Chapter 7

Angiogenesis and Lymphangiogenesis in Peritoneal Dialysis

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Abstract

The ultrafiltration failure during peritoneal dialysis (PD) is related to inflammatory responses induced by bio-incompatible PD fluids, which may lead to deterioration of peritoneal membrane (PM) function. Mesothelial cells, lymphocytes, macrophages and other cell types present in the peritoneal cavity are stimulated to produce cytokines and growth factors that promote pathological processes. Due to these factors, blood and lymphatic vessels proliferate and could be responsible for hyperfiltration and PM failure type III and IV. Vessels proliferation may be related to fibrosis, being the cause and/or effect of the mesenchymal conversion of different cell types such as mesothelial (MMT), bone marrow-derived (fibrocytes) or endothelial (vascular- and lymph-endo-MT) cells. Lymphangiogenesis in PD is a poorly analysed process; however, its contribution to peritoneal function disorders has been recently recognized. VEGF production is associated with blood and lymphatic vessels proliferation, while specifically lymphangiogenesis is mainly regulated by VEGF-C and VEGF-D. Excessive lymphatic fluid drainage from the abdominal cavity may be related with macromolecule and isosmotic solutions reuptake and convective reabsorption of solutes that were cleared from plasma by diffusion. Some drugs have been shown to modulate tissue fibrosis, MMT, EndoMT, angiogenesis and lymphangiogenesis and could represent interesting therapeutic strategies to protect the PM.

Keywords: peritoneal membrane, lymphangiogenesis, angiogenesis, inflammation, ultrafiltration, peritoneal dialysis

1. Introduction

Peritoneal dialysis (PD) is based on the use of the peritoneal membrane (PM) as a semi-permeable membrane across which ultrafiltration (UF) and diffusion take place [1], thus allowing diffusive exclusion of uraemic toxins and exchange of solutes between circulation and PD fluid (PDF) to maintain solute and fluid equilibrium in uraemic patients [2]. However, it has also some disadvantages that include the risk of peritonitis, peritoneal tissue remodeling and vessels proliferation [3].

The efficacy of PD depends on the structural and functional PM integrity. It consists of a monolayer of mesothelial cells (MCs) supported by connective tissue that covers the inner surface of the abdominal wall and most visceral organs. During PD, the peritoneum is continuously exposed to large volumes of bio-incompatible solutions (hyperosmolar, acidic and with high glucose content), leading to morphological and functional alterations of the PM. Furthermore, PDFs contain glucose degradation products (GDPs), potentially toxic to the PM [4]. Glucose can also contribute to PM alterations through formation of advanced glycation end products (AGEs). AGEs can bind with some receptors, such as the receptor of AGEs (RAGE), activating intracellular signals that produce oxidative stress and synthesis of inflammatory cytokines [5]. All these bio-incompatible features induce an immunological response in the peritoneal cavity that involves MCs, macrophages, lymphocytes and neutrophils. When stimulated, these cells produce a wide variety of cytokines, chemokines and growth factors, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8, IL-17, transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-2, monocyte chemotactic protein (MCP)-1 and many others, therefore increasing inflammation and causing structural and functional alterations [6, 7]. Consequently, histology of patients chronically exposed to PDFs reveals mesothelial cell loss, increase of the submesothelial extracellular matrix (ECM) deposition (fibrosis), angiogenesis and lymphangiogenesis. All these changes are interconnected factors associated with alterations on fluid and solute removal; they ultimately lead to different spectra of PM ultrafiltration failure (UFF) types (type I–IV) (**Table 1**) (**Figure 1**) [8].

Types of UFF	Clinical characteristics	Anatomic/physiologic bases	Actual therapeutic measure
Type I	Increased peritoneal exchange surface area	PM hyper-permeability	Avoid Icodextrin long PD dwells
Type II	Low osmotic conductance to glucose	AQP-1 channels dysfunction	Peritoneal resting and adhesions surgery
Type III	Diminished peritoneal exchange surface area	EPS, abdominal adhesions	Peritoneal resting, hypertonic glucose or icodextrin long PD dwells
Type IV	Increased lymphatic absorption rate	Increased lymphatic absorption	Avoid large and long volume dwells

Adapted from Prasad and Gupta [8].

Table 1. Clinical characteristics and accepted therapeutic option for UFF.

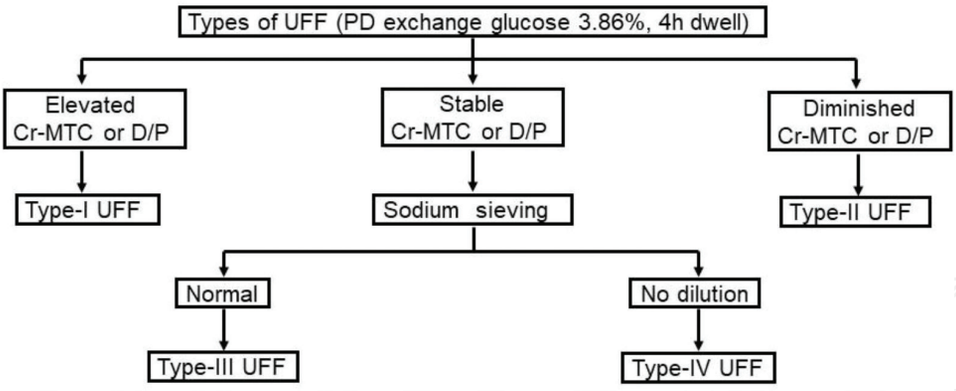

Figure 1. Characteristics of the different types of UFF.

Consequently, there is an extracellular volume overload [9, 10], which compromises treatment efficacy and patient outcomes, who have to be transferred to hemodialysis.

Therefore, to improve PM longevity in PD, it is mandatory to diminish or block the up-regulation of the molecular mechanisms implicated in the onset of the UFF. Herein, we update the knowledge about the mechanisms implicated in the PM failure, especially those associated with angiogenesis and lymphangiogenesis, and we propose some therapeutic alternatives.

1.1. PM failure in PD: clinical features

In 1993, B. Rippe described the three-pore model of peritoneal transport [11], according to which the main peritoneal exchange route for water and water-soluble substances is a protein-restrictive pathway ("first pathway", small pores), accounting for approximately 99% of the total exchange area and approximately 90% of the total UF coefficient. For their passage through the PM, proteins are confined to the "second pathway" (large pores, extremely few in number, about 0.01%), more or less non-restrictive with respect to protein transport. The "third pathway" ("water-only, solute-free transport", ultra-small pores) accounts for about 2% of the total UF coefficient and is permeable to water but impermeable to solutes, and it has been associated to aquaporin (AQP)-1 channels (a membrane protein). Transcellular water permeability mediated by AQP-1 is an essential component of the water removal across the PM. Studies in AQP-1 KO mice confirmed that AQP-1 is responsible for approximately 50% of the UF when using a crystalloid osmotic agent such as glucose, and that its expression is necessary to observe the sodium sieving [12].

The UF rate has been linked with high survival in a prospective observational study (EAPOS study). Besides, UF was also predictive of survival in anuric automated PD patients [13]. Although in this report the authors did not find association with survival when analysing time-averaged UF (time dependently), in another study (NECOSA-D study) a time-dependent survival relationship was found [14]. Although UFF can occur at any stage, it usually happens in long-term PD. The first studies reported an accumulative risk for permanent loss of net UF capacity to be 2.6% at first year, 9.5% after 3 years, and more than 30% for patients on CAPD [8]. In 2000, the International Society for Peritoneal Dialysis (ISPD) committee performed a

standardized test using a 3.86 /4.25% glucose exchange with 4 h of permanence. They defined a net UF of <400 mL after a four hours' dwell. Based on this criterion, new studies have demonstrated that UFF prevalence is between 23 and 36% [8] (**Figure 1**).

UFF is an increased complication in long-term PD patients associated with fluid overload, mainly when associated with high solute peritoneal transport. The importance of UFF is related to the increased cardiovascular mortality [15]. UFF could be explained by a combination of two processes occurring in parallel: changes in vascularization and production of fibrotic tissue in the PM [12]. Four types of UFF have been defined according to their specific features.

1.1.1. Type I UFF

High solute transport, with a dialysate-to-plasma ratio (D/P) of creatinine >0.81. It represents the largest UFF type and usually happens during/after peritonitis episodes. PM shows an inflammatory process with subsequent hyper-permeability. The anatomical status is probably the result of both tissue fibrosis and angiogenesis resulting in a large effective exchange surface area. Angiogenesis leads to an increased number of perfused capillaries under the fibrotic matrix, which rapidly dissipate the glucose-driven osmotic pressure. This hyper-permeability has been demonstrated as a predictor of increase in mortality [13]. The uraemic state itself prolongs the exposure to glucose and GDPs and increases the cumulative effects of inflammation. These, in turn, are associated with angiogenesis with leaky capillaries, culminating in increased effective peritoneal surface area and rapid solute transport with diminished UF capacity [14].

1.1.2. Type II UFF

AQP-l dysfunction; low/high average solute transport, D/P of creatinine = 0.5–0.8. The transcapillary movement of free water via AQP-1 accounts for 40 to 50% of total UF across the PM [16, 17]. This UFF is characterized by an increase in solute transport (for creatinine or glucose), residual volume, or lymphatic absorption. However, it has been reported that in these patients normal sodium sieving effect (drop in dialysate sodium concentration) is lost [18]. This selective defect attributed to AQP-l channels dysfunction is responsible of water transport failure rather than structural PM injuries [19]. Its cause has been not yet elucidated, but there is relevant information pointing to the roles of glycosylation or endothelial nitric oxide. Moreover, the PM AQP-1 expression can be up-regulated [20]. Free water transport can be estimated by subtracting the UF through small pores from the total UF over a period of 1 h, and with this method, free water transport ≤26% of total UF is consistent with impaired AQP-1 function [17].

1.1.3. Type III UFF

Patients with low solute transport rates (D/P creatinine <0.5). This is the less common cause for UFF. Anatomically, there is a severe reduction in effective PM surface area and permeability [21]. Clinically, these patients may therefore present signs of volume overload, symptoms of inadequate solute removal, or both. The diffuse hypo-permeability of the PM may be caused by the effects of pro-fibrotic mediators such as TGF-β and as a consequence of a process of mesothelial to mesenchymal transition suffered by MCs (MMT) [6, 22]. This is observed in patients who have recurrent and relapsing peritonitis, sclerosis of PM (sclerosing peritonitis), and extensive

intra-abdominal adhesions [22]. In early stages (simple peritoneal sclerosis), there is a diminution in peritoneal transport without serious clinical consequences. In advanced conditions, encapsulating peritoneal sclerosis (EPS) may be developed; it is a clinical syndrome characterized by bowel obstruction through persistent PM adhesions frequently associated to calcification [23]. This complication leads to a high mortality due to intestinal obstruction and malnutrition.

1.1.4. Type IV UFF

Alterations in dialysate solute concentrations. The D/P creatinine ratio does not change with increased lymphatic flow, although net UF can be considerably reduced. Increased lymphatic flow, net UF and solute clearance are inversely related to lymphatic fluid absorption [22]. This represents no more than 10–30% of the total fluid absorbed via lymphatic vessels [24]. The estimation of fluid loss may be done by examining the egress rate of radio-labeled albumin from the peritoneal cavity (averages 1.52 ml/min, with 2 L exchange) [25]. Factors influencing lymphatic absorption are dialysate volume, intraperitoneal pressure and mass transfer area coefficient of PM. Factors not influencing lymphatic absorption are body surface area, tonicity of the dialysate, position of the patient and probably duration of PD. The pathogenesis of this UFF type is poorly understood. It has been suggested that TGF-β1 may play a role in promoting lymphangiogenesis in a rat model [9].

2. Fibrogenic capacity of peritoneal populations

Fibroblastic-like cells may originate from different sources in the peritoneal matrix, collaborating in the fibrotic process that leads to PM malfunction. These cells are able to produce ECM components and acquire the ability to produce inflammatory, fibrogenic and angiogenic factors.

Well-known cells that may overcome a mesenchymal transition as a consequence of PDFs bio-incompatibility, acquiring a fibroblastoid phenotype, are the mesothelial cells lining the peritoneal membrane (suffering MMT) [26]. MMT is a complex process characterized by the disruption of intercellular junctions, loss of apical-basolateral polarity and acquisition of migratory and invasive properties. During the MMT, there is a strong up-regulation of VEGF and TGF-β in the peritoneum, which provides enhancement of the local vascular networks, leading to vessel proliferation [27]. Cells that undergo a mesenchymal transition acquire mesenchymal markers, including alpha smooth muscle actin (α-SMA), fibroblast-specific protein 1 (FSP-1) and fibronectin [28–30]. It has been described that even a 37% of fibroblastic-like cells present in the injured peritoneum of PD patients can derive from MCs that have undergo MMT as a consequence of PDFs exposure [30].

Additionally, there are other cell populations in the peritoneum that may also undergo a mesenchymal transition and collaborate in fibrotic diseases and specifically in PD-related fibrosis, as inflammatory bone marrow-derived circulating cells (fibrocytes), that could represent a 34% of total $FSP1^+$ fibroblasts, and endothelial cells from blood vessels (endo-MT) (approximately 5%) [27, 29–33]. Besides TGF-β, it has been shown that endothelin-1 (ET-1) may also participate in endo-MT [28]. Interestingly, adipose tissue macrophages can experiment a mesenchymal transition [34]. Moreover, it has been recently observed that endothelial cells from

lymphatic vessels may also suffer a partial endothelial-mesenchymal transition [35]. Other studies also pointed to a mesenchymal status of lymphatic endothelial cell [36, 37]. This mesenchymal conversion of LECs (Lymph-endo-MT) has not been analysed yet in biopsies of PD patients nor *in vitro* or *in vivo* studies, and its possible implication in the damage peritoneum remains unknown. On the other hand, the adipocytes themselves, apart from their capacity to promote a mesenchymal transition in other cells, had been also postulated as a possible source of mesenchymal cells in the peritoneal tissue [38, 39].

3. Blood and lymphatic vessels

Blood vessels deliver oxygen and nutrients to cells, whereas lymphatic vessels drain the interstitial fluid that is collected in tissues, and serve as a conduit for immune cell trafficking and fat absorption [40]. The correct functionality of both types of vessels is essential for PD treatment as it is intimately related to the UF capacity of the PM. An important change in PD is the so-called hyalinizing vasculopathy, which consists in the thickening of the wall of the blood peritoneal vessels and a luminal narrowing, or even a luminal complete occlusion [41], altering their functionality. Through histology, four degrees of vasculopathy have been defined according to the decrease in vessel lumen [42, 43], and its clinical repercussion has not yet been well defined.

New vessels formation is another undesirable consequence of the PD treatment, and this process has been observed both in blood and lymphatic vessels, presenting some common inductors.

3.1. Angiogenesis in PD

Angiogenesis is a process characterized by the formation of new capillaries. It supposes an increased effective surface area of exchange, which results in a decrease in the glucose-driven osmotic pressure of the PDF, favoring the emergence of UFF. Furthermore, the thickening of the vascular wall and the increase of permeability cause changes in fluid and solute transport in PD patients. In fact, there is an increase in small solute transport and a reduction time for exchanging waste products [3].

The major regulator of both physiologic and pathologic angiogenesis is VEGF cytokine. VEGF is a potent pro-angiogenic factor that binds to specific receptors on the endothelial cells lining blood vessels and that is involved in endothelial cell proliferation and vascular permeability [44]. VEGF also stimulates nitric oxide synthase production and the consequent vasodilation, and initiates inflammatory responses [45]. The biological activity of VEGF family is mediated by three receptors (VEGFRs): VEGFR-1/Flt-1, VEGFR-2/KDR and VEGFR-3/Flt-4. These receptors have an intracellular tyrosine kinase domain that, once activated, leads to the induction of different signal transduction pathways [46, 47]. The effect of VEGF is also regulated by a family of cell surface glycoproteins called neuropilins (Nrps). This family is composed by two members, Nrp-1 and Nrp-2. Nrp-1 has been described as an isoform-specific VEGF co-receptor expressed in endothelial and tumor cells, enhancing VEGF binding to VEGFR-2 and its bioactivity. Nrp-1 may also signal independent of VEGFR-2 in endothelial cells to mediate VEGF-triggered migration and adhesion. Moreover, Nrp-1 may also interact with other growth factors, such as TGF-β1. Nrp-1 expression has been recently described in many other cell types including MCs. In this context, it has been shown that during MMT process of mesothelial cells,

there is not only a strong induction of VEGF, but also of Nrp-1. In contrast, the expression of the receptors VEGFR-1 and VEGFR-2 is down-regulated. It has also been demonstrated that MCs which have undergone an MMT proliferate less and acquire an increased invasion capacity compared with epithelial-like MCs. Furthermore, this enhanced invasion could be partially inhibited by treatment with anti-VEGF or anti-Nrp-1b, which strongly suggests that the interaction of VEGF with Nrp-1 may have a role in MCs invasion and PM thickness [47].

The expression of VEGF in human peritoneal mesothelial cells (HPMCs) could be up-regulated by several pro-inflammatory cytokines, such as IL-1α and TNF-α. This suggests that intraperitoneal inflammation might increase peritoneal permeability by inducing angiogenesis [48]. Some studies have shown that MCs from omentum have the capacity to produce VEGF in response to a variety of stimuli such as GDPs, AGEs or TGF-β. This up-regulation of VEGF in MCs is due to the process of MMT. Furthermore, it was found that PD patients with non-epithelioid MCs showed increased expression of VEGF compared with those patients with epithelial-like MCs, supporting that MMT not only induces fibrosis, but also peritoneal angiogenesis [27].

3.2. Lymphangiogenesis in PD

Another alteration due to PD and associated with inflammation, MMT and peritoneal fibrosis is lymphangiogenesis, a process that has been recently recognized as a contributor to peritoneal function disorders [9]. Lymphangiogenesis is the growth of lymphatic vessels from preexisting vessels, and it is essential in embryonic development but, in adults, it is involved in many pathological processes such as lymphedema, metastasis, inflammatory diseases, renal transplant rejection, tubule-interstitial fibrosis and also in rat unilateral ureteral obstruction models [9, 49]. Of note, transient lymphangiogenesis and angiogenesis have also been detected during wound healing [50]. Wound healing is a necessary process to repair damage but it could convert into a pathological condition when dysregulated, promoting fibrosis and vessel formation by secreting cytokines and growth factors.

In PD, lymphatic vessels proliferation with fenestration of the anastomotic mouths is mainly visible in the diaphragm (**Figure 2**). These changes increase the lymphatic absorption rate (measured by the rate at which intraperitoneally administered radioactive serum albumin or dextran 70 disappears) [9]. Given that the net UF is determined by the effective lymphatic absorption and the trans-capillary UF, the increased of lymphatic absorption leads to diminished UF capacity. This makes it so important to control lymphatic absorption in order to obtain higher drained volume [51, 52].

Inflammation is thought to be an important contributor to lymphangiogenesis in human diseases as PD [53]. Particularly, macrophages have been suggested to stimulate lymphangiogenesis through the production of VEGF-C and VEGF-D [54]. VEGF-C is one of the most important mediators of lymphangiogenesis, and it has been shown that its content in the PD effluent correlated with the membrane transport rate [55]. Thus, if VEGF-C concentration in the PD effluent increases, the PM transport rate will be higher. In other words, there is a positive correlation between both factors [9]. Some sources for VEGF-C are pericytes of blood vessels, tumor cells and, in inflammatory and neoplastic conditions, tissue macrophages [46, 56, 57].

It has been found that expression of VEGF-C and markers of lymphatic vessels is higher in the peritoneum of patients with UFF (in fact, these tissues contain more lymphatic vessels) [9].

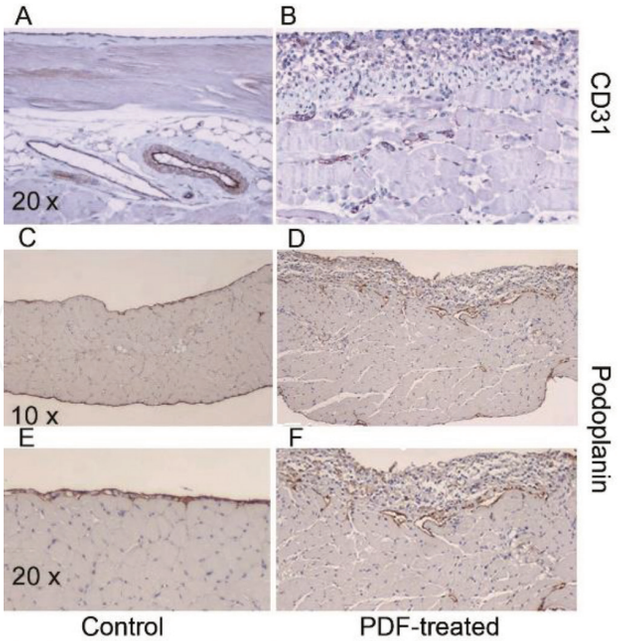

Figure 2. (A, B) Mice parietal PMs stained with an anti-CD31 antibody (Abcam, Cambridge, UK). (A) Control sample of a saline-treated mouse. (B) PDF-treated mouse with an increased CD31 staining. (C–F) Mice diaphragms stained with an anti-podoplanin antibody (PA2.26, from Dr. Gamallo, Laboratory of Pathology, La Princesa Hospital, Madrid, Spain). The staining shows the MC monolayer and the lymphatic vessels that drain into the thoracic duct. (C, E) Control sample of a saline-treated mouse. (D, F) PDF-treated mouse with a thickening of the PM that covers the peritoneal cavity and a proliferation of lymphatic vessels with fenestrated anastomotic mouths. Panels A, B, E, F with 20× magnification. Panels C and D with 10× magnification, showing the abdominal (upper) and thoracic sides (down). Figure modified from Gonzalez-Mateo et al. (BioMed Research International, 2015; use under http://creativecommons.org/licenses/by/3.0/ for CC BY) [33].

However, although the vessel density of non-PD patients is lower than in PD patients, this measure did not differ between PD patients with or without UFF. These findings suggest that factors other than increased vascular density are involved in disease states associated with increased transport of PM [9].

Immuno-histochemical analyses of lymphatic and blood vessels and expression of VEGF-C in the peritoneum of patients with UFF or in pre-dialysis situation showed that these elements were observed when there is an UFF, but they were hardly detected in the pre-dialysis peritoneum. Moreover, expression level of VEGF-C and number of lymphatic vessels correlated with one another [9]. In fact, VEGF-C has been shown to be required for a normal development of lymphatic vessels [49, 53].

VEGF production is regulated not only by glucose from PDFs, vascular hyper-permeability and PD dysfunction, but also by other growth factors and cytokines such as TGF-β [53, 58]. There are some studies that have investigated the roles of TGF-β in the progression of lymphangiogenesis through VEGF-C induction. In these investigations, the effect of TGF-β1 in VEGF-C expression in the human MC line Met-5A and ex vivo cultured HPMCs was studied. The experiments showed that VEGF-C (both mRNA expression and protein production) increases in response to TGF-β1 treatment in both Met-5A and HPMCs cultures. Moreover, the number of macrophages was suppressed by a TGFβR-I inhibitor in a mice model. These findings support that TGF-β1 is an important inducer of VEGF-C, leading to lymphangiogenesis that is associated

with peritoneal fibrosis in PD patients [9]. Other studies have also demonstrated that TGF-β1 induced significant up-regulation of VEGF-C expression in cultured human proximal tubular epithelial (HK-2) cells, collecting duct (M-1) cells, and macrophages (RAW264.7) [53]. All these results could indicate that lymphangiogenesis in the PM is linked with the fibrotic process via the TGF-β-VEGF-C pathway [53, 59, 60]. Therefore, prevention of TGF-β induction may reduce fibrosis and lymphangiogenesis, resulting in the avoidance of the UFF.

VEGF-D, which is homologous to VEGF-C, is also implicated in the regulation of the peritoneal lymphangiogenesis. It had been shown in cultured macrophages and fibroblasts that VEGF-D increased by PGE2 and by inflammatory cytokines. However, in contrast to VEGF-C, VEGF-D has been reported to be down-regulated by TGF-β. Moreover, although cultured human MCs strongly express VEGF-C, they do not express VEGF-D [55]. Either VEGF-C or VEGF-D induce growth of the lymphatic vessels via activation of VEGFR-3, which is localized on the surface of lymphatic endothelial cells. Signaling via VEGF-C and VEGF-D/VEGFR3 seems to be the most central pathway for lymphangiogenesis and survival of endothelial cells, providing a new therapeutic target to increase net ultrafiltration by suppression of lymphangiogenesis and lymphatic absorption. In a murine model of peritoneal injury induced by the GDP methylglyoxal (MGO), a precursor of AGEs, VEGFR-3 was up-regulated and the drained volume tended to be increased compared with the control group (although not statistically significant) [55]. In addition, inhibition of this signaling pathway using an adenovirus expressing soluble VEGFR-3 fused with human IgG and using function-blocking antibody entirely blocked lymphatic sprouting after infection, but had no effect on blood vessel remodeling [61].

3.3. Endothelial and lymphatic vessels: overlapping markers

As commented before, the lymphatic and blood systems serve different but complementary functions to maintain the homeostasis of the tissues. Given that lymphatic endothelial cells (LECs) derive from embryonic blood vascular endothelial cells (BECs) during embryogenesis [62], it is not surprising that both cell types have some properties and features in common and, therefore, share many markers. In this regard, both types of vessels express CD31, CD34, podocalyxin, von Willebrand factor and other markers [63]. These facts pose a challenge to distinguish both lineages but still there are markers that can be used to differentiate them. Thereby, in healthy tissues LECs express specifically podoplanin, the lymphatic vessel endothelial hyaluronan receptor (LYVE-1) [64–67], VEGFR-3 [68], and prospero-related homeobox domain 1 (Prox1) [65, 69]. Prox1 is essential for lymphangiogenesis and helps to drive the expression of lymphatic-specific genes that transform venous progenitor cells into functional LECs [40]. In fact, it has been demonstrated that loss of Prox1 expression in mice results in arrested lymphangiogenesis [70]. Furthermore, the continued expression of Prox1 in LECs of adult animals is required for the maintenance of these vessels, as conditional deletion of Prox1 in adult mice causes the reversion of lymphatic endothelium to venous endothelium [71].

However, the expression of these markers in healthy LECs may not necessarily apply in the lymphatic disease settings [72], so when employing them it is necessary to consider the tissue or organ and the possible presence of inflammation or pathological processes. Thus, during inflammation, there is an up-regulation of VEGFR-3 on most proliferating blood vessels, which makes this marker not useful to distinguish between the lymphatic and blood vessels in this

situation [73] (and so during PD exposure, since there is a chronic inflammatory status). In regard to podoplanin, this molecule seems to play a role in the pathogenesis of encapsulating peritoneal sclerosis (EPS, a severe complication of PD treatments) [74], but is expressed by peritoneal mesothelial and fibroblast-like cells [75–78] (**Figure 2**). It is interesting also to note that Prox1 is expressed in normal and pathologic human tissues (lymphedema) [69], but its functions are not exclusive to lymphatic vessels, since recent studies have shown that Prox1 is required for the development and maintenance of venous valves [79]. In conclusion, to selectively distinguish between both types of vessels, a good strategy could be to use a combination of two or more markers (accordingly, as an example $CD31^+$/podoplanin cells would be considered as BECs).

Nonetheless, other molecules have recently emerged as potential markers to specifically label LECs, but still need confirmation. In this regard, it has been suggested that the Integrin $\alpha 9$, a receptor for VCAM-1 (vascular cell adhesion molecule-1), could be a potential marker of mouse LECs [80], but it still requires validation since it is not clear whether the application of the antibody in human tissues is reliable [72]. Likewise, COLEC 12, a gene that codes for Collectin-12 protein (a scavenger receptor), has also been suggested as another LEC marker [62]. The expression of CLEVER-1 (common lymphatic endothelial and vascular endothelial receptor-1), also known as stabilin-1 or FEEL-1, has been reported in response to inflammation in skin LECs, macrophages and BECs [81], but also requires to be confirmed as a suitable marker for abnormal or diseased human LECs identification [72].

3.4. Specific secretion of cytokines and chemokines

The specialization of endothelial cells extends also to the secretion of biologically relevant chemotactic factors. In this regard, LECs, but not BECs, constitutively secrete the chemokine receptor CCR7 ligand, secondary lymphoid tissue chemokine (SLC)/CCL21 at their basal side, while both subsets, upon activation, release macrophage inflammatory protein (MIP)-3α/CCL20 apically [63].

4. Therapeutic strategies

Clinical diagnosis is of high value due to the limitations obtaining PM biopsies. Until now, procedures include general care actions to avoid fluid overload (use of diuretic agents in patients with residual renal function shorten dwell times and volumes of dialysate fluids or temporarily discontinue PD) (**Table 1**). Depending on the UFF type, general recommendations are as follows.

Regarding the type I UFF, clinical evidence supports the peritoneal resting [82] and the blockade of the renin-angiotensin-aldosterone system with angiotensin converting enzyme inhibitors or angiotensin receptor blockers [83, 84]. The use of neutral pH low GDP fluids may be beneficial as well, but the evidence to date is inconclusive [85, 86]. With regards to the type II UFF, it has been observed that the use at early stages of high doses of steroids or an agonist of AQP1 (AqF026) can improve water transport by modulating the expression of AQP1 channels [20, 87, 88]. Since the type III PM failure is associated with fibrosis, that in its maximum degree leads to EPS, adhesiolysis and peritoneal rest are indicated [89, 90]. Moreover, corticosteroids,

azathioprine, mycophenalate, rapamycin and its derivative everolimus have all been tried with limited success [91, 92]. More recently, the use of tamoxifen has been reported to be beneficial in the treatment of EPS [90, 92, 93]. In this regard, a recent study showed that mortality was significantly decreased in patients treated with immunosuppression compared to the group with tamoxifen as well [94]. Nutritional support of these patients is also mandatory. The clinical management of liquid overload may be treated with icodextrin PD exchanges at least temporarily. Given the clinical characteristics of PM failure type IV, the long-term absorption of dialysate and long dwelling should be included in therapeutic management [14].

But if the treatment is crucial once the UFF is set, what is even more important is to prevent this status, what means to focus on the origin of the damage. The use of PD has increased over the last years due to the development of different strategies which have allowed the improvement of the treatment. During the last years, researchers have been trying to develop biocompatible PDFs using new osmotic agents to substitute glucose, such as amino acids or icodextrin, to avoid the formation of GDPs and AGEs. However, considering that PDFs of new generation are expensive, another alternative is using drugs to treat and prevent peritoneal damage caused by long exposure to PDFs [95] (**Figure 3**) (**Table 2**).

In this context, there are several studies about blocking MMT process, because of its identification as a key event in peritoneal damage. These therapeutic strategies were also designed either to prevent or reverse the MMT, or to reduce the MMT-inducing stimuli. Nevertheless, it has to be taken into account that MMT is a physiologic process necessary for wound healing during PD. Another possibility is to act on the consequences of MMT or mesenchymal transition of other cells populations instead, such as the increased angiogenesis or lymphangiogenesis [33, 47]. The therapeutic options tested until the date are exposed below in detail and summarized in **Table 2**. These data encourage conducting clinical trials to solidify therapeutic evidences.

4.1. Anti-angiogenic therapy

4.1.1. VEGF

Many studies have been carried out to reduce angiogenesis by the development of angiogenesis inhibitors which modulate the expression of VEGF, which is a well-known potent angiogenic factor associated with vascular proliferation in PD patients. On this line, some studies used *cyclooxygenase (COX)-2 inhibitors*, an induced enzyme that stimulate angiogenesis by up-regulation of the expression of VEGF and that is more expressed in non-epithelioid cells that had undergone MMT than epithelioid MCs. One of them is Celecoxib, which is able to avoid PD-induced angiogenesis in the omentum and parietal peritoneum and to restore UF in rat and mice models of standard PDF exposure through an implanted peritoneal catheter. Moreover, as COX enzymes are implicated in prostaglandin synthesis too, this treatment was also useful decreasing peritoneal inflammation and fibrosis [97, 98].

Another kind of VEGF inhibitors are the *tyrosine kinase inhibitors*, such as Sunitinib, which is able to block the VEGF signaling. Indeed, it has been observed that its administration to a female PD patient with end stage renal disease and metastasic renal cell carcinoma helps to stabilize the abdominal metastasis as well as the thickness of the PM, and the D/P creatinine ratio remains stable [100].

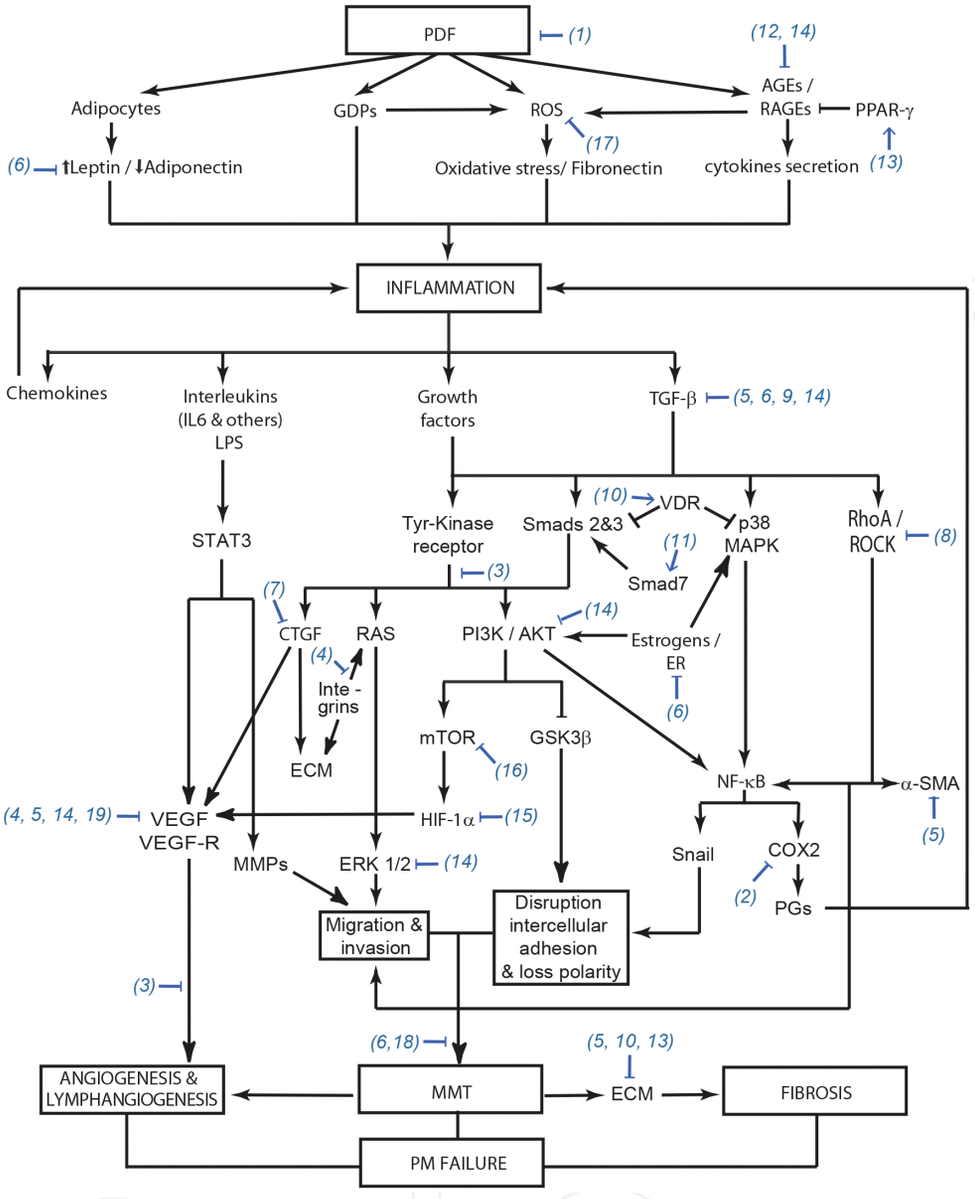

Figure 3. Pathways implicated in PM failure and therapeutic options. Numbers in parenthesis correspond with drugs tested described in **Table 2**.

Endostatin, a 20-kDa C-terminal fragment of type XVIII collagen, has also been described as a potent endogenously inhibitor of angiogenesis [102]. Endostatin blocks angiogenesis by directly binding to both VEGFR-1 and -2, and blocking VEGF interaction with these receptors, preventing all downstream signaling events induced by VEGF [103]. Endostatin also competes with fibronectin, a pro-angiogenic ligand, to bind to its cell surface receptor integrin $\alpha_5\beta_1$, to interrupt cell migration [106]. The anti-angiogenic activity of endostatin has been recently found to be mediated also by its intrinsic ATPase activity *in vivo*, by inhibiting endothelial cell proliferation, migration, tube formation and adhesion [130]. Moreover, the therapeutic efficacy of endostatin peptide treatment in ameliorating alterations has been demonstrated in a diabetic nephropathy mouse model [131] and in a chlorhexidine gluconate (CG)-induced mice peritoneal sclerosis model [105].

Route in Figure 3	Action	Drug	Target molecules	Processes blocked			
				Angiogenesis	Lymphangiogenesis	Fibrosis	Others
(1)	More bio-compatibility	New osmotic agents	Receptors of glucose and degradation products	Yes [96]		Yes [96]	Inflammation [96]
(2)	COX-2 inhibition	Celecoxib	VEGF	Yes [97, 98]	Yes [99]	Yes [97, 98]	Inflammation [97, 98]
(3)	Tyrosin-kinase inhibition	Sunitinib, Sorafenib and Regorafenib	VEGF	Yes [100, 101]	Yes [101]		
(4)	Inhibition of VEGF/VEGFR pathway and ATPase activity	Endostatin	VEGF	Yes [102, 103]	Yes [104]	Yes [105]	Cell migration [106]
(5)	Inhibition of cytokines or growth factors/ receptors interaction and ECM deposition	Suramin	TGFβ and VEGF α-SMA and FDF	Yes [107]		Yes [107]	Inflammation [107]
(6)	Estrogen receptor modulation	Tamoxifen	TGFβ, VEGF and leptin	Yes [93, 108]		Yes [109]	
(7)	CTGF antagonist	FG-3019	VEGF	Yes [110]			
(8)	Inhibition of Rho/ROCK pathway	Fasudil Y-27632	VEGF	Yes [111]		Yes [111]	
(9)	TGFβ blockade	BMP7	TGFβ	Yes [112]		Yes [112]	
		Blocking peptides (p17 and p144)	TGFβ	Yes [30]		Yes [30]	
(10)	Vit D receptor activator	Calcitriol and paricalcitol	TGFβ (and inflammatory cells)	Yes [7, 113]	Yes rats [114]	Yes [7, 113]	Inflammation [7]
(11)	Inhibition of TGFβ/Smad pathway	Smad7	TGFβ	Yes [115]			

Route in Figure 3	Action	Drug	Target molecules	Processes blocked			
				Angiogenesis	Lymphangiogenesis	Fibrosis	Others
(12)	Transketolase activation and direct anti-oxidative effects	Benfotiamine	AGEs	Yes [116]		Yes [116]	Inflammation [116]
(13)	PPARγ	Rosiglitazone	AGEs	Yes [117]			
(14)	Serine protease inhibition	Kallistatin	VEGF and AGEs	Yes [118]	Yes [101]		Inflammation and oxidation [119].
(15)	HIF-1α blockade	LMWH	VEGF and HIF-1α	Yes [120]	Yes [121]	Yes [120]	Inflammation [120]. Elevate UF [122]
(16)	mTOR blockade	Rapamycin and Everolimus	HIF-1α	Yes [33, 123, 124]	Yes [33, 125, 126]		
(17)	Oxidative stress reduction	N-acetylcysteine	TGFβ, VEGF and eNOS,	Yes [127]	Yes [128]		
(18)	β1-AR blockade	Nebivolol	β1-AR	Yes [129]		Yes [129]	Inflammation [129]

Table 2. Drugs already tested to block different pathways implicated in the alterations suffered in the PM during PD treatments. Bibliographic references in brackets.

Recent investigations reported that *Suramin*, a polysulfonated naphthylurea, is able to down-regulate VEGF expression in the peritoneum of a fibrosis rat model induced after CG injection. These results suggest that Suramin might inhibit angiogenesis and improve UF by suppressing production of angiogenic growth factors such as VEGF. Furthermore, Suramin also inhibited the expression of TGF-β, α-SMA and the deposition of ECM protein in the peritoneum in this rat model, which may indicate that it could be a potent agent for attenuation of peritoneal fibrosis too [107].

Tamoxifen, an estrogen receptor (ER) modulator used for the treatment of breast cancer [132], has shown the capacity to affect the expression of the VEGF in mice peritoneal tissue exposed to PDF through an access port. As a result, there is a decrease in the number of vessel that allows the maintenance of the UF capacity [93]. This decrease may also be due to a down-regulation of leptin expression, because this molecule can also produce interference in the induction of neovascularization [93, 108]. In addition, Tamoxifen has demonstrated to have anti-fibrotic activity, being able to inhibit TGF-β1 [109].

It has been found that connective tissue growth factor (CTGF/CCN2), whose expression is increased in human fibrotic diseases [133], is required for VEGF-A production in response to TGF-β1 in fibroblast and mouse peritoneal MCs. In addition, the use of the CTGF antagonist FG-3019 suppressed the increase in VEGF-A production and peritoneal angiogenesis induced by CG. The mechanism by which CTGF is acting remains unknown, but it could be through direct physical interactions. However, it seems to be a difference in CTGF action depending on cell type [110].

It has been suggested that the GTPase Rho and its downstream effector Rho-kinase (ROCK), that play a leading role in smooth muscle contraction, cell migration, proliferation and gene expression [134], may also contribute to development of peritoneal angiogenesis and fibrosis induced by PD [135]. In fact, this pathway is able to regulate VEGF expression in endothelial cells [136], and the activity of Rho-kinase has been found to be up-regulated in the peritoneum after PD. For this reason, it has been investigated whether the inhibition of Rho/ROCK pathway could have a therapeutic effect on PD-induced angiogenesis and fibrosis. This theory has been validated with Fasudil, a Rho-kinase inhibitor, which inhibited peritoneal angiogenesis and fibrosis and improved peritoneal function in a rat PD model. This effect may be due to the effective reduction of VEGF and TGF-β in the peritoneum [111].

The specific ROCK inhibitor Y-27632 has also shown an effect in preventing tubule-interstitial fibrosis in mice kidneys with unilateral ureteral obstruction [137]. On the other hand, the 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins and usually employed as potent inhibitors of cholesterol biosynthesis, are also able to inhibit Rho/ROCK pathway through suppressing isoprenylation of small RhoGTPases [138], which suggests that statins may have a therapeutic effect on peritoneal damage related to PD [139].

4.1.2. Transforming growth factor (TGF)-β

Another strategy to block the process of angiogenesis is to act on the factors that induce the expression of VEGF, instead of inhibiting its expression directly. In this context, one of the factors that enhance VEGF expression in several cell lines is TGF-β [47, 140]. It has been demonstrated

that the administration of *TGF-β1-blocking peptides* to mice exposed to PDF significantly reduced peritoneal angiogenesis and fibrosis [30]. Administration of *bone morphogenic protein-7 (BMP-7),* that antagonizes TGF-β1, reduced new vessel formation in a PDF-exposed rat model [112].

Calcitriol, the most active form of *vitamin D*, also protected against CG-induced injury in rats by decreasing levels of TGF-β and angiotensin II, leading to a decreased peritoneal angiogenesis and fibrosis [113]. However, it has to be considered that blocking the action of TGF-β is not feasible because it is a pleiotropic factor that regulates several functions and, as a result, there may be many side effects [30]. Hence, another possibility could be to identify and act over downstream signaling pathways.

On this context, it has been reported that TGF-β exhibits its biological effects through TGF-β/Smad signaling pathway and that *Smad7* negatively regulated the TGF-β induced VEGF [141]. Considering this, it has been demonstrated that Smad7 transfection prevents the experimental peritoneal angiogenesis by inhibiting the activation of TGF-β/Smad signaling pathway *in vivo*, in a rat model of PD associated with peritoneal fibrosis induced by daily intraperitoneal injection of Dianeal and intraperitoneal injection of LPS. These results suggest that Smad7 treatment might be an effective therapeutic approach for preventing peritoneal angiogenesis [115].

However, it is important to know that TGFβ is involved in the development and function of regulatory T cells (Tregs) [142–144], as adult mice deficient in TGFβ signaling exhibit a defective Treg phenotype with normal numbers, decreased suppressive function, and an incomplete TCR repertoire [145–148]. Tregs cells are extremely important for the maintenance of the peritoneal protection during PD [149], so treatments intended to block TGF-β signaling should take into account the complete cytokine environment and consider this side effect.

4.1.3. Advanced glycation end products (AGEs)

On the other hand, taking into account that AGEs are another factor leading to peritoneal damage by induced angiogenesis [150], some researchers have focused on the prevention of glucose and GDP-induced toxicity. Results showed that the treatment with *Benfotiamine*, a derivative of Vitamin B, brings to a decreased of expression of AGEs and RAGEs in the peritoneum and kidney of rats in a uraemic PD model. Moreover, Benfotiamine reduced neovascularization, fibrosis and markers of inflammation, leading to an improvement of peritoneal transport in this model [116].

The *peroxisome proliferator–activated receptor γ* (PPAR-γ) has been also evaluated as a potential target to reduce peritoneal damage in PD. Indeed, it has been demonstrated in a mouse PD model that the administration of the PPAR- γ agonist rosiglitazone (RSG) is able to diminish angiogenesis *in vivo*, probably by reducing the accumulation of AGEs [117].

Kallistatin, a serine protease inhibitor with anti-inflammatory and anti-oxidative properties, has been also recognized as an endogenous anti-angiogenic agent. It may reduce the phosphorylation of VEGFR-2 in human umbilical vein endothelial cells, by which it can inhibit angiogenesis [118]. It has been recently verified that Kallistatin overexpression in kidney tubules of *db*/*db* mice inhibited RAGE expression in the diabetic kidney and AGE-stimulated cultured proximal tubular cells. Furthermore, there are other mechanisms involved in its renoprotective effect, such as inhibition of TGF-β pathway or attenuation of oxidative stress [119].

4.1.4. Hypoxia inducible factor (HIF)-1α

Chronic hypoxia has also been linked to angiogenesis, MMT and fibrosis. One of the factors that mediate the cellular hypoxic response is the hypoxia inducible factor (HIF)-1α, which has demonstrated to play an important role not only in angiogenesis, but also in peritoneal fibrosis, extracellular matrix metabolism and inflammatory reaction [120]. Recent studies have shown, using a peritoneal fibrosis rat model induced by high glucose, that the *low molecular weight heparin* (LMWH) protects peritoneal structure and function through inhibiting the process of angiogenesis, inflammation and fibrosis. These effects of LMWH may be due to suppression of HIF-1α expression and its downstream target VEGF [120]. In addition, LMWH reduces peritoneal permeability to small solutes and elevates UF in PD patients [122]. LMWH has been commonly used until now to diminish fibrin deposition and to prevent the occlusion of the peritoneal catheter and intra-abdominal adhesion [120].

Rapamycin, an antibiotic with an immune-suppressant activity with pleiotropic effects, including anti-angiogenic capacity, is also able to suppress HIF-1α. This anti-angiogenic effect is associated with the blockage of the *mammalian target of rapamycin (mTOR)*, because it is an upstream activator of HIF-1α. In fact, it has been observed in hypoxic cells that rapamycin can interfere with HIF-1α activation by increasing the rate of its degradation [123]. Moreover, the anti-angiogenic activity of rapamycin is also due to the decrease in VEGF expression both *in vitro* and *in vivo* [33, 124], and to the reduction in the response of vascular endothelial cells to stimulation by VEGF [124].

4.1.5. Others

Oxidative stress is another factor involved in the changes in PM during PD. It has been reported that the reactive oxygen species (ROS) generated by PDF are responsible, at least in part, for the PM hyper-permeability and peritoneal fibrosis *in vivo*. This suggests that *antioxidants* could be a therapeutic strategy to prevent the damage during long-term PD. In fact, the use of the antioxidant N-acetylcysteine (NAC) inhibited the increase of VEGF, TFG-β1 and the endothelial NOS (eNOS) [151], which plays a role in the control of vascular tone, permeability and angiogenesis [127, 128].

Blocking *β1-adrenergic receptor* (β1-AR) expressed in peritoneal MCs is another therapeutic strategy to reduce angiogenesis induced during PD [129] since it has been observed that the block of this receptor is related with anti-angiogenic effects [152]. Indeed, the β1-AR antagonist Nebivolol has demonstrated to attenuate submesothelial vessel formation in a mice model of PD obtained by instillation of PDFs through a peritoneal catheter. This effect may be associated with its direct interaction with the β1-AR, but it could also be due to the reduction of fibrosis and MMT [129].

New studies also have pointed to the possibility that peritoneal adipocytes could also contribute to inflammation and angiogenesis that lead to UFF in PD. That means that targeting the changes in adipocytes as well as the secretion of adipokines (or their activation/receptors) might provide another therapeutic approach for preventing them [153].

4.2. Anti-lymphangiogenic therapy

4.2.1. Vitamin D receptor

Despite the fact that Vitamin D analogs have been shown to have anti-angiogenic (as well as anti-fibrotic and anti-inflammatory) effects in PD models [7], the potential effects of Vitamin D on LECs and lymphangiogenesis remain poorly studied. However, a recent study demonstrates that calcitriol attenuated murine LEC tube formation and proliferation *in vitro.* In addition, Paricalcitol significantly decreased lymphangiogenesis in the kidneys of nephrotic rats [114].

4.2.2. Vascular endothelial growth factor (VEGF)

Endostatin, which has been described previously as an anti-angiogenic factor, also exerts anti-lymphangiogenic effects by competitively inhibition of the interaction between VEGF-C or -D and VEGFR-3 *in vitro* [104]. New drugs have very recently been identified as possible therapies to reduce lymphangiogenesis. LHbisD4, the conjugate of LMWH, has been revealed as a potent anti-angiogenic drug that could also suppress the formation of new lymphatic vessels by blocking VEGF-C signaling pathway. This drug suppressed the proliferation, migration and formation of tubular structures of human dermal LECs *in vitro* even in the presence of high VEGF-C concentrations, and significantly diminished the density of lymphatic vessels in primary tumor tissue in breast cancer-bearing mice [121].

Apart from its anti-angiogenic action over blood vasculature previously commented, Kallistatin also presents anti-lymphangiogenic properties as it is able to block LECs proliferation, migration and tube formation. Kallistatin inhibits expression of VEGFR-3 and downstream signaling pathways such as phosphorylation of ERK and Akt in LECs [101].

COX-2, VEGF-A, and -C expression levels were elevated in a uraemic rat PD model, showing increased density of $CD31^+$ and $LYVE\text{-}1^+$ microvessels in the peritoneum. These changes were partially reversed with Celecoxib [99]. In another rat model, intraperitoneal administration of PDF resulted in increased angiogenesis, lymphangiogenesis, submesothelial matrix thickness, and also enhanced expression of mesothelial AQP1 in parietal peritoneal tissues. Celecoxib exposure drastically reduced PGE2 levels, angiogenesis, lymphangiogenesis, fibrosis and milky spot formation, but did not modify mesothelial AQP1 expression nor VEGF tissue expression and inflammatory markers [97].

Many inhibitors of lymphangiogenesis or angiogenesis, such as Sorafenib and Regorafenib, are VEGF receptor tyrosine kinase inhibitors, which inhibit the phosphorylation of VEGFR-3, while other drugs act by down-regulating the expression of VEGFR-3 [101].

4.2.3. Mammalian target of rapamycin (mTOR)

The specific mTOR inhibitor, rapamycin, has been recently shown to inhibit lymphangiogenesis in different studies [125, 126]. Moreover, it shows a protective effect against type I PM failure in PD, inhibiting the angiogenesis, lymphangiogenesis and Endo-MT. Furthermore, rapamycin also seems to be able to selectively decrease the synthesis and release of the pro-lymphangiogenic factors VEGF-C and -D in MCs [33].

4.2.4. Others

N-acetylcysteine has been shown to inhibit tumor angiogenesis and lymphangiogenesis [128] due to its antioxidant properties, though it could represent possible therapeutic strategies also in PD, although it has not been studied yet.

Tetracycline, minocycline and doxycycline are substances with antibacterial properties, which also have other recognized actions that include anti-inflammatory, anti-fibrotic and anti-angiogenic effects. This is possibly mediated by NF-κB inhibition [154]. In fact, in an ischemic-reperfusion renal rat model, doxycycline showed a prolonged renal function due to its protective anti-inflammatory effect [155].

In conclusion, angiogenesis and lymphangiogenesis processes in PD are closely related with peritoneal transport alterations, especially PM failure type III and IV. Considering that both processes can take place in the early stages, they should be recognized by biochemical markers in the PD effluent. Therefore, it is important to carry out clinical and basic research in order to elucidate the role of both processes in the PM damage and to determine the most appropriate therapeutic approach.

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