafiltration failure [37,38]. Vascular wall thickening and increased permeability cause an increase in small solute and glucose transport, thereby effectively reducing the time for exchanging waste products [39]. In vivo studies in rats have demonstrated a connection between increased VEGF production and conventional vs. biocompatible PD fluid use [40]. Furthermore, AGEs are known to upregulate VEGF [14,41]. Studies in PD patients demonstrated a correlation between time on glucose-based PD, increased VEGF production, and ultrafiltration failure. Intriguingly, after patients were switched to a glucose-free PD regime, VEGF levels decreased, indicating a possible role of high glucose concentration in the upregulation of peritoneal VEGF production [42]. In this context, several studies demonstrated that EMT is closely linked to angiogenesis. Aroeira et al. found peritoneal effluent-derived mesothelial cells with typical non-epitheloid morphology suggestive of EMT to be the main source of VEGF production ex vivo [43]. Further in vitro studies in omentum- and peritoneal effluent-derived mesothelial cells showed differential changes in VEGF receptors and coreceptors, where downregulation of Flt-1/VEGFR-1 and Kdr/VEGFR-2 was associated with EMT in human mesothelial cells [44]. In addition, VEGF has been shown to be upregulated during PD-associated EMT in mice [32]. Similarly, a study seeking to evaluate the effect of interaction between TGF-β and VEGF signaling demonstrated that stimulation with TGF-β induced VEGF production in human peritoneal mesothelial cells and a fibroblast cell line [45]. The authors also showed that pharmacological TGF-β inhibition in a rat model of PD decreased not only peritoneal fibrosis but also VEGF production, suggesting the close relationship between TGF-β and VEGF signaling.

Angiogenesis and fibrosis are thus closely interconnected through common initiating growth factors and inflammatory cytokines as well as the EMT process, which has made dissecting specific mechanisms contributing to peritoneal membrane failure a challenging undertaking. There is, however, a growing body of evidence for conserved pathways involved in peritoneal fibrosis and inflammation, of which a selection of

the most detailed and frequently studied ones is outlined below.

4. Selected molecular pathways and their regulation

4.1. TGF-β, Smad-dependent, and Smad-independent

A key fibrogenic factor involved in PD-associated peritoneal fibrosis is TGF-β. The TGF-β superfamily comprises TGF-β isoforms, bone morphogenetic proteins (BMPs), activins, and other related proteins [46]. Those proteins exert multiple biological functions, such as cell proliferation, apoptosis, differentiation, autophagy, embryonic development, and organ fibrosis [46,47]. Activation of TGF-β is an important early event that mediates fibrogenesis via glucose, glucose-degradation products (GDPs) and advanced glycation end products (AGEs) in the context of bioincompatible PD solutions: It is known that TGF-β production can be induced in mesothelial cells by exposing them to spent dialysate from PD patients or by exposure to PD solutions containing high concentrations of glucose [48]. High glucose concentrations upregulate TGF-β receptor types I and II (TGFR1, TGFR2) in mesothelial cells [49]. It has been demonstrated that this TGF-β upregulation is mediated through activation of mesothelial protein kinase C-α (PKC-α) [32], which in turn is under the negative control of PKC-β, as PKC-β deficiency results in pro-inflammatory M1 polarization of peritoneal macrophages, driving mesothelial PKC-α upregulation and TGF-β-mediated fibrosis development [50]. In addition, GDPs have been shown to alter mesothelial cell function and proliferation [51] and to induce ECM production and TGF-β expression [52]. Furthermore, TGF-β levels in peritoneal effluents of stable PD patients are higher with increasing treatment duration [53,54] and correlate with properties of solute transport [55]. Adenoviral overexpression of TGF-β in the rat and mouse peritoneum causes peritoneal fibrosis, increases vessel density, and deteriorates solute transport as well as ultrafiltration capacity [56,57]. Furthermore, the pharmacological blockade of TGF-β protects the peritoneal membrane from dialysate-induced damage [58]. Similarly, siRNA-mediated knockdown of TGF-β inhibits peritoneal fibrosis in a short-term PD mouse model [59].

TGF-β acts through well-described canonical or non-canonical signaling pathways (Fig. 2). Along the canonical Smad signaling pathway, Smad2 and Smad3 are phosphorylated for example by PKC [60] and activated by TGFR1 and activin receptor I-β (ACTR1B). Consequently, Smad4 then binds the activated Smad2/3 complex, enabling translocation to the nucleus, where specific downstream target genes are transcribed [46]. Other canonical signaling pathways involve Smad1, Smad5, and Smad8, which are activated by ALK-1, ALK-2, BMP-RIA/ALK-3, and BMP-RIB/ALK-6 in response to BMP1-4 or other ligands. Of note, some TGF-β responses can occur in the absence of Smad4 [46]. Smad7 is a well-known inhibitory Smad, which is activated independently of Smad3 activation, in turn inhibiting Smad2/3 phosphorylation by blocking access to TGFRs. Several studies have demonstrated positive effects of Smad7 overexpression on peritoneal fibrosis, such as attenuation of PD-induced peritoneal fibrosis, angiogenesis, and inflammation in a rat peritoneal fibrosis model and in mesothelial cells [61–64]. Furthermore, Smad3 inhibition and Smad7 induction were responsible for decreased peritoneal fibrosis, submesothelial capillary density, and increased ultrafiltration capacity in a long-term uremic-PD rat model following treatment with tamoxifen and recombinant BMP7 [65], as well as in other short-term rat models following treatment with BMP7 and valproic acid, respectively [66,67]. Moreover, Loureiro et al. demonstrated that mesothelial cells constitutively express BMP-7 and that BMP-7-dependent Smads 1/5/8 are downregulated in vitro in response to conventional peritoneal dialysate [68]. In PD fluid-instilled rats co-administration of BMP-7 ameliorated peritoneal fibrosis and increase of capillary density, showing reciprocally antagonistic effects of TGF-β and BMP-7 on mesothelial cell phenotype [68]. Another approach for alleviation of TGF-β-mediated peritoneal damage was studied for parthenolide, a naturally occurring phytochemical, which in vivo reduced peritoneal fibrosis. The authors noted inhibition of Smad2/3 phosphorylation in HMrSV5 cells, whereas Smad1/5/9 and downstream AKT, ERK, and p38 MAPK were unaffected [69].

Non-Smad signaling pathways, on the other hand, are much more diverse and include TGFR1- or TGFR2-mediated activation of c-Jun N-

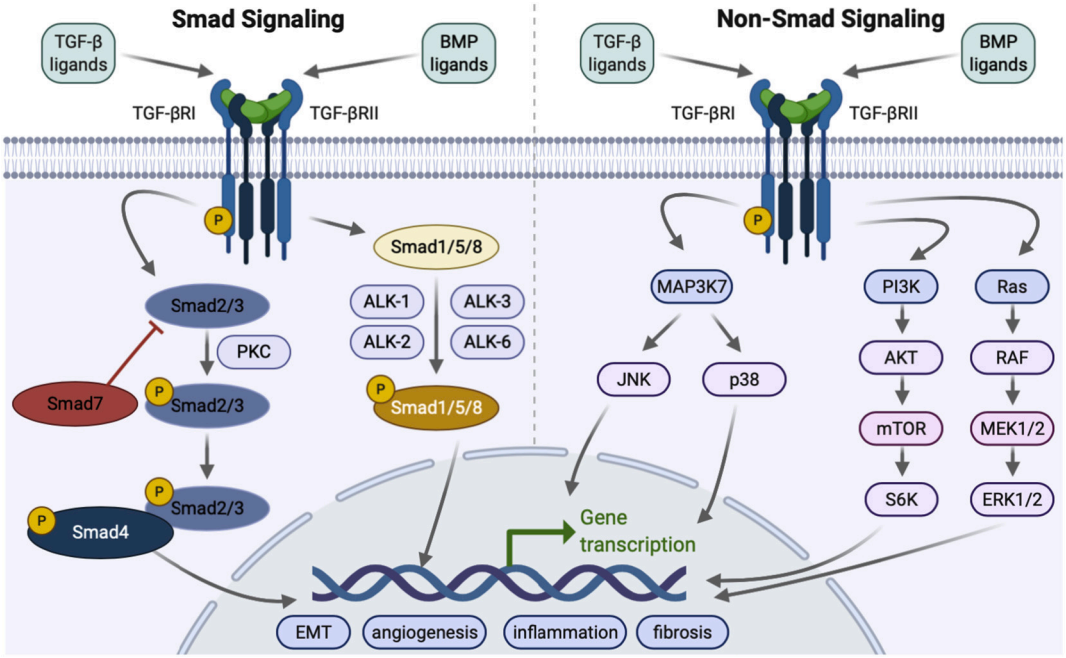

Fig. 2. Smad- and non-Smad TGF-β signaling. Selected molecular mechanisms of Smad and non-Smad TGF-β signaling contributing to peritoneal EMT, angiogenesis, inflammation and fibrosis. After activation of TGF-βRI and II by TGF-β or BMP ligands, the most well-known Smad-dependent pathways involve phosphorylation of Smad2/3 (facilitated by PKC) and consecutive translocation of Smad4-Smad2/3 complex into the nucleus, as well as Smad1/5/8 phosphorylation by ALKs. Non-canonical signaling is much more complex and involves signaling through MAP3K7, PI3K and Ras.

terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) via TGF-β-activated kinase-1 (TAK1)/MEKK1, ERK MAPK via Ras, p160ROCK via RhoA or S6K via PP2A as well as PKC signaling [46,47]. With respect to the peritoneum, high glucose mediates the phosphorylation of PKC [32] and MAPK [70] in mesothelial cells, which in turn leads to increased monocyte chemoattractant protein-1 (MCP-1) production [32,71]. Another study at the peritoneal level found that Akt (also known as protein kinase B), a phosphatidylinositol-3 kinase (PI3K) target, was upregulated both in Smad3-deficient and wild-type mice after adenoviral-mediated TGF-β exposure, indicating the implication of non-Smad signaling in peritoneal EMT and fibrosis [72]. Primary rat peritoneal mesothelial cells with either pharmacological or genetic inhibition of JNK activation demonstrated attenuated TGF-β-induced Smad3 activation as well as reduced EMT signatures [73,74]. Experiments in mice employing a pharmacological inhibitor of p38 MAPK demonstrated its involvement in peritoneal fibrosis [75]. In addition, mesothelial cells treated with a polyphenolic extract from olive oil demonstrated inhibition of TGF-β-induced EMT, which was mediated by reduction of both Smad2/3-dependent as well as non-Smad signaling via ERK, JNK, and p38 MAPK pathways [76]. Interestingly, these observations were in contrast to findings published earlier by others that inhibition, not activation, of p38 signaling in primary mesothelial cells from human omentum led to EMT, which relied on TAK1-NF-κB signaling [77]. While TAK1-NF-κB-independent effects could not be excluded by the authors, these discrepancies warrant further analyses of the context-dependent effects of p38 signaling in mesothelial cells. Along those lines, it has been shown by the same group that TAK1 inhibition may limit NF-κB-mediated EMT-related events in mesothelial cells [78]. Further in vitro studies in human mesothelial cells confirmed that TAK1 inhibition reduced the transcriptional activity of NF-κB and Smad3, as well as the phosphorylation of cJun, while enhancing Smad1-5-8 activity [79]. Rat in vivo and in vitro studies demonstrated that the TAK1-NF-κB pathway can be targeted pharmacologically with a PPARβ/δ agonist [80]. Also NF-κB inhibitor parthenolide was recently shown to alleviate peritoneal fibrosis via inhibition of TGF-β-induced Smad2/3 phosphorylation and nuclear translocation, while Smad1/5/9 phosphorylation or other downstream signaling pathways such as AKT, ERK or p38 were not affected [69]. Although relevant for elucidation of peritoneal fibrosis pathophysiology, pharmacological targeting of ubiquitous pathways in a non-cell-specific manner might have undetected off-target effects and hamper translation into a human setting.

4.2. Connective tissue growth factor (CTGF)

Connective tissue growth factor (CTGF) is a member of a family of matricellular proteins made up of Cyr61 (CCN1), CTGF (CCN2), and NOV (CCN3). This family of proteins is therefore sometimes referred to as CCN and in addition to CCN1-3 also encompasses CCN4 (ELM1), CCN5 (RCOP1), and CCN6 (WISP3) [81]. CTGF is a downstream mediator of TGF-β. Its expression is strongly upregulated by TGF-β in fibroblasts cultured in vitro [82]. Among its multiple functions, CTGF most notably promotes ECM accumulation, cell proliferation, adhesion, and migration [81]. CTGF can be detected in peritoneal dialysate effluent from patients with and without peritonitis [83,84]. In addition, it has been shown that human and murine peritoneal mesothelial cells express low amounts of CTGF under steady-state conditions [85,86]. Most interestingly, CTGF in peritoneal effluents is increased in patients with high peritoneal solute transport and peritoneal biopsy tissue analysis demonstrated more than 11-fold higher CTGF mRNA expression in peritoneal membranes of patients with ultrafiltration failure than in peritoneum of uremic pre-PD patients [87]. Along those lines, CTGF expression correlated well with peritoneal membrane thickness in PD patients with and without EPS [87,88]. Drug-inducible genetic deletion of CTGF in mice significantly ameliorated peritoneal fibrosis by inhibiting angiogenesis and inflammation [89]. Factors driving the upregulation of CTGF involve advanced glycation end products (AGEs) and glucose degradation products (GDPs), which are common in commercial PD solutions [87,90]. Recently, microRNA-302c has been found as a mediator of TGF-β signaling negatively regulating CTGF expression [91]. While investigations in CRP-transgenic mice link increased CTGF to exacerbated inflammation [92], others have demonstrated the correlation of CTGF with peritoneal lymphangiogenesis and speculate that via this route, CTGF might be involved in promoting ultrafiltration failure during peritoneal dialysis [93].

CTGF transcription is activated by TGF-β via a responsive element in the promoter region of the CTGF gene [94] and mediated by Smad3 and Smad4 [95]. Its profibrotic properties have been shown in multiple mesenchymal cells, in which CTGF is a downstream effector of TGF-β [96]. Interestingly, other growth factors than TGF-β, such as EGF, PDGF or FGF, do not induce CTGF expression in cultured fibroblasts [97] and in epithelial cells, CTGF production does not seem to be dependent on TGF-β expression [98]. Because of its downstream location within the TGF-β pathway, targeting CTGF in an effort to prevent or treat peritoneal fibrosis might confer benefits compared with targeting TGF-β, which exerts multiple physiologic properties. While CTGF is clearly implicated in peritoneal fibrosis pathogenesis, the lack of a specific receptor of CTGF, however, has made its mechanistic analysis challenging and context-dependent. With its four different domains, CTGF can bind to multiple ligands involved in peritoneal fibrosis pathogenesis such as TGF-β, bone morphogenic factors, VEGF, Wnt, integrins, heparan sulfate proteoglycans, and epidermal growth factor receptor (EGFR) [99]. Future studies should, therefore, aim to delineate the diverse biological actions of CTGF in the context of a well-defined cell type microenvironment.

4.3. NOD-like receptor protein 3 (NLRP3)/interleukin (IL)-1β signaling

The well-defined NOD-like receptor protein 3 (NLRP3) inflammasome is a critical component of the innate immune system. Its intracellular complex consists of multiple proteins that mediate caspase-1 activation and regulate the release of pro-inflammatory cytokines interleukin (IL)-1β and IL-18 in response to microbial infection and/or cellular damage and its aberrant activation is involved in several inflammatory disorders [100]. Recent evidence links the NLRP3 inflammasome to peritoneal inflammation and consecutive structural and functional peritoneal membrane changes. It has been shown in endothelial cells in culture that exposure to serum samples collected from chronic PD patients induces the assembly of NLRP3 components and caspase-1 activation [101]. Similarly, application of high glucose-based PD fluids triggers the activation of NLRP3/IL-1β in immortalized peritoneal mesothelial cells and human peritoneal mesothelial cells [102,103]. Intriguingly, the NLRP3 inflammasome is activated during acute bacterial peritonitis in PD patients, which associates with IL-1β activation and release into the dialysate [104]. Moreover, genetic deletion of NLRP3 abrogates solute transport defects and peritoneal morphological alterations [104]. Similarly, genetic deficiency of NLRP3, IL-1β, or apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) reduced inflammatory and fibrotic response to a methylglyoxal-induced peritoneal fibrosis model in mice, where the source of peritoneal inflammation was sterile and not in response to bacteria [105]. The authors of the same study also found that while myeloid cell-specific ASC deficiency failed to inhibit MGO-induced peritoneal fibrosis, genetic ASC deficiency in vascular endothelial cells ameliorated reactive oxygen species generation and cell death and that global ASC deficiency inhibited hemorrhagic ascites and vascular endothelial dysfunction in an MGO-induced peritoneal fibrosis model [105], thereby highlighting again the intricate interplay between endothelial dysfunction and submesothelial peritoneal fibrosis as well as membrane failure (Fig. 3). Because additive effects of TGF-β in combination with IL-1β have been observed in the development of both EMT and PKC-α activation in mesothelial cell culture [31,32], reports

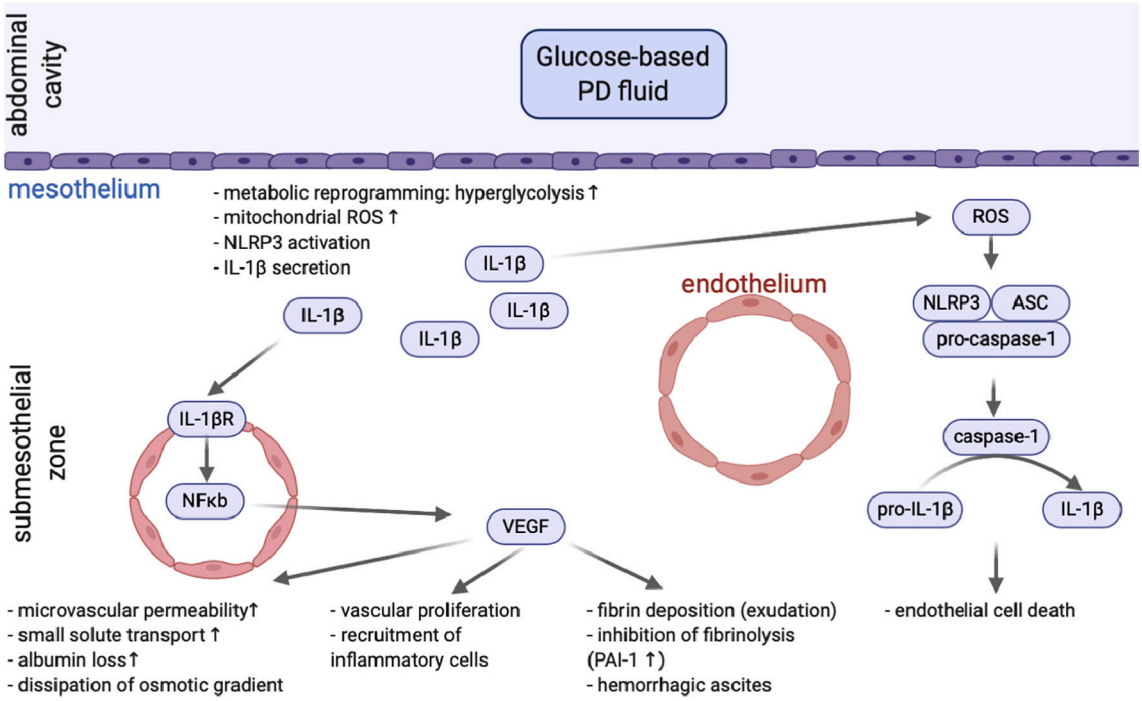

Fig. 3. Interplay of mesothelium and endothelium in the context of IL-1β-mediated VEGF and NLRP3 activation. Glucose-based PD fluids lead to metabolic reprogramming towards hyperglycolysis and increased mitochondrial ROS production. After NLRP3 activation, IL-1β is secreted and acts via its receptor (IL-1βR) to transcriptional activation of NFκb, which in turn leads to enhanced production and secretion of VEGF, promoting increased microvascular permeability, proliferation and fibrin deposition. Endothelial ROS production leads to activation of NLRP3/ASC complex, which in turn leads to caspase-1-mediated conversion of pro-IL-1β to IL-1β and endothelial cell death.

of successful treatment of structural and functional peritoneal membrane changes in a PD peritonitis model via IL-1β receptor antagonist anakinra pose an interesting potential therapeutic perspective [104]. Moreover, although old evidence demonstrates that inhibition of caspases might be beneficial for bacterial clearance by preventing neutrophil apoptosis [106,107] and that caspase-9 is involved in GDP-mediated human peritoneal mesothelial cell death [108], further studies need to clarify the interconnected roles of caspases as well as the inflammasome, bacterial clearance, and peritoneal fibrosis development.

4.4. IL-6, IL-17, other cytokines and acute and chronic peritoneal inflammation

One of the most studied proinflammatory cytokines in peritoneal membrane research is IL-6, as its local expression and systemic levels are easily increased at a multitude of stimuli and the diversity of IL-6 function is increasingly uncovered [109]. IL-6 can signal either through a classic pathway via membrane-bound IL-6 receptor (IL-6R) and glycoprotein 130 or through *trans*-signaling allowing cells that do not express the membrane-bound IL-6R to respond to IL-6 via a complex made up of IL-6 and the soluble form of IL-6R (sIL-6R) [110,111]. Intriguingly, soluble glycoprotein 130 acts as a natural inhibitor of IL-6 *trans*-signaling by preventing agonistic IL-6/sIL-6R complex interaction with membrane-bound glycoprotein 130 [112]. IL-6 is produced locally at the peritoneal level in PD patients even under stable conditions [113] and dialysate levels increase shortly before or at the onset of acute peritonitis [114–116]. Dialysate IL-6 levels are associated closely with the amount of glucose loading with PD fluids [117] as well as with peritoneal solute transport [118–120]. From looking at dialysate and serum inflammatory biomarkers in a subset of patients from the GLOBAL fluid study it was shown that peritoneal inflammation such as increased dialysate TNF-α levels as well as dialysate and serum IL-6 levels precede the onset of encapsulating peritoneal sclerosis, thereby linking active inflammation with later fibrosis development [121]. By using a model of acute peritoneal inflammation, others demonstrated how repeated inflammatory activation promotes fibrotic tissue injury. In this context, fibrosis was strictly dependent on IL-6-mediated T helper 1 cell effector commitment and STAT1 activity, and mice lacking IL-6, interferon-ɣ, STAT1 or RAG-1 resisted the development of fibrosis after acute peritoneal inflammation [122]. Just recently, IL-6 *trans*-signaling via a STAT3-dependent pathway linked peritoneal inflammation to fibrosis development [123]. The authors showed that inhibiting IL-6 *trans*-signaling ameliorated EMT in human peritoneal mesothelial cells in vitro, a process that was mediated via TGF-β/Smad3, and that pharmacological inhibition with glycoprotein 130 strongly ameliorated high glucose-mediated peritoneal fibrosis development in vivo via inhibiting STAT3 phosphorylation [123]. This is in keeping with earlier findings that in vitro IL-6 promoted EMT of HPMCs possibly through the JAK/STAT3 signaling pathway [124]. Most interestingly, it was found that in HPMCs and in HUVECs IL-6 *trans*-signaling only activates STAT3 but no other known cascades implicated in IL-6 signaling such as phosphatidylinositol 3-kinase/Akt or MAPK [112]. Intriguingly, IL-6 *trans*-signaling seems to be connected to TGF-β/Smad3 signaling, as blockade of TGF-β or Smad3 using siRNA inhibited IL-6/sIL-6R-mediated EMT in HPMCs [123].

Given the fact that acute bacterial peritonitis episodes are a risk factor for future peritoneal membrane deterioration, research has looked into shedding light on immunological host responses mediating acute peritoneal inflammation. It is known that IL-6 is a key mediator in regulating early peritoneal response to infection-related inflammation, such as the switch from early rapid peritoneal neutrophil accumulation towards mononuclear cells, monocytes, and macrophages [125,126]. It has been shown that IL-6 modulates a rich set of chemokines and adhesion molecules involved in apoptosis and leukocyte recruitment [127]. For example, through analysis of mononuclear cell infiltration in IL-6-deficient mice during peritoneal inflammation, it was found that IL-6 selectively governs T cell infiltration by regulating chemokine

secretion (CXCL10, CCL4, CCL5, CCL11, and CCL17) and chemokine receptor (CCR3, CCR4, CCR5, and CXCR3) expression on the CD3+ infiltrate [128]. Similarly, recent in vivo and in vitro studies highlight the importance of macrophage-mesothelial cell crosstalk through CX3CR1-CX3CL1 interaction, which was shown to enhance mesothelial TGF-β production and promote peritoneal fibrosis in response to dialysate exposure, again linking the process of chronic inflammation amid PD solution exposure to peritoneal fibrosis development [129]. Another cytokine involved in the peritoneal neutrophil response to bacterial infection is IL-17, which exerts strong effects on mesothelial cell cytokine production such as CXCL1 [130]. IL-17 has been shown to be present in the peritoneum of PD patients and to correlate with both the duration of PD and extent of peritoneal inflammation and fibrosis [131]. Similarly, chronic PD fluid exposure in mice leads to peritoneal infiltration of T helper17 and γδ T cells as probable sources of increased peritoneal IL-17 [131,132]. IL-17 is critically involved in acute bacterial peritonitis and higher dialysate levels seem to be related to rapid clearance of bacterial infection amid antibiotic treatment [133,134]. Recent investigations showed that IL-17-induced neutrophil chemoattraction via CXCL1 is highly context-dependent in that IL-17 and neutrophil levels correlated only in patients with low but not high effluent IFN-γ levels [135]. The authors also show that IFN-γ dose-dependently suppressed IL-17-induced activation of transcription factor SP1 and consecutive mesothelial CXCL1 production through a transcriptional mechanism involving STAT1 [135]. It remains to be investigated, however, whether IFN-γ-mediated IL-17 suppression is also mechanistically involved in the development of chronic inflammation and peritoneal fibrosis development. Interestingly, in a study evaluating effects of alanyl-glutamine on rats and mice exposed to PD fluids, the resulting reduction of peritoneal fibrosis associated with reduced peritoneal IL-17 expression [136].

5. Concluding remarks and outlook

While the research community in the field of PD has come a long way during the last several years in elucidating peritoneal fibrosis pathophysiology, there is a considerable gap in translating this accumulated knowledge into further patient benefits, which is partly due to the limitations of the animal models used. Major leaps forward in enhancing PD quality and patient safety that were fueled by a better understanding of peritoneal membrane pathophysiology include the development of disconnect systems and double-chamber bags, recognizing the deleterious effects of both peritonitis episodes and GDPs on the peritoneum. However, these improvements were made quite some time ago in the 1980s and 1990s. Since the implementation of pH-neutral more biocompatible solutions low in GDPs, major translational efforts have been scarce. Recent efforts in peritoneal membrane research to translate pathophysiology findings from in vitro and in vivo studies to the patient, such as the development of PD solution additives (e.g. alanyl-glutamine), permit an encouraging outlook, though. Along those lines, there is a clear need for future research in translating mechanistic findings from animal models to patient cohorts.

In addition, clinical and experimental studies as well as mathematical modeling of solute and water transport across the peritoneal membrane have considerably increased our knowledge about the function of the peritoneal membrane and the influence of environmental factors involved in the development of peritoneal fibrosis and PD technique failure (glucose, GDPs, AGEs, uremia, mechanical irritation of the peritoneum, peritonitis episodes, etc.). Still, we do not know a priori which patients, due to the genetic make-up of their peritoneum, are optimal candidates for PD. Studies even on smaller scales analyzing the genetic contribution to one individual's risk for development of peritoneal fibrosis or a high glucose transport status are lacking. In an age of personalized medicine, this is still a major untapped source of knowledge.

Moreover, insights leveraging cell type-specific information such as conditional knockout experiments and information on a single cell level such as transcriptomic studies are rare or non-existent and would further enhance our knowledge on the cellular crosstalk at play during fibrosis development and progression. Future studies to further resolve the intricate interplay between the peritoneal fibrotic program itself and other contributing processes such as chronic inflammation, as well as a better understanding of the specific contribution of resident and invading cell types to peritoneal fibrosis progression are warranted to raise the potential of developing novel treatment options for prolonging peritoneal membrane viability and translate this into clinical benefits for PD patients.

Disclosures

The author has no conflict of interest to disclose.

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