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*Review Article*

# Peritoneal Membrane Injury and Peritoneal Dialysis

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For patients with chronic renal failure, peritoneal dialysis (PD) is a common, life sustaining form of renal replacement therapy that is used worldwide. Exposure to nonbiocompatible dialysate, inflammation, and uremia induces longitudinal changes in the peritoneal membrane. Application of molecular biology techniques has led to advances in our understanding of the mechanism of injury of the peritoneal membrane. This understanding will allow for the development of strategies to preserve the peritoneal membrane structure and function. This may decrease the occurrence of PD technique failure and improve patient outcomes of morbidity and mortality.

## 1. Introduction

PD involves both diffusive and convective clearance driven mainly by glucose-based hyperosmolar PD fluid. The peritoneal membrane overlies the surface of all intra-abdominal organs, the diaphragm, and the parietal peritoneal wall. The peritoneal membrane is a fairly simple structure, with a superficial epithelial-like cell layer—the mesothelium—which is attached to a basement membrane (Figure 1). Beneath the basement membrane is a submesothelial layer consisting of connective tissue, fibroblasts, and blood vessels. Under optimal conditions, the peritoneum acts as an efficient, semipermeable dialysis membrane, enabling removal of metabolites, uremic toxins, salt, and water from the patient.

The rate of removal of these products from the blood correlates with the vascular surface area in contact with PD fluids in the peritoneal cavity [1]. Peritoneal membrane solute transport is commonly quantified as a dialysate to plasma ratio of solute (i.e., d/p creatinine). Increased peritoneal membrane solute transport should confer benefit for the patient as blood clearance would be more efficient. However, many studies have demonstrated the opposite [2]. A meta-analysis of observational studies demonstrated that every 0.1 increase in d/p creatinine carries a 15% increased risk of mortality [3]. This risk may be modified by the use of nocturnal cycling PD and use of alternate fluids such as icodextrin [4]. The mechanism whereby increased peritoneal solute transport is associated with increased mortality has not been clearly elucidated. Increased peritoneal membrane solute transport leads to increased absorption of glucose from the PD fluid [5]. This causes a rapid loss of the ultrafiltration gradient with decreased ultrafiltration, chronic volume expansion [6], hypertension [7], and adverse cardiovascular outcomes [8]. Furthermore, the increased glucose absorption may decrease food intake and lead to malnutrition [4]. There may also be common mechanisms, such as inflammation, which underlie both the increased solute transport and the increased mortality [9].

Solute transport is associated with peritoneal vascular surface area and has been modeled using the "three-pore" concept from Rippe and colleagues [10]. The "three-pore" model assumes the peritoneal membrane is a two-dimensional structure and the main barrier to solute and water transport is the endothelial cell layer of the blood vessels. The "three pores" refers to 3 different structures—aquaporin, small, and large pores—within the endothelial cell layer, which are size selective in restricting solute transport. Aquaporin-1 composes the smallest pore in the three-pore model. These channels allow for water transport by way of the crystalloid osmotic gradient. Small pores do the majority of the work in PD and mediate the transport of low molecular weight solutes. Large pores allow for the passage of proteins with higher molecular weight such as albumin, transferrin, and IgG [10].

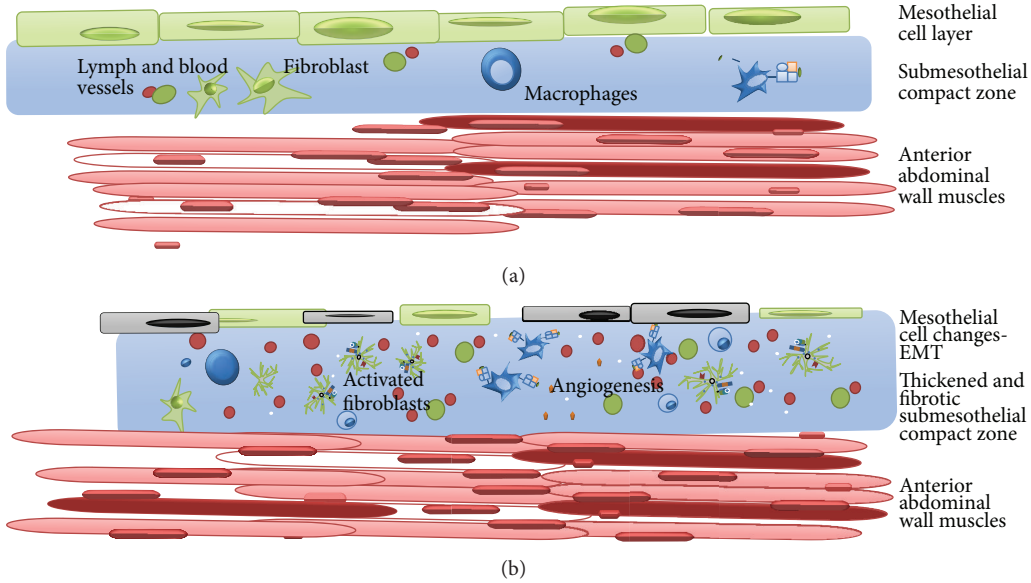


Figure 1: Changes in the peritoneal membrane with dialysis treatment. (a) Normal peritoneal membrane consists of an intact mesothelium overlying a thin submesothelial compact zone containing extracellular matrix, blood vessels, and a few scattered cells—fibroblasts and peritoneal macrophages. (b) After time on dialysis, activated fibroblasts or myofibroblasts appear along with increased submesothelial extracellular matrix and angiogenesis. Mesothelial cells are injured and sometimes denuded from the peritoneal surface.

Ultrafiltration is more complex and clinical modeling data suggests that both angiogenesis and increase in extracellular matrix (i.e., fibrosis) are required for ultrafiltration dysfunction [11]. Neovascularization of peritoneal tissue also has implications for ultrafiltration. Increasing vascular surface area causes increased loss of glucose from the peritoneal cavity effectively contributing to a reduction in the osmotic gradient as well [12]. These histologic changes are driven by clinical factors such as nonbiocompatible dialysate, glucose, uremia, peritonitis, and inflammation. One common downstream mediator of both peritoneal membrane fibrosis and angiogenesis appears to be transforming growth factor beta (TGFB) [13].

Therefore, ultrafiltration dysfunction is common and progresses over time on therapy and eventually leads to technique failure [14]. There is increasing evidence that both angiogenesis and expansion of the vascular surface along with peritoneal fibrosis are required for ultrafiltration failure to develop [11].

## 2. Profiling of the Peritoneal Membrane over Time

In a seminal study, Williams and colleagues studied peritoneal biopsies from 113 PD patients [15]. They demonstrated that over time on dialysis there was a progressive increase in submesothelial thickening and a unique vasculopathy. The vasculopathy appeared as vessel wall sclerosis and luminal narrowing. The degree of vasculopathy correlated with time on PD treatment and with overall submesothelial fibrosis [16]. There was an increase in the number of blood vessels in the peritoneal tissues of patients on PD which was more pronounced in those with peritoneal membrane ultrafiltration failure [15]. These histologic changes are associated with changes in peritoneal membrane function. This has been elegantly demonstrated by Davies in observations from a large PD patient cohort followed over time [17]. These changes include a progressive increase in solute transport measured by d/p creatinine and an associated decrease in ultrafiltration capacity [17].

There is a progression in the histologic changes seen in the peritoneal membrane with time on dialysis. Early on, changes in the mesothelium manifest as microvilli loss and signs of mesothelial injury such as cellular hypertrophy and increased vacuolation. Eventually, mesothelial cells detach from their basement membrane [18]. Over time, the presence of visceral and parietal simple sclerosis becomes evident and is quite common in patients who have been on long-term PD [19]. Mesothelial cell denudation as well as acellular sceloritic changes within the submesothelial connective tissue may also occur in conjunction with peritoneal sclerosis. A different and more rare form of peritoneal fibrosis, encapsulating peritoneal sclerosis (EPS), can occur and have fatal outcomes. Aberrations at the cellular and molecular level that are characteristic of EPS include fibrin deposition, fibroblast activation, and capillary angiogenesis [20]. The role of inflammation in EPS has been described [18].

## 3. Epithelial to Mesenchymal Transition

Central to the progression of peritoneal fibrosis and angiogenesis are changes in the epithelial-like mesothelial cell layer that lines the peritoneal cavity. Injury to the peritoneal tissues induces transition of the mesothelial cells to a

mesenchymal phenotype—a phenomenon referred to as epithelial mesenchymal transition (EMT). This phenomenon has been described in various biological settings including organogenesis [21], metastatic transformation of cancer [22], and fibrosis [23]. EMT involves downregulation of epithelial markers such as the intercellular adhesion molecule E-Cadherin, upregulation of mesenchymal markers such as alpha-smooth muscle actin (a-sma), cytoskeletal rearrangement leading to increased cellular motility, and invasion into the interstitial tissue, usually across a basement membrane barrier. The injured epithelial cell transitions into a submesothelial myofibroblast [24]. Myofibroblasts are specialized extracellular matrix secreting cells with contractile properties that are highly associated with fibrotic tissue [25].

In the setting of peritoneal fibrosis, EMT has been experimentally induced by a number of agents associated with PD including high glucose concentration [26], glucose degradation products (GDP) [27], and peritoneal inflammation [28]. We have identified TGFB as a direct mediator of EMT in the peritoneum [29]. TGFB is a member of a large family of structurally related cytokines involved in growth and differentiation that includes activins and bone morphogenic proteins (BMP). Epithelial transition appears to occur when a balance between pro-EMT growth factors, such as TGFB, overbalances the protective factors such as BMP7. Peritoneal EMT can be reversed and the peritoneal membrane preserved by overexpressing the protective BMP7 [30].

The members of the TGFB superfamily signal through common receptors and utilize common signaling molecules. The canonical signaling pathway involves the SMAD proteins. We have further dissected this pathway by examining the role of SMAD3 in TGFB induced peritoneal fibrosis [31]. We found that in SMAD3$^{-/-}$ mice, TGFB did not induce fibrosis or angiogenesis. There was, however, persistence of TGFB induced EMT that was abrogated by blockade of the mammalian target of rapamycin (mTOR) pathway. Although the SMAD signaling pathway is the dominant pathway involved in response to TGFB, multiple other signaling pathways are also activated in the setting of TGFB induced fibrosis. We demonstrated in vivo that TGFB induced beta-catenin signaling and this effect was inhibited by rapamycin [31].

Further down the signaling pathway, the EMT program appears to be controlled by a group of transcription factors including Snail1, Snail2 (Slug), and Twist [32]. These factors regulate expression of genes involved in the EMT process such as E-Cadherin and the matrix metalloproteinases (MMP) [33].

Although we have provided substantial evidence for TGFB mediated peritoneal EMT using standard dual labeling studies along with electron microscopy [29], and this has been supported by studies from other groups using different stimuli [26, 30, 34, 35], EMT as a prime mechanism of fibrosis has come under question recently. For example, EMT of renal tubular epithelial cells was once felt to be a major source of interstitial myofibroblasts and renal fibrosis [36]. Careful studies using cell lineage marking has shown that the pericyte appears to be the origin of interstitial myofibroblast leading to fibrosis [37]. More recently, by tracking the fate of mesothelial cells using cell specific promoters, Chen and colleagues have demonstrated that transitioned mesothelial cells make up few, if any, of the interstitial myofibroblasts in the peritoneum [38]. These results are intriguing and suggest that we will need to rethink the role of the mesothelium in peritoneal membrane injury and fibrosis. These cells are unlikely to be direct participants as transformed myofibroblasts, instead, they likely remain an essential component of peritoneal fibrosis by transmitting the injury signal in the peritoneal cavity to the submesothelial fibroblasts and vasculature in the form of fibrogenic and angiogenic cytokines.

Under certain circumstances, we have found that epithelial cells can undergo injury and transition to a mesenchymal phenotype without invasion into the submesothelial tissue. After adenovirus mediated overexpression of platelet derived growth factor (PDGF) B [39] or hypoxia inducible factor 1 alpha (HIF1a) [40], we found clear evidence of cellular transition with dual labeling of mesothelial cells (cytokeratin) with myofibroblast markers (a-sma). Despite this, no dual labeled cells were observed in the submesothelial tissue. In the case of PDGF-B, we attributed this phenomenon to a lack of induction of MMPs, specifically MMP2 and MMP9, which we hypothesized were necessary to degrade the basement membrane to allow for mobilization of transitioned epithelial cells [39].

We have also demonstrated that transitioned epithelial cells are a source for vascular endothelial growth factor (VEGF) and thus promote peritoneal angiogenesis [41]. This is supported by evidence from Aroeira and colleagues from ex vivo peritoneal mesothelial cell cultures [42]. They showed that if cells from peritoneal effluent had a fibroblast as opposed to an epithelial phenotype in culture, this was associated with peritoneal membrane injury and EMT. These fibroblast-like cells were grown from patients with increased peritoneal membrane transport and these cells produced more VEGF than epithelial-like cells [42].

Therefore, although there is some controversy as to the role of EMT in establishing submesothelial myofibroblasts and peritoneal fibrosis, it is clear that mesothelial cells play a role in peritoneal membrane damage; they undergo cellular changes in response to injury and secrete various factors such as VEGF that are responsible for the histologic changes in the peritoneal tissues. Whether the peritoneal mesothelial cell is a direct or indirect agent in peritoneal membrane fibrosis and angiogenesis, protecting the mesothelium is arguably a logical therapeutic goal in preserving long-term peritoneal membrane function.

## 4. A Central Role for TGFB in Peritoneal Membrane Injury

TGFB is a growth factor that is central to the development of sis [43] and associated with the fibrotic and angiogenic responses observed in long-term PD patients (Figure 2). Published evidence from our group and others [13, 44] indicates that TGFB plays an essential role in peritoneal fibrosis and EMT. Glucose [45], GDPs [46], and inflammation [47] are linked to increased TGFB expression in mesothelial cells.

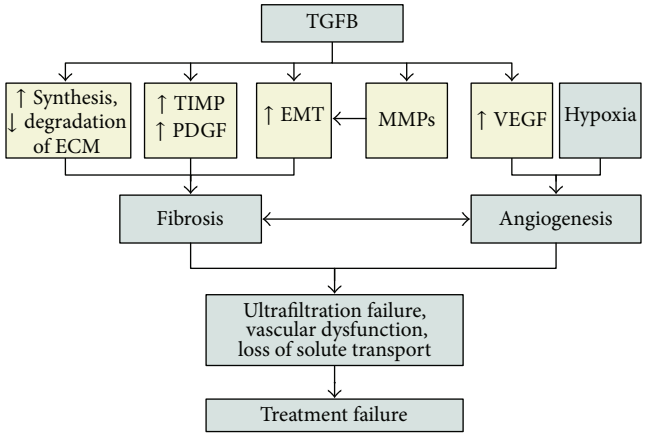


Figure 2: Role of transforming growth factor beta (TGFB) in peritoneal membrane injury. TGFB has multiple actions directly on elaboration of extracellular matrix (ECM), upregulation of various growth factors and metalloproteinases (MMPs), and induction of epithelial mesenchymal transition (EMT). TGFB also induces blood vessel growth directly through vascular endothelial growth factor (VEGF) and secondarily through hypoxia driven mechanisms.

In animal models, it has been shown that blocking TGFB signalling using SMAD7 [48, 49] or BMP7 [50] prevents mesothelial cell transition and peritoneal injury. Finally, there is increasing human data including our own observations [51], demonstrating an association between peritoneal effluent TGFB concentration to peritoneal solute transport [52].

We have shown that adenovirus-mediated gene transfer of TGFB1 to the peritoneum results in functional and structural changes similar to those seen in patients on long-term PD in both rats [13] and mice [31]. These changes include fibrosis, angiogenesis, increased solute transport, and ultrafiltration dysfunction. Furthermore, using a helper dependent adenovirus to deliver prolonged TGFB1 expression in mice, we observed peritoneal changes including bowel encapsulation and adhesion identical to that seen in PD patients with EPS [53].

The SMAD signaling pathway is integral to TGFB induced peritoneal fibrosis and angiogenesis. We have shown that these processes are abrogated in SMAD3$^{-/-}$ mice exposed to and adenovirus expressing TGFB [31]. Other TGFB mediated pathways are likely involved. Peng and colleagues reduced peritoneal fibrosis and angiogenesis in rats on daily PD by using fasudil to inhibit the Rho/Rho associated protein kinase (ROCK) pathway [54]. Recently TGFB associated kinase-1 [55] and p38 [56] have been identified as TGFB regulated molecules important in peritoneal membrane injury and fibrosis.

## 5. TGFB and the Role of Angiogenesis in Peritoneal Membrane Dysfunction

Angiogenesis is a complex process involving initiation, progression, and maintenance of new vasculature arising from existing blood vessels. The association between vascularization of the peritoneal tissue and ultrafiltration dysfunction has been demonstrated in animal models [12, 57] and in human biopsy studies [58, 59]. We have directly demonstrated the causative effect of peritoneal vascularization using adenovirus-delivered antiangiogenic therapy in an animal model of peritoneal membrane injury. We showed that an adenovirus expressing angiostatin reduced peritoneal vascularization and improved ultrafiltration function [12].

Several lines of evidence support a direct role of TGFB in angiogenesis. TGFB1 deficient mice have lethal defects in blood vessel maturation and hematopoiesis [60]. The TGFB receptor ALK-1 is involved in the signaling that leads to vascular maturation [61, 62]. TGFB has been hypothesized to have a role in the maturation of VSMCs after their recruitment by PDGF [63]. TGFB synergistically acts with HIF 1a [64, 65] and high glucose [66] in upregulating VEGF and induces expression of angiopoietin-1, thus stabilizing blood vessels during fibrogenesis [67, 68].

TGFB is responsible for peritoneal angiogenesis through at least two mechanisms. As mentioned above, TGFB directly induces VEGF and angiogenesis [13]. This is best seen in mesothelial cells which undergo an EMT process in response to TGFB and become a source for VEGF [41, 42]. TGFB also induces an expansion of the submesothelial extracellular matrix. We have shown that this expanded submesothelial tissue becomes hypoxic, and this hypoxia drives a secondary angiogenic response [40]. Specifically, we found that TGFB-induced submesothelial tissue expressed HIF1a which is a key regulator of the hypoxic response. Regulation of hypoxia is mainly at the posttranslational level [69]. However, several cytokines and signaling pathways have been demonstrated to increase gene expression of HIF1a, most notably the PI3K/Akt pathway. This interaction occurs through mTOR and inhibition of this pathway with rapamycin downregulates HIF1a gene expression [70]. We demonstrated that in the peritoneum, rapamycin did not block the direct TGFB induced angiogenesis but did prevent the secondary hypoxia driven angiogenic response [40].

We also demonstrated that HIF1a overexpression alone could induce fibrosis and angiogenesis in the mouse peritoneum [40]. Therefore, fibrosis appears to induce a hypoxic response, but hypoxia can also induce fibrosis. Hypoxia has been shown to upregulate TGFB in human umbilical endothelial cell culture [71, 72]. In cultured lung fibroblasts, hypoxia and TGFB were found to interact to alter the MMP/tissue inhibitor of metalloproteinase balance [73]. This balance is important in collagen metabolism and the establishment of a "profibrotic environment" [47, 74]. Connective tissue growth factor, a cysteine rich protein strongly associated with fibrosis [75], has a hypoxia responsive element in the promoter region and is upregulated in cultured renal tubular cells exposed to low oxygen tension [76]. Higgins and colleagues demonstrated that HIF1a could directly induce EMT and fibrosis in renal tubular epithelial cells [77].

## 6. Risk Factors for Peritoneal Membrane Injury

Commonly used PD solutions are characterized by acidic pH, high glucose concentration, high lactate concentrations, high

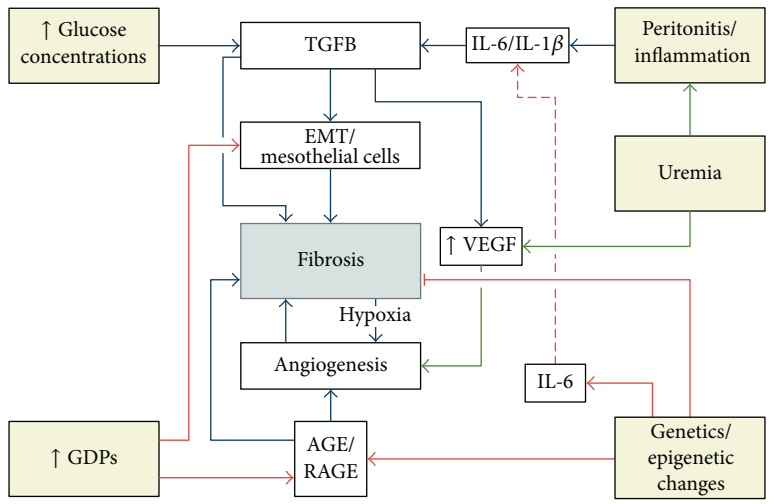


Figure 3: Mechanisms of peritoneal membrane injury. Factors related to PD solutions (increased glucose exposure and glucose degradation products (GDPs)) along with patient specific factors (peritonitis, inflammation, uremia, and genetic predisposition) are responsible for injury to the peritoneal membrane. Transforming growth factor beta (TGFB) is a central player in translating the injury signal to changes in the tissue. Inflammation is mediated by interleukin (IL) 6. GDPs induce advanced glycation end-products (AGEs) that can bind to the receptor for AGE (RAGE) to directly induce fibrosis. Angiogenesis is mediated by vascular endothelial growth factor (VEGF) and hypoxia.

overall osmolality, and GDPs which are a by-product of standard sterilization procedure. The demonstrated detrimental effect of these bioincompatible solutions on the peritoneal membrane has led to the development and testing of novel strategies and solutions in an attempt to preserve the peritoneal membrane [78]. The overall clinical impact of these more biocompatible solutions is not clear [79]. However, in addition to solution type, modifiable patient risk factors are equally important in patients undergoing PD (Figure 3).

*(1) PD Fluid Related Factors.* Long-term exposure of the peritoneal membrane to high glucose concentrations will cause changes in membrane permeability and structure. In vitrostudies by Kang and colleagues demonstrated that bioincompatible solutions containing high glucose concentrations will indeed stimulate the mesothelial cells to produce TGFB [80]. From a functional standpoint, patients exposed to hypertonic glucose dialysate demonstrate an earlier loss in residual renal function [81]. Moreover, high glucose concentrations have been recently linked with an increased mortality secondary to cardiovascular disease emphasizing the need for biocompatible solutions [82].

Glucose likely has a detrimental effect on the peritoneal membrane both from systemic hyperglycemia and local effects of dialysis fluid. Rodent studies suggests that streptozotocin induced diabetes causes increased peritoneal membrane solute transport, an effect that is mediated by VEGF [83]. In patients, the association between diabetes and solute transport at initiation of dialysis has been observed in some studies [84] but not others [85].

The heat sterilization process of PD fluids creates GDPs, which react with proteins to produce advanced glycation end-products (AGE). Both GDPs and AGEs have been shown to have a detrimental effect on the peritoneal membrane, perhaps mediated through the receptor for AGE [86]. Newer solutions have been developed which drastically reduce the concentration of GDPs created during sterilization. These biocompatible solutions have shown some clinical promise in PD patients [87], with a suggestion of a beneficial effect on peritoneal membrane function [88]. Longer duration studies are likely required to definitively assess the true effect of these solutions.

*(2) Patient Related Factors.* Peritonitis is a well-recognized complication seen in patients treated with PD. Animal models have demonstrated that frequent peritonitis occurrence may cause increased circulating TGFB mRNA expression in peritoneal cells [89]. Subsequent research from our group showed that adenovirus mediated gene transfer of interleukin (IL) 1B or tumor necrosis factor (TNF) mimicked inflammatory changes seen in peritonitis. Persisting fibrotic response, angiogenesis, and ultrafiltration dysfunction were related to overexpression of IL-1B, whereas TNF induced transient changes in the peritoneal membrane [90]. A single episode of peritonitis has been shown to have a detrimental effect on the peritoneal membrane as measured by changes in solute transport rates [91, 92].

End stage kidney disease is known to induce systemic inflammation. IL-6 is a pleiotropic cytokine with a diverse range of function that was first isolated in 1986 [93]. IL-6 has been implicated in the pathogenesis of peritoneal inflammation in those undergoing PD and is associated with increased peritoneal solute transport [94]. Later, in the global fluid study of over 900 PD patients, Lambie and colleagues demonstrated that systemic inflammation, measured by serum IL-6, was associated with increased risk of mortality, whereas peritoneal inflammation was a distinct process and associated with increased peritoneal solute transport [95]. This cytokine, released following exposure to dialysate, has a role in the regulation of the switch from acute to chronic inflammation

of the peritoneal membrane. IL-6 also stimulates the downstream production of acute phase proteins such as angiogenic molecules, chemokines, and adhesion molecules [94].

Interestingly, the uremic state alone induces changes in the peritoneal membrane. This was best observed in peritoneal biopsy data where biopsies from uremic patients at the time of PD catheter insertion and before any exposure to dialysis fluid already showed significant submesothelial thickening [15]. The impact of uremia on the peritoneal membrane is supported by observations in rodents [96]. The presence of uremia in the background of diabetes has also showed to contribute to peritoneal thickening primarily through hyalinizing vasculopathy within capillaries [97]. These alterations become more apparent with PD and can affect transport.

*(3) Genetics*. There is increasing evidence to suggest that genetic variation plays a significant role in peritoneal membrane solute transport and peritoneal membrane fibrosis. There is evidence to support an association between peritoneal membrane solute transport and gene polymorphisms of IL-6 [98, 99], endothelial nitric oxide synthase [100, 101], and the receptor for AGE [102]. An association was not found between solute transport and VEGF [98, 102, 103], IL-10 [99, 104], and TNF [99, 104]. An association was found between a RAGE gene polymorphism and the presence of EPS [105].

Recently, we evaluated the peritoneal fibrogenic response in 4 mice strains that span the genetic spectrum of inbred mice [106]. Strain dependence of the fibrogenic response has also been observed in models of kidney [107], liver [108] and heart [109] disease and supports the hypothesis that genetics play a role in the peritoneal membrane response to PD therapy.

*(4) Epigenetics*. A hallmark of fibrogenic changes is that the condition tends to progress even when the inciting stimulus is removed [110, 111]. This is specifically relevant for EPS; Balasubramaniam reported on a cohort of 111 PD patients who developed EPS [112]. Fifty-one patients were diagnosed after the cessation of PD, with 21 being diagnosed after more than 3 months on hemodialysis. Additional 14 patients were diagnosed after a renal transplant. This suggests that the fibrogenic process, once initiated, is sustained despite removal of the inciting agent (PD therapy). One compelling explanation is that environmental triggers induce epigenetic changes in the resident cells (mesothelial cells or fibroblasts), and these "reprogrammed" cells take on a persisting fibrogenic phenotype. These "activated" fibroblasts have been observed in many disease processes involving fibrosis [111]. In a seminal paper, Bechtel and colleagues found that activated fibroblasts in a model of renal fibrosis demonstrated hypermethylation of the promoter region of the RASAL1 gene [113]. This hypermethylation decreased RASAL1 gene expression and allowed for persisting activity of the RAS pathway.

The epigenetic controls over gene expression primarily include methylation of cytosine residues and histone modifications. These processes have been observed in diseases associated with fibrosis [114]. Histones can be modified by a range of enzymes, and these modifications can lead to increased or decreased gene transcription [115]. Histone acetylation is an attractive target for intervention as histone deacetylase inhibitors are available and have shown efficacy in a broad range of fibrogenic diseases [116]. Whereas histone modifications are not clearly heritable, DNA methylation is stable and passed on from mother to daughter cells with high fidelity [117].

## 7. Summary

The peritoneal membrane is a fairly simple structure of vital importance to patients who are reliant on PD dialysis as their renal replacement modality. Injury to the peritoneal membrane is a complex process brought about by the dialysis procedure and patient specific factors including genetic predisposition and epigenetic modification. Remarkable strides have been made in understanding the basic mechanisms of peritoneal membrane injury and we hope that these insights will lead to therapeutic interventions that will improve the quality and quantity of life of dialysis patients.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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