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Angiogenic Activity of the Peritoneal Mesothelium: Implications for Peritoneal Dialysis

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1. Introduction

Functional deterioration of the peritoneum as a dialyzing organ is a leading cause of peritoneal dialysis (PD) failure. The problem usually develops 2-4 years after the initiation of therapy (Davies et al., 1996; Struijk et al., 1994) and may affect as many as 50% of all PD patients (Kawaguchi et al., 1997). The alterations that develop in the peritoneal membrane over time include submesothelial thickening, fibrosis, angiogenesis, and vascular degeneration (Honda et al., 2008; Mateijsen et al., 1999; Williams et al., 2002; Williams et al., 2003). These changes are associated with an increase in peritoneal solute transport with resultant dissipation of the osmotic gradient and loss of ultrafiltration. Indeed, it has been estimated that up to 75% of patients with ultrafiltration failure will have increased vascular area (Heimburger et al., 1990; Ho-Dac-Pannekeet et al., 1997). Pathological angiogenesis not only increases vascular surface area of the peritoneum but is also a key step in the progression of fibrosis (Wynn, 2007). Therefore, it is essential to understand how PD environment impacts on peritoneal vasculature.

2. Vascular endothelial growth factor

The process of angiogenesis requires tight coordination of cell proliferation, differentiation, migration, and cell-matrix interactions. The most important molecules that control blood vessel growth and permeability are vascular endothelial growth factors (VEGFs). VEGF-A (also designated and further referred to as VEGF) is the founding member of the VEGF family and was originally discovered by its ability to enhance vascular permeability (Nagy et al., 2007). In mammals, other VEGF family members include VEGF-B, -C, and -D, as well as placenta growth factor (PlGF). Structurally, the VEGFs are related to the family of platelet-derived growth factors (PDGF) (Olsson et al., 2006). VEGF is a highly conserved, disulfide-bonded dimeric glycoprotein, encoded by a single gene. The human *Vegf* gene is located on the short arm of chromosome 6 and alternative RNA splicing gives rise to peptide isoforms of 121, 145, 165, 189, and 206 amino acids. VEGF exerts its biologic effects

mainly through cell-surface tyrosine kinase receptors VEGFR-2, and - to lesser extent - VEGFR-1 (Nagy et al., 2007). Although VEGF isoforms display similar basic activities, their bio-availability may be modulated by proteolytic processing and differences in binding to co-receptors such as heparan sulphate proteoglycans and neuropilins (Olsson et al., 2006).
VEGF is an extremely potent and rapid inducer of vascular permeability (Olsson et al., 2006). This effect depends on the production of nitric oxide (NO) by endothelial NO synthase (eNOS). Consequently, targeted deletion of eNOS abrogates VEGF-induced permeability (Fukumura et al., 2001). Other biological effects of VEGF include vasodilation, endothelial cell proliferation, migration and tube formation. It also delays senescence of endothelial cells, promotes their survival, and mobilizes endothelial cell precursors (Nagy et al., 2007; Otrock et al., 2007). Inactivation of a single *Vegf* allele in mice results in early embryonic lethality caused by impaired development of endothelial cells and blood vessels (Carmeliet et al., 1996; Ferrara et al., 1996). In turn, an increase in VEGF expression is commonly associated with pathological angiogenesis observed in malignancies, inflammation, and wound healing (Nagy et al., 2007).

2.1 VEGF in the peritoneal cavity

Given its role in controlling vascular permeability and proliferation, VEGF became an obvious target in research efforts to define the mechanism of peritoneal membrane failure. VEGF was promptly detected in the effluent dialysate (Zweers et al., 1999) in concentrations higher than could be expected on the basis of simple diffusion from the circulation (Selgas et al., 2001; Zweers et al., 1999). This pointed to the local production of VEGF in the peritoneum. Moreover, the rate of VEGF appearance in the dialysate was found to increase with time on PD (Cho et al., 2010) and to be elevated in patients with high peritoneal transport status (Pecoits-Filho et al., 2002; Rodrigues et al., 2007). Further analyses showed that the dialysate appearance of VEGF correlated also with that of cancer antigen 125 (CA125) (Cho et al., 2010; Rodrigues et al., 2004; Rodrigues et al., 2007). CA125 is thought to reflect the mass of peritoneal mesothelial cells (Krediet, 2001), therefore the mesothelium was considered to be the main source of intraperitoneal VEGF. Indeed, immunochemical staining of peritoneal biopsies showed that VEGF expression was confined mainly to the mesothelial monolayer (Aroeira et al., 2005; Combet et al., 2000). The mesothelial origin of peritoneal VEGF was ultimately confirmed in an elegant study, during which various cell types were isolated from the peritoneal lavage and the omentum, and analysed by several techniques for the ability to generate VEGF (Gerber et al., 2006). It transpired that omental mesothelial cells were responsible for the majority of peritoneal VEGF produced. These results were corroborated by the demonstration of constitutive VEGF secretion by mesothelial cells isolated either from the dialysate effluent (Selgas et al., 2000) or from the omentum (Mandl-Weber et al., 2002). Moreover, VEGF released by mesothelial cells was shown to exhibit biologic activity (Boulanger et al., 2007). The formation of capillary tubes by endothelial cells in vitro was found to increase either in the presence of peritoneal mesothelial cells or after the addition of conditioned medium from mesothelial cell cultures. These effects could be abolished by anti-VEGF antibodies (Boulanger et al., 2007).

3. Mesothelial cell VEGF expression during PD

The above data have given support to a long held belief that although the mesothelium forms only a single-cell layer over the peritoneum, it may significantly impact on the dialytic

function of the whole peritoneal membrane by producing powerful mediators that act on the peritoneal interstitium and vasculature. Immunochemical analysis of peritoneal biopsies revealed only weak mesothelial expression of VEGF in control subjects, but extensive VEGF staining in patients undergoing PD (Aroeira et al., 2005; Combet et al., 2000). In an interesting experimental model mesothelial cells were isolated from dialysate effluent of PD patients, propagated ex vivo and analysed for the ability to release VEGF (Aroeira et al., 2005). It turned out that mesothelial cells isolated from patients with high peritoneal permeability secreted more VEGF compared to cells from patients with lower peritoneal transport properties.

Several factors have been implicated in the pathogenesis of increased peritoneal permeability in PD. They include the state of uraemia, episodes of peritonitis, and chronic exposure to dialysis fluids (Margetts & Churchill, 2002). Increasing evidence indicate that such conditions may modulate the release of VEGF by mesothelial cells. It is therefore essential to delineate mesothelial cell responses to these challenges.

3.1 Peritonitis

An increase in vascular permeability is a hallmark of inflammation. As a result, when acute peritonitis occurs during PD, it leads to rapid absorption of instilled glucose and a decrease in osmotic gradient-driven ultrafiltration. Modelling of PD-associated peritonitis in mice revealed significant increases in vascular density, the relative endothelial area, and the diameter of peritoneal vessels (Ni et al., 2003). These alterations were evident several days after bacterial infection and were accompanied by a huge increase in the dialysate VEGF concentration.

The inflammatory response is orchestrated by a coordinated release of cytokines with interleukin-1β (IL-1β) and tumour necrosis factor-α (TNFα) acting as crucial promoters of the reaction. The concentrations of IL-1β and TNFα in PD effluent increase very early and dramatically in the course of peritonitis (Brauner et al., 1996; Moutabarrik et al., 1995; Zemel et al., 1994). Transient, adenovirus-mediated over-expression of either IL-1β or TNFα in the rat peritoneum was found to increase the expression of VEGF in the peritoneal tissue and fluid (Margetts et al., 2002). This effect was followed by extensive angiogenesis, increased peritoneal permeability, and impaired ultrafiltration. In keeping with these results, it has been demonstrated that either IL-1β or TNFα were capable of inducing time- and dose-dependent VEGF production in mesothelial cells in vitro (Mandl-Weber et al., 2002). Moreover, in vitro exposure of mesothelial cells to dialysate effluent drained during peritonitis resulted in a significantly increased VEGF release compared to when cells were maintained in the non-infected dialysate (Witowski & Jörres, personal observations).

3.2 Exposure to dialysis fluids

The observation that the ultrafiltration capacity of the peritoneum decreases with time on PD (Davies et al., 1996; Heimburger et al., 1999) suggested that long-term exposure to bioincompatible PD fluids might have a deleterious impact on the peritoneal membrane. Early experiments pointed to low pH, high concentrations of lactate and glucose, and the presence of glucose degradation products (GDPs) as the elements curtailing biocompatibility of standard PD solutions (Wieslander et al., 1991). In recent years particular attention has been paid to GDPs. They are reactive carbonyl derivatives of glucose (such as formaldehyde, methylglyoxal or 3-deoxyglucosone), which are formed predominantly

during heat sterilization of PD fluids. It has been demonstrated that conventional PD fluids with high GDPs content recruited capillaries and induced vasodilation of mesenteric arteries in the rat peritoneum (Mortier et al., 2002). Moreover, the peritonea of rats injected intraperitoneally for several days with methylglyoxal were found to display increased vascularization (Nakayama et al., 2003) and VEGF expression (Inagi et al., 1999). Subsequent experiments confirmed that extensive peritoneal expression of VEGF in rats receiving methylglyoxal-containing PD fluids was associated with neoangiogenesis and increased permeability (Hirahara et al., 2006). Furthermore, it has been demonstrated that direct in vitro exposure of mesothelial cells to several GDPs (methylglyoxal, 3,4-dideoxy-glucosone-3-ene, 2-furaldehyde) resulted in an increased VEGF expression (Inagi et al., 1999; Lai et al., 2004; Leung et al., 2005).

The adverse effects of GDPs on the peritoneal membrane can also be mediated through advanced glycation-end products (AGEs). GDPs react with amino groups of proteins to form AGEs and it has been demonstrated that PD fluids with high GDP levels significantly promote the generation of AGEs (Tauer et al., 2001). Animal experiments showed that intraperitoneal infusion of GDP-containing solutions led to the accumulation in the peritoneal membrane of both methylglyoxal and AGEs (Mortier et al., 2004). The presence of AGE deposits was associated with increased expression of VEGF, increased vascular density, and lower ultrafiltration. These observations were in line with earlier data showing that the intensity of peritoneal AGE accumulation in PD patients correlated with changes in peritoneal transport and ultrafiltration (Honda et al., 1999; Nakayama et al., 1997). Moreover, mesothelial cells were found to bear a receptor for AGEs (RAGE) and to up-regulate its expression following exposure to GDP in either in vitro (Lai et al., 2004) or in vivo setting (Mortier et al., 2004). In turn, incubation of mesothelial cells with AGEs led to a dose-dependent increase in VEGF production (Boulanger et al., 2007; Mandl-Weber et al., 2002). Interestingly, GDP-induced VEGF release by mesothelial cells could be reduced by aminoguanidine, an inhibitor of AGE formation (Lai et al., 2004). Also, a rise in peritoneal VEGF expression and vascular density that was induced in wild-type mice by chronic exposure to GDP-containing fluids, did not occur in RAGE-deficient animals (Schwenger et al., 2006). Correspondingly, the promoting effect of AGE-treated mesothelial cells on capillary tube formation could be substantially diminished by the blockade of RAGE with specific antibodies (Boulanger et al., 2007). These data indicate that GDPs exert their effect by inducing glycation of proteins that subsequently activate RAGE on mesothelial cells and stimulate them to release angiogenic VEGF (Fig. 1).

3.3 Uraemia

After analysing peritoneal specimens from a large cohort of individuals, the Peritoneal Biopsy Study Group concluded that in many patients with uraemia some changes in the peritoneum occurred even before the commencement of PD (Williams et al., 2002). Compared to healthy individuals, such patients often had significant thickening of the submesothelial compact zone and extensive vasculopathy. These changes are generally attributed to the build-up of uraemic toxins, however, their exact nature remains poorly defined. The peritonea of rats made uraemic by subtotal nephrectomy were found to have increased permeability and showed focal areas of vascular proliferation, up-regulation of VEGF and accumulation of AGEs (Combet et al., 2001). Furthermore, there was the evidence of mesothelial cell conversion into myofibroblasts (De Vriese et al., 2006). A more recent

study in humans confirmed the presence of submesothelial thickening, focal fibrosis, and increased vascularization in the uraemic peritoneum (Kihm et al., 2008). These alterations were accompanied by increased peritoneal expression of methylglyoxal-induced AGEs, RAGE, VEGF, as well as of nuclear factor-κB (NF-κB) and interleukin-6 (IL-6). The peritoneal accumulation of AGEs and RAGE in uraemia may be not so surprising, since it is now well recognized that the uraemic state is associated with increased generation of glucose-derived dicarbonyl compounds (such as glyoxal, methylglyoxal, or 3-deoxyglucosone), which are strong inducers of AGEs (Miyata et al., 1999; Miyata et al., 2001) (Fig. 1). In turn, binding of AGEs to RAGE on mesothelial cells can activate NF-κB and increase the production of NF-κB-controlled inflammatory cytokines, including IL-6 (Nevado et al., 2005).

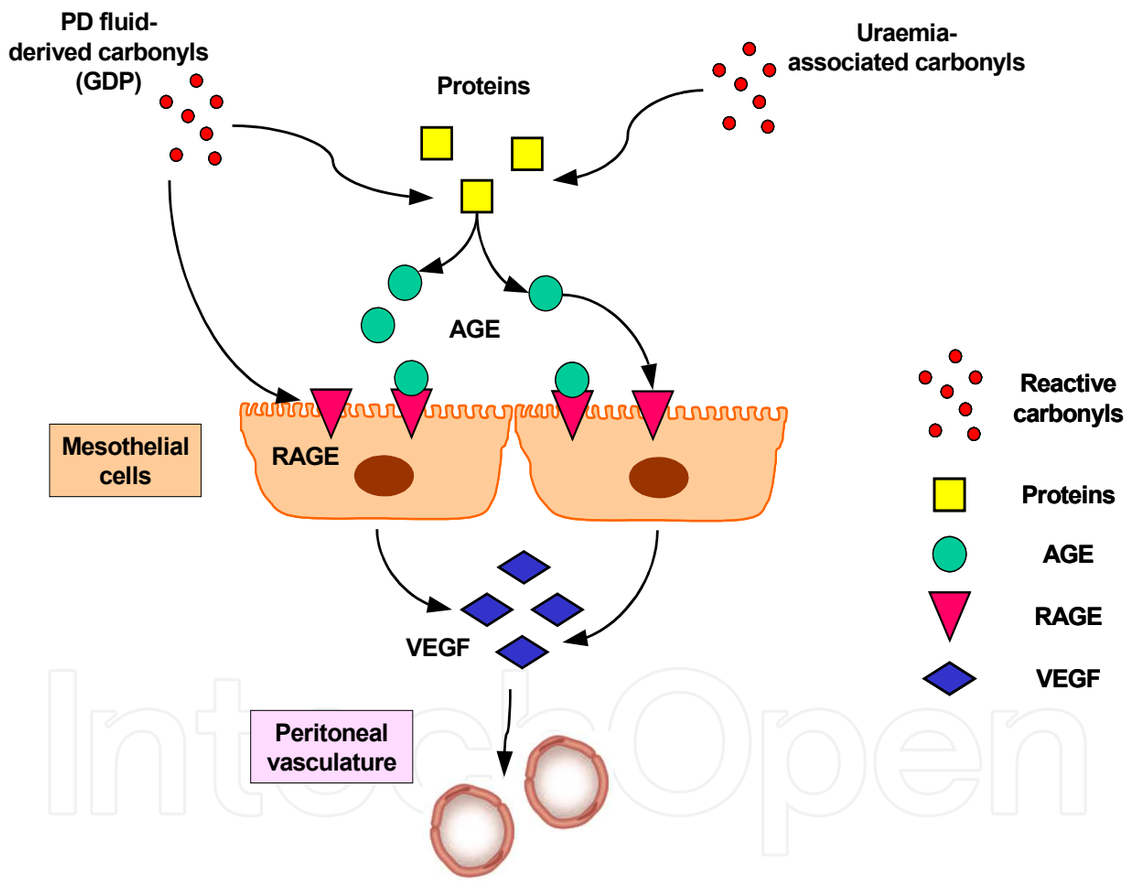

Fig. 1. Effect of reactive carbonyls and advanced glycation end-products on VEGF release by mesothelial cells.

4. Mesothelial cell phenotype and VEGF expression

It is now clear that mesothelial cells may undergo some phenotypic changes both in vitro and in vivo. These changes are related to distinct biological programmes activated by cells exposed to environmental challenges. The exact context at which certain stimuli trigger a given cellular response is not fully understood. Nevertheless, increasing evidence suggest

that such reactions may occur also in the milieu of PD. Interestingly, transforming growth factor-β (TGF-β) has emerged as a mediator being critically involved at several steps of these pathways.

4.1 Epithelial-to-mesenchymal transition

During epithelial-to-mesenchymal transition (EMT) epithelial cells adapt a fibroblast-like phenotype. It includes the loss of distinctive apical-basal cell polarity, disassembly of tight intercellular junctions, and the acquirement of ability to migrate and shape extracellular matrix. Mounting evidence indicate that during PD mesothelial cells differentiate into submesothelial fibroblasts and impact on the underlying stroma and vasculature (Aroeira et al., 2007). Mesothelial cells isolated from dialysate effluent of PD patients were found to exhibit phenotypes ranging from the typical epithelial cobblestone-like appearance to the fibroblast spindle-like morphology (Yanez-Mo et al., 2003). The occurrence of fibroblast-like mesothelial cells increased with time on PD (Yanez-Mo et al., 2003) and was greater in patients who exhibited increased peritoneal permeability (Aroeira et al., 2005) or received PD solutions with high GDP concentrations (Aroeira et al., 2009; Bajo et al., 2011). The role of mesothelial cell phenotypic conversion in inducing functional alterations in peritoneal transport could be linked to the augmented VEGF and TGF-β1 release. Mesothelial cells with fibroblast-like morphology were found to release significantly more TGF-β1 and VEGF when propagated ex vivo compared to cells with classic epithelioid appearance (Aroeira et al., 2005; Bajo et al., 2011). A precise study with the use of immunofluorescence-aided laser capture microdissection confirmed that phenotypic changes in rat mesothelial cells occurred after adenoviral over-expression of TGF-β1 in the peritoneum and were associated with increased VEGF expression (Zhang et al., 2008). The process was largely mediated through Smad3, a crucial element of the TGF-β signalling pathway (Patel et al., 2010a). These data indicate that the gradual accumulation of transdifferentiated mesothelial cells in the peritoneum of PD patients may favour the development of excessive peritoneal vascularization and/or permeability.

Studies on the molecular mechanisms coordinating EMT identified TGF-β1 and bone morphogenetic protein-7 (BMP-7) as the key mediators (Zavadil & Bottinger, 2005; Zeisberg et al., 2003). As in other cell types, TGF-β1 was shown to induce EMT in mesothelial cells both in vitro (Yang et al., 2003) and in vivo (Margetts et al., 2005; Patel et al., 2010a; Zhang et al., 2008). In contrast, BMP-7 was found to act as an inhibitor of EMT and blocked the mesothelial cell conversion (Loureiro et al., 2010; Vargha et al., 2006; Yu et al., 2009). Interestingly, it has recently been demonstrated that PD fluids with high GDP content induced EMT in mesothelial cells either during short-term direct in vitro exposure or following chronic PD regimen (Bajo et al., 2011). This finding was in line with earlier observations of EMT in the peritoneal membrane of rats treated with chronic intraperitoneal administration of methylglyoxal (Hirahara et al., 2009). The process was associated with increased peritoneal expression of TGF-β and RAGE. Interestingly, in uraemic rats the inhibition of signalling from RAGE decreased the extent of mesothelial EMT and TGF-β expression (De Vriese et al., 2006). Moreover, PD fluid-induced EMT of mesothelial cells in rats could be substantially reduced by peritoneal rest (Yu et al., 2009), which has long been advocated as a means of restoring ultrafiltration in patients with the hyperpermeable peritoneum (de Alvaro et al., 1993; Rodrigues et al., 2002). It has also been demonstrated that PD fluid-induced EMT was associated with increased signalling from Notch receptors in

mesothelial cells and the process was mediated through TGF-β1 (Zhu et al., 2010). Notch receptors are involved in the determination of cell fate, differentiation, and maintenance. The inhibition of Notch signalling resulted in the attenuation of both TGF-β1-induced EMT in vitro and PD fluid-induced EMT and peritoneal fibrosis in vivo (Zhu et al., 2010). Importantly, in both processes, the blockade of Notch led to a decrease in mesothelial cell VEGF expression. In a recent intriguing study (Patel et al., 2010b), platelet derived growth factor B (PDGF-B) was found to induce some, but not all, features of EMT in mesothelial cells. They included, however, increased VEGF expression.

4.2 Cell senescence

Gradual senescence of cells, which can easily be seen in vitro, has been believed to reflect the process of organismal aging. Extensive studies over the past decade have revealed, however, that cellular senescence is a more general phenomenon. It appears to be a cellular stress response set off by factors that may put the integrity of the genome in danger (Campisi, 2010). They include DNA breaks, dysfunctional telomeres and mitochondria, oxidative stress, disrupted chromatin, or excessive mitogenic stimulation. The hallmark of cellular senescence is an essentially irreversible growth arrest. As this prevents the transmission of potentially oncogenic mutations to daughter cells, the senescence response is thought to have evolved as a powerful cancer suppression mechanism. Other features of senescence include an enlarged morphology, the expression of senescence-associated β-galactosidase (SA-β-gal), and the up-regulation of p16, a cyclin-dependent cell cycle inhibitor.

Human peritoneal mesothelial cells in vitro enter the senescent state relatively quickly (Ksiazek et al., 2006). The process does not result from critical telomere shorthening (Ksiazek et al., 2007c), but is associated with extensive accumulation of DNA double-strand breaks in non-telomeric DNA regions. The damages are most likely caused by oxidative stress (Ksiazek et al., 2008b), which is viewed as one of the main triggers of premature senescence. As increased generation of reactive oxygen species occurs in hyperglycaemia (Bashan et al., 2009), it was logical to examine how glucose impacted on senescence of mesothelial cells. It turned out that chronic exposure to high glucose accelerated the development of senescent features in mesothelial cells, and the effect could be largely prevented by antioxidants (Ksiazek et al., 2007a). Interestingly, a further downstream mediator of the process appeared to be TGF-β1, since some features of the high glucose-induced senescent phenotype could be abolished by anti-TGF-β antibodies or reproduced by exogenous TGF-β1 (Ksiazek et al., 2007b).

The presence of senescent mesothelial cells in vivo is only scarcely documented. Cells expressing SA-β-Gal were found in freshly explanted human omenta (Ksiazek et al., 2008b), in mesothelial cell imprints from mice exposed to PD fluids (Gotloib et al., 2003) or in mesothelial cell derived from PD effluents (Gotloib et al., 2007). The detection of senescent cells following in vivo exposure to PD fluids or after in vitro exposure to high glucose rises an interesting question of whether dialysate glucose and/or glucose derivatives promote the senescence of mesothelial cells. Some date indicate that direct exposure to GDP-containing PD fluid may, indeed, result in increased expression of SA-β-Gal in mesothelial cells (Witowski et al., 2008).

The potential significance of such a change in the mesothelial cell phenotype is that senescent cells display an altered pattern of secretion of various cytokines, growth factors,

proteases, and matrix components. The senescence-associated secretory phenotype may contribute to tissue dysfunction and pave the way for other pathologies (Coppe et al., 2010). VEGF has been identified as one of the mediators released at increased levels by senescent cells (Coppe et al., 2006). As a matter of fact, senescent mesothelial were also found to release significantly more VEGF than their pre-senescent counterparts (Witowski et al., 2008). Moreover, media obtained from cultures of senescent mesothelial cells promoted endothelial cell growth to a greater degree compared with young cells (Ksiazek et al., 2008a). The increase in VEGF secretion by senescent mesothelial cells could be partly related to the senescence-associated oxidative stress, since the antioxidant precursors of glutathione were found to decrease VEGF release (Witowski et al., 2008). It could also be mediated by the augmented activity of TGF-β1 observed in senescence (Ksiazek et al., 2007b). In this respect TGF-β1 has been shown to induce VEGF in many cell types, including mesothelial cells (Szeto et al., 2005).

An interesting aspect of the process delineated above is the involvement of TGF-β1 in both EMT and cellular senescence. Intriguingly enough, TGF-β1 may also act as a mediator of apoptosis (Siegel & Massague, 2003). Indeed, TGF-β1 was found to increase the rate of apoptosis in mesothelial cells, probably by down-regulating the expression of an anti-apoptotic gene *bcl-2l* (Szeto et al., 2006). Therefore, it remains to be elucidated how cells read TGF-β1 signals so that the response proceeds along a given pathway. Furthermore, it is not clear whether there is some relationship between the resulting processes. It has been suggested that the senescence-associated secretory phenotype may promote EMT in neighbouring cells (Coppe et al., 2008).

5. VEGF polymorphism

The *Vegf* gene is a highly polymorphic gene with several variations identified in a 5'-promotor region of the gene (Brogan et al., 1999). Such polymorphisms are thought to bear functional significance and may, for example, affect VEGF production by mononuclear leukocytes (Watson et al., 2000) or malignant cells (Schneider et al., 2009). Several known *Vegf* polymorphisms were analysed in the context of PD. They were found to have no association with baseline permeability of the peritoneal membrane at the start of PD (Gillerot et al., 2005; Maruyama et al., 2007; Szeto et al., 2004). Interestingly, however, patients with the A allele at –2578 position of the *Vegf* gene had higher mRNA VEGF expression in the sediment of effluent cells compared to the individuals with the C allele (Szeto et al., 2004). Moreover, this genotype was associated with a gradual increase in peritoneal transport over time and with greater patient mortality. The data suggest that certain genotypes may predispose to increased local VEGF release in response to PD environment and thus impact on peritoneal membrane function. Since mesothelial cell EMT or senescence are associated with increased secretion of VEGF, it would be interesting to know whether certain genotypes have an effect on the incidence of such changes in PD patients.

6. Conclusions

The mesothelium is the main source of peritoneal VEGF. By secreting VEGF, mesothelial cells impact on peritoneal vasculature. In PD patients the exposure of mesothelial cells to uraemic environment, bioincompatible dialysis fluids, and the bouts of infection may

change the secretory phenotype of mesothelial cells so that they release more VEGF. In some patients (possibly with a certain genetic background), VEGF secretion may become excessive, and mediate pathological angiogenesis. On the other hand, however, VEGF-induced neoangiogenesis cannot be viewed as the sole culprit of the peritoneal membrane dysfunction. Computer simulations suggest that an increase in peritoneal exchange surface area alone will not account for a massive decrease in drained volumes (Rippe et al., 1991). One has to bear in mind, however, there exists a tight link between angiogenesis and fibrosis (Wynn, 2007). In fact, detailed studies of peritoneal biopsies showed that the degree of peritoneal fibrosis correlated with greater vascular density and, conversely, fibrosis occurred infrequently in the absence of vasculopathy (Williams et al., 2002). Thus, the contribution of mesothelial cell-derived VEGF to the peritoneal membrane dysfunction is probably multifactorial, and is related both to a direct increase in peritoneal permeability and the involvement in peritoneal fibrosis (Fig. 2).

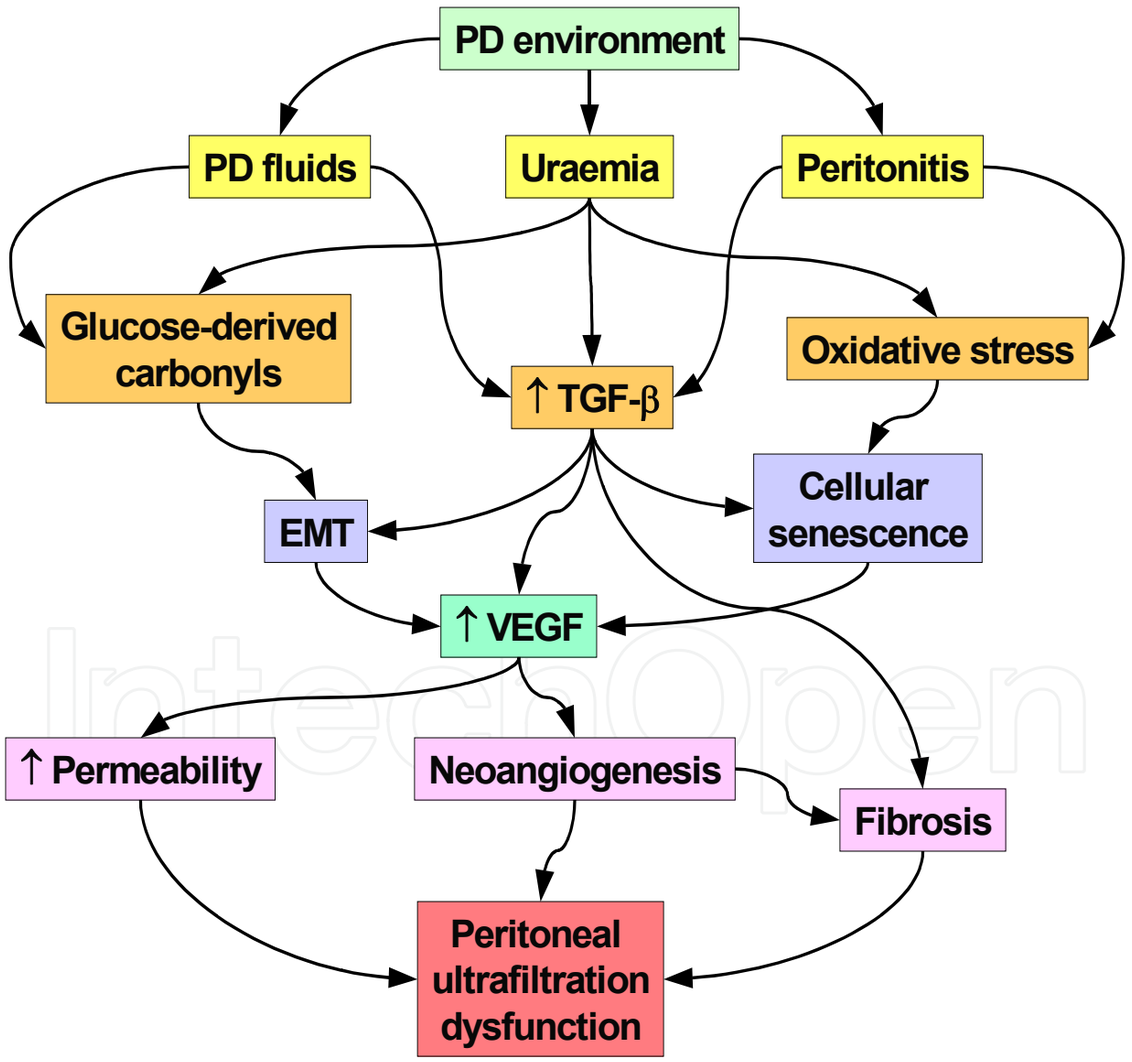

Fig. 2. Possible impact of PD environment on mesothelial cell VEGF expression and peritoneal membrane dysfunction.

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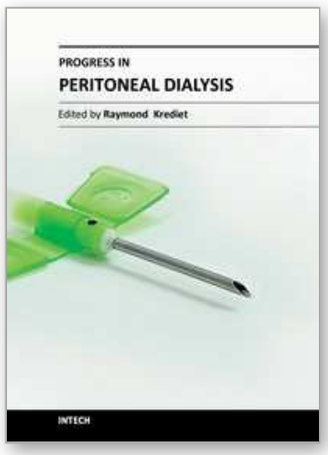

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Progress in Peritoneal Dialysis is based on judgement of a number of abstracts, submitted by interested people involved in various aspects of peritoneal dialysis. The book has a wide scope, ranging from in-vitro experiments, mathematical modelling, and clinical studies. The interested reader will find state of the art essays on various aspects of peritoneal dialysis relevant to expand their knowledge on this underused modality of renal replacement therapy.

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