Peritoneal Dialysis International, Vol. 29, pp. 605–617
Printed in Canada.

0896-8608/09 $3.00 + .00

REVIEW

FACTORS CONTRIBUTING TO PERITONEAL TISSUE REMODELING IN PERITONEAL DIALYSIS

Margot N. Schilte,[1] Johanna W.A.M Celie,[1] Piet M. ter Wee,[2]
Robert H.J. Beelen,[1] and Jacob van den Born[1a]

Departments of Molecular Cell Biology and Immunology[1] and Nephrology,[2]
VU University Medical Center, Amsterdam, The Netherlands

Peritoneal dialysis (PD) is associated with functional and structural changes of the peritoneal membrane. In this review we describe factors contributing to peritoneal tissue remodeling, including uremia, peritonitis, volume loading, the presence of a catheter, and the PD fluid itself. These factors initiate recruitment and activation of peritoneal cells such as macrophages and mast cells, as well as activation of peritoneal cells, including mesothelial cells, fibroblasts, and endothelial cells. We provide an overview of cytokines, growth factors, and other mediators involved in PD-associated changes. Activation of downstream pathways of cellular modulators can induce peritoneal tissue remodeling, leading to ultrafiltration loss. Identification of molecular pathways, cells, and cytokines involved in the development of angiogenesis, fibrosis, and membrane failure may lead to innovative therapeutic strategies that can protect the peritoneal membrane from the consequences of long-term PD.

***Perit Dial Int* 2009; 29:605–617** **www.PDIConnect.com**

KEY WORDS: Cytokines; peritoneal cells; peritoneal rest; therapeutic interventions; tissue remodeling.

Peritoneal dialysis (PD) is a therapy used to replace kidney function in end-stage renal disease patients. The therapy is based on the ability of the peritoneal membrane to function as a dialyzing membrane, allowing exchange of solutes and waste products between the PD fluids (PDF) and the circulation. Peritoneal dialysis fluid is instilled in the peritoneal cavity via a permanent catheter and contains an osmotic agent, mostly glucose, which facilitates fluid movement from the bloodstream to the peritoneal cavity, leading to removal of metabolic waste products and water. Continuous removal of waste products achieved using PD results in improved well-being of patients (in contrast to hemodialysis, where waste products accumulate between dialysis treatments). Furthermore, patients on PD have increased mobility compared to patients on hemodialysis since PD can be done at home. In addition, PD is less expensive. Drawbacks of PD include the risks of peritonitis and peritoneal membrane damage upon exposure to PDF. The latter induces inflammation and regeneration processes, as well as tissue remodeling.

In this review we describe causes, mediators (peritoneal cells, cytokines), and molecular pathways involved in PD-related tissue remodeling. In addition, we discuss possibilities for intervention strategies aimed at prolongation of PD treatment and regression of peritoneal damage.

PERITONEAL DIALYSIS-RELATED TISSUE REMODELING

The efficacy of PD depends on the structural and functional integrity of the peritoneum, that is, the inner

[a] Now at: Department of Nephrology, University Medical Center Groningen, Groningen, The Netherlands.

Correspondence to: M.N. Schilte, Department of Molecular Cell Biology and Immunology, H269, VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.
m.schilte@vumc.nl
Received 24 October 2008; accepted 3 February 2009.

surface of the abdominal wall (parietal peritoneum), omentum, and mesentery (visceral peritoneum). The peritoneum consists of a mesothelial cell monolayer and underlying connective tissue interstitium comprising extracellular matrix (ECM), blood vessels, lymphatics, fibroblasts, and innate immune cells.

Peritoneal dialysis exposure models have shown that several weeks of PD results in loss of mesothelial cells and denuded areas in the mesothelial layer [Figure 1(a,b)] (5). Liver imprints of rats show increased mesothelial cell density, indicating mesothelial regeneration [Figure 1(c,d)] (4,6). Vimentin-positive spindle-shaped cells are found among the mesothelial cells, indicating the process of epithelial-to-mesenchymal transition (EMT) (2). Changes also take place in the submesothelial interstitium. Thickness of ECM is significantly increased upon PD [Figure 1(e,f)] (3,7,8). In the parietal peritoneum, granulation tissue (immune cell aggregates) is observed within the matrix layer (4). Significantly higher numbers of leukocytes are found in the effluents of PD-treated animals compared to non-treated animals. Although the percentages of macrophages and lymphocytes do not change, an exchange of mast cells and eosinophils for neutrophils is seen after PD treatment (3,8). Increased numbers of activated macrophages are seen in peritoneal tissues upon PD (2), including accumulations around vessel networks in the omentum, known as milky spots [Figure 1(g,h)] (3,9). Normally, milky spots occupy a small percentage of the total surface area of the omentum, whereas, after PDF exposure, this percentage increases dramatically (6,10). New blood vessels [Figure 1(i,j)] (3) and lymphatics are formed throughout the peritoneal tissues. Angiogenesis leads to a large effective surface area exchange, whereas lymphangiogenesis results in increased lymphatic absorption rates (11,12). (Lymph)angiogenesis enhances reabsorption of glucose, causing a decrease in the glucose-driven osmotic pressure of the PDF and subtle changes in the vessel wall, leading to elevation of small solute transport across the peritoneal membrane, thus contributing to ultrafiltration loss (11,12). The thickened submesothelial fibrotic layer hampers osmotic pressure further and reduces the efficacy of the exchanges (7).

In summary, loss of mesothelium, submesothelial fibrosis, and (lymph)angiogenesis are typical morphologic features seen in long-term PD contributing to technique failure (7,13).

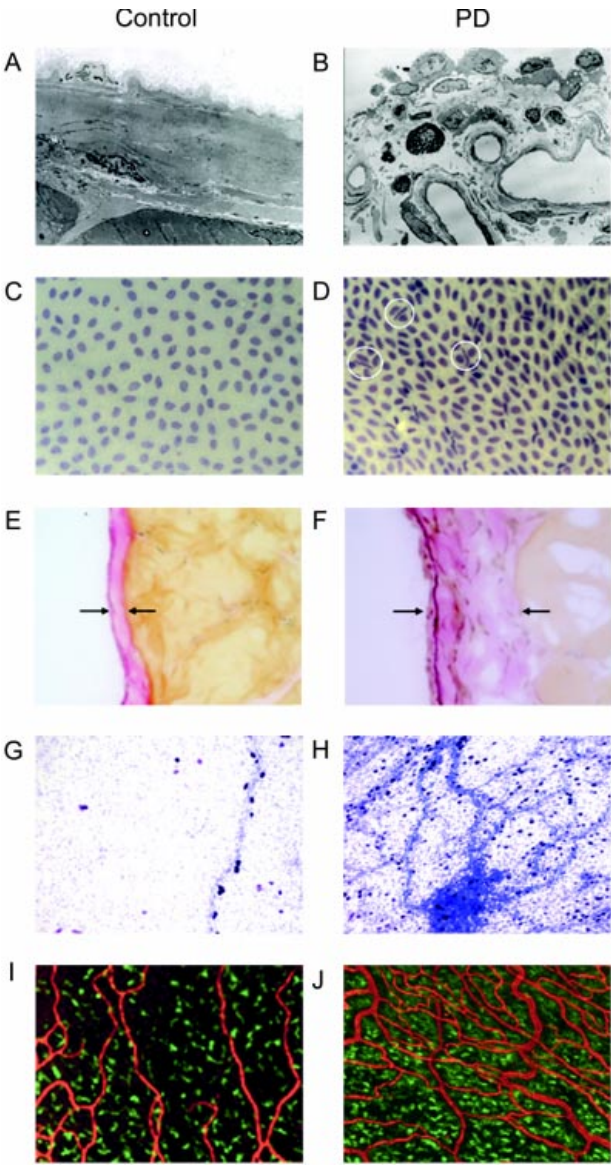

Figure 1 — Histological changes after long-term peritoneal dialysis (PD) treatment. Electron microscopy shows loss of mesothelial cells, leukocyte adhesion, and PD-induced new vessel formation (B) compared to untreated rat (A) [adapted from Ref. (1)]. May–Grünwald–Giemsa staining of liver imprint shows increased PD-induced mesothelial cell density and spindle-shaped cells (indicated by circles) (D) compared to control (C) [adapted from Ref. (2)]. Van Gieson staining of parietal peritoneum shows thickening of extracellular matrix upon PD (F) compared to control (E) [adapted from Ref. (3)]. Toluidine blue staining of omentum shows induction of milky spots and angiogenesis in PD-treated rats (H) and control rat (G) [adapted from Ref. (4)]. Staining of mesentery of macrophage influx (ED2, green) and blood vessel formation (CD31, red) of PD-treated rats (J) and control (I).

CAUSES OF PD-INDUCED PERITONEAL MEMBRANE CHANGES

Several factors can contribute to PD-related tissue remodeling, including uremia, peritonitis, the presence of the catheter, and instillation of the PDF itself. Different components of PDF, including buffer, low pH, glucose concentration, and glucose degradation products

(GDPs) generated during heat sterilization, influence peritoneal remodeling (14) (Table 1). The presence of the catheter partly induces PD-related morphological changes (8,15). Moreover, pressure itself is an inflammatory trigger. Zareie *et al.* showed that instillation of lactate buffer without glucose or GDPs results in increased cell influx, mesothelial regeneration, angiogenesis, and increased number of milky spots, although it does not significantly enhance fibrosis (3,8). Addition of glucose to the buffer enhances angiogenesis and mesothelial regeneration and induces fibrosis and cell influx (3,8,13). The presence of GDPs further enhances all mentioned peritoneal changes except cell influx and mesothelial regeneration (3,8,16–18). In addition to GDPs, advanced glycation end products (AGEs) formed by heating of glucose contribute to the toxicity of PDF (19).

It has become increasingly clear that more biocompatible PDF (bicarbonate/lactate buffer, low GDPs) induce less damage and less impaired ultrafiltration (6,8, 17,20). In addition, supplementing PDF with aminoguanidine, which scavenges GDPs and prevents AGE formation, results in less mesothelial denudation (21), fibrosis, and angiogenesis in omentum and parietal peritoneum (22).

Apart from the composition of PDF, other factors have been suggested to contribute to PD-related tissue remodeling. In uremic patients, AGEs, vascular endothelial growth factor (VEGF), and inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor-alpha (TNF-α) are significantly increased and are known to modulate the structure and function of the peritoneal membrane (23). Studies have shown that uremia leads to thickening of the ECM and mild vasculopathy, indicating that uremia induces inflammation and tissue remodeling in the peritoneum (7,24). Animal studies confirmed the increase in vascular network as a result of uremia in non-PD treated animals. However, only minor differences between uremic and nonuremic PD-treated rats were found, suggesting that there is no prominent effect of uremia in PD therapy (4,25).

In contrast, peritonitis episodes significantly contribute to peritoneal changes by inducing mesothelial damage, massive inflammatory response, and increased vascularization of peritoneal tissue, leading to impaired membrane function (11,26,27).

CELLS THAT CONTRIBUTE TO PERITONEAL TISSUE REMODELING

Peritoneal tissue remodeling resembles a chronic low-grade inflammation. Major cell types involved include macrophages and mast cells, together with mesothelial cells, fibroblasts, and endothelial cells. Figure 2 shows the cellular system known to contribute to PD-induced changes and includes the cytokines and chemokines produced.

Peritoneal Macrophages: Mononuclear phagocytes are the predominant cell type found in dialysates and form the first line of defense against invading microorganisms (28). During PD, macrophage numbers increase due to recruitment of their precursors (monocytes) from the blood (28,29). Activated macrophages release prostaglandin-E2 (PGE-2), IL-1, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and TNF-α and thereby participate in intraperitoneal inflammation (11,30,31). In addition, macrophages can produce growth factors that enhance cell proliferation and ECM production, leading to fibrosis (31,32). We are not aware of any PD intervention studies aimed at blocking macrophage recruitment (chemokine receptor antagonists) or macrophage function (corticosteroid treatment).

TABLE 1
Peritoneal Changes Occurring After Long-Term Exposure to Peritoneal Dialysis Fluid in Rats

	Extrinsic factors			Fluid characteristics		
Peritoneal changes	Catheter	Uremia	Peritonitis	(Lactate) Buffer	Buffer + glucose	Buffer + glucose + GDPs
Ultrafiltration failure	–	+	+	+	++	+++
Effluent cell number	–	–	+	–	++	++
Angiogenesis	+	+	+	+	++	+++
Fibrosis	–	–	+	–	++	+++
Omental mast cells	–	+	+	++	++	+++
Omental milky spots	–	–	+	++	++	+++
Mesothelial regeneration	–	–	+	++	+++	+++

GDPs = glucose degradation products.
Peritoneal changes are indicated as – (no changes) and + (weak) to +++ (very strong) compared to control rats.

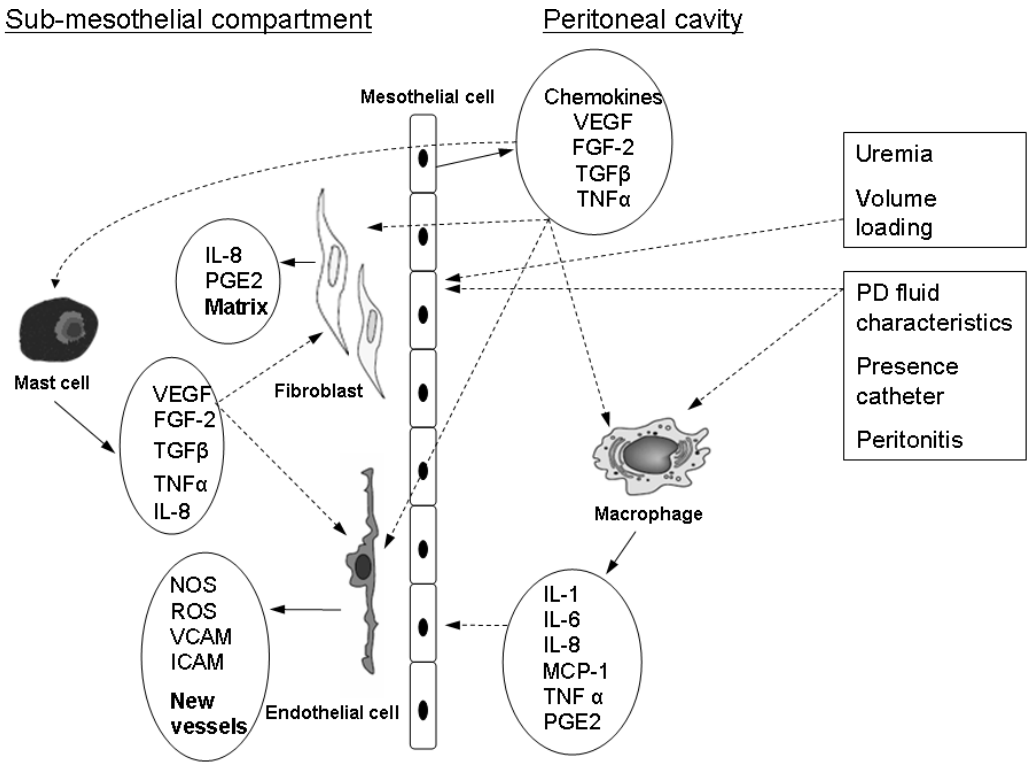

Figure 2 — Cellular system of inflammatory response, including production of cytokines and chemokines, upon exposure to peritoneal dialysis (PD) fluid. Extrinsic factors and PD fluid characteristics activate macrophages and mesothelial cells, which start producing inflammatory cytokines and growth factors. These activate fibroblasts, endothelial cells, and mast cells, which secrete angiogenic and fibrotic cytokines and growth factors, which play a role in tissue remodeling after long-term PD. Dotted lines indicate activation of peritoneal cells; straight lines indicate production of cytokines and growth factors. IL = interleukin; PGE2 = prostaglandin E2; VEGF = vascular endothelial growth factor; FGF-2 = basic fibroblast growth factor; TGF-β = transforming growth factor beta; TNF-α = tumor necrosis factor alpha; NOS = nitric oxide synthase; ROS = reactive oxygen species; VCAM = vascular cell adhesion molecule; ICAM = intercellular adhesion molecule; MCP-1 = monocyte chemoattractant protein 1.

Mesothelial Cells: By secreting prostaglandins, chemokines, and cytokines, mesothelial cells contribute to the recruitment of leukocytes (11,33). Chronic exposure to PDF and peritonitis episodes damage mesothelial cells, which leads to their partial disappearance from the peritoneal membrane (34). The remaining mesothelial cells become activated (35,36) and produce angiogenic and fibrotic factors such as VEGF, basic fibroblast growth factor (FGF-2), transforming growth factor-beta (TGF-β), and hyaluronic acid (HA) (37). Exposure of human mesothelial cells to GDPs specifically resulted in a dose-dependent inhibition of cell growth, cell viability, and IL-6 and TNF-α release, and increased synthesis of TGF-β and VEGF (37). Regeneration of denuded areas occurs by proliferation and migration of the remaining mesothelial cells (36,38). Although mesothelial cell transplantation may seem beneficial, animal studies have shown that successful mesothelial cell transplantation is accompanied by enhancement and prolongation of the inflammatory status of the peritoneum (35,39).

Recent data suggest that mesothelial cells undergo EMT during PD, which may play an important role in peritoneal fibrosis leading to failure of peritoneal membrane function (5,40,41). Mesothelial cells undergoing EMT show increased expression of angiogenic molecules, including VEGF, suggesting that EMT, angiogenesis, and fibrosis may be interconnected processes mediated by injury to and response of the mesothelium (42). Since TGF-β is the major inducer of EMT, strategies inhibiting TGF-β signaling are a plausible way to prevent EMT during PD. Treatment of cultured human mesothelial cells with either bone morphogenetic protein-7, an endogenous antifibrotic protein and member of the TGF-β superfamily, or the TGF-β inhibitor rapamycin respectively reverted or inhibited TGF-β-induced EMT (43,44).

Mast Cells: In the normal peritoneum, mast cells are present and their numbers increase upon inflammation. High mast cell numbers have been found in peritoneal tissues of PD patients and during peritonitis (45,46). The biological functions of mast cells include a role in immunomodulation, tissue repair, fibrosis, and angio-

genesis (46,47). Activated mast cells can induce angiogenesis by producing potent proangiogenic factors such as VEGF, FGF-2, and TGF-β and can also produce TNF-α and IL-8, as well as tryptase and chymase (48,49).

Peritoneal cell influx and omental changes (milky spots and angiogenesis) are significantly reduced in mast cell-deficient rats. Mesothelial damage, angiogenesis, and fibrosis in other peritoneal tissues as well as functional parameters proved to be mast cell independent. Similar results were observed in wild-type rats treated orally with the mast cell stabilizer disodium cromoglycate (50). These data show that mast cells contribute to PDF-induced omental tissue remodeling and peritoneal cell influx and may be targeted therapeutically.

(Myo)Fibroblasts: Many inflammatory mediators produced by damaged/activated mesothelial and inflammatory cells can affect peritoneal fibrosis by stimulating resident fibroblast proliferation, inducing tissue repair and ECM deposition. In addition, dedifferentiated mesothelial cells can acquire fibroblast characteristics after EMT (51–53). Fibroblasts can in turn produce cytokines (including IL-8) upon their activation with IL-1 and TNF-α, suggesting a role in the regulation of inflammatory events (54–56). (Myo)fibroblasts are stimulated to secrete PGE-2, HA, and collagen, which alter the structure of the peritoneal membrane (57,58). Deleting fibroblasts prevented fibrosis in a mouse model for peritoneal fibrosis (59). Due to these characteristics, (myo)fibroblasts likely play a role in fibrosis during PD.

Endothelial Cells: Prominent changes in endothelial activation can be observed upon PD. For example, exposure of endothelial cells to high glucose concentrations induces the expression of reactive oxygen species (ROS) (60). Exposure of endothelial cells to proinflammatory cytokines, including IL-1β and TNF-α, induces the production of IL-8 and MCP-1, the recruitment of leukocytes to the cell surface, and cell death (61).

Endothelial cells of the vessels observed in the milky spots of PD-treated animals are greatly enlarged, suggesting their activation (6). Indeed, rolling, adhesion, and extravasation of leukocytes is dramatically increased in newly formed blood vessels in mesenteries of animals treated long term with PD (62,63). Apart from its role in inflammation, the endothelium lining peritoneal capillaries is the most important barrier for solute transport during PD. Water transport during PD requires ultrasmall pores in capillary endothelium and is impaired in the case of peritoneal inflammation (64). The water channel aquaporin-1 has been proposed to be the ultrasmall pore in animal models (64). Neither uremia nor PD alters aquaporin-1 expression within peritoneal capillary endothelium, suggesting that a quantitative loss of ultrasmall pores itself may not be responsible for ultrafiltration failure (64).

CYTOKINES, GROWTH FACTORS, AND HORMONES THAT MEDIATE PERITONEAL TISSUE REMODELING

Proinflammatory Cytokines/Chemokines: As mentioned, activated macrophages play a key role in PD-mediated tissue remodeling as one of the main producers of proinflammatory cytokines, including IL-1β, IL-6, IL-8, TNF-α, and MCP-1 (65).

Overexpression of IL-1β and TNF-α in the rat peritoneum leads to an acute inflammatory response and expression of VEGF and TGF-β, resulting in angiogenesis and fibrosis (66). Interleukin-8 promotes accumulation and activation of neutrophils (65), whereas MCP-1 recruits mononuclear cells (30). Interleukin-8 and MCP-1 are found in steady state PD effluents and their levels increase upon peritonitis. However, even after recovery from the infection, continuous production of these chemokines has been observed in PD effluents (27). Interestingly, HA fragments induce the release of IL-8 and MCP-1 by mesothelial cells (67). Mesothelial cells are considered a source of HA upon inflammation and wound healing (68). High molecular weight HA is thought to support healing of the injured mesothelium by creating a fibrin network and limiting the damaging effects of free radicals (67). Increased levels of HA are found in PD effluents although it is not clear whether this represents HA fragments or high molecular weight, or both.

Growth Factors: Several growth factors contribute to peritoneal tissue remodeling, of which VEGF and TGF-β are the most important. VEGF is an endothelial-specific growth factor produced in the peritoneum by mesothelial cells. VEGF affects endothelial permeability and contributes to the induction of angiogenesis (69). Inhibition of VEGF function by anti-VEGF antibodies prevents peritoneal angiogenesis, leading to normalized small solute transport rates upon high glucose exposure (70). It is noteworthy that glucose may exert little effect on VEGF production, whereas GDPs or AGEs greatly enhance VEGF production. TGF-β is strongly upregulated by high glucose concentrations, inducing peritoneal fibrosis (69). Overexpression of TGF-β in the peritoneum causes peritoneal fibrosis, angiogenesis, EMT, increased peritoneal membrane transport, and reduced ultrafiltration (40,71). On the other hand, inactivation of TGF-β does not affect ultrafiltration rate or angiogenesis but does reduce fibrosis (72). Some experimental work done on platelet-derived growth factor and FGF-2 (73–76) suggests that these growth factors might be involved in PD-related tissue remodeling.

Prostaglandins: Prostaglandins are mediators of inflammation and are released upon exposure to PD (77). PGE-2 is produced by many cells, including fibroblasts, mesothelial cells, and macrophages, by the action of cyclo-oxygenase-2 (COX-2), which can be induced by IL-1 and TNF-α (58). Topley *et al.* showed increased prostaglandin release by mesothelial cells after incubation with supernatant from IL-1- and TNF-α-stimulated peritoneal macrophages (78). Analysis of the effluents of PD patients demonstrated increased levels of PGE-2 (79). Also, during peritonitis, which is associated with vasodilatation and decreased peritoneal membrane function, the concentration of PGE-2 in the effluent is markedly elevated (79).

Renin–Angiotensin–Aldosterone System (RAAS): The RAAS plays an important role in the progression of renal disease and peritoneal injury. Renin increases TGF-β in mesangial cells and the synthesis of fibrotic extracellular components, suggesting that renin contributes to fibrotic diseases (80). Angiotensin II (AII) is the main peptide of RAAS and is a growth factor that regulates cell proliferation, apoptosis, and fibrosis (81). Angiotensin II stimulates macrophages and fibroblast-like cells to secrete TGF-β and regulates the synthesis of proinflammatory cytokines (IL-6, TNF-α), chemokines (MCP-1), and angiogenic growth factors such as VEGF (82,83). Angiotensin II also stimulates the production of aldosterone, which plays a role in regulating extracellular volume (84) and in the development of fibrosis (85,86).

The RAAS plays a key role in the regulation of peritoneal function in rats on PD (87). Early intervention with angiotensin-receptor blockers (ARBs) protects against deterioration of peritoneal function, fibrosis, and peritoneal sclerosis during PD. Aldosterone-receptor blockers as well as ARBs were able to reduce peritoneal fibrosis in a rat model of bacterial peritonitis (88). In models of renal injury, blocking AII via angiotensin-converting enzyme inhibitors or ARBs decreased fibrosis but also proteinuria, inflammatory cell infiltration, and gene expression of matrix proteins and growth factors (81). This suggests that angiotensin-converting enzyme inhibitors and ARBs may have beneficial effects in preventing long-term peritoneal membrane changes induced by PD.

Reactive Oxygen Species (ROS): ROS are continuously generated in living organisms by metabolic pathways and are molecules that activate protein kinases, transcription factors, and gene expression (89). High glucose, AGEs, AII, and TGF-β all increase intracellular ROS (90). ROS can mediate TGF-β-induced cellular responses, including EMT, in various cells and activate mitogen-activated protein kinases (MAPK) (91). Generation of ROS as a consequence of high glucose can be prevented by extracellular neutralizing TGF-β antibodies (92). Noh *et al.* have shown that ROS generated by conventional PDF is responsible for progressive membrane hyperpermeability, angiogenesis, accumulation of ECM, and peritoneal fibrosis. Treatment with antioxidants or AII inhibitors resulted in preservation of the structural and functional integrity of the peritoneal membrane during long-term PD (93).

SIGNALING PATHWAYS INVOLVED IN PERITONEAL TISSUE REMODELING

Activation of peritoneal cells, including mesothelial cells and recruited leukocytes, induces a number of cellular signaling pathways.

Cyclo-Oxygenase-2: The COX pathway is known to affect tissue remodeling during PD. COX-2 is an inducible enzyme that catalyzes the rate-limiting step in prostaglandin synthesis from arachidonic acid. Its expression has been demonstrated in several tissues and cells under inflammatory and proliferative conditions (94). COX-2 is present at the site of inflammation and is expressed by macrophages and monocytes. It is induced by IL-1, TNF-α, and growth factors (95). In cancer, COX-2 downstream products (mainly PGE-2) mediate angiogenic processes through mechanisms including VEGF production and enhanced endothelial cell survival (96). *In vitro* experiments demonstrated that mesothelial and inflammatory cells express COX-2 under PD-like conditions (73,97). Fibroblasts involved in peritoneal healing after abdominal surgery have been found positive for COX-2 expression (98). In a recent chronic PD animal study, the COX-2 inhibitor celecoxib improved ultrafiltration and largely prevented angiogenesis and fibrosis in peritoneal tissues (99).

p38 MAPK: The p38 MAPK pathway is strongly activated by environmental stressors, including proinflammatory cytokines and osmolality changes. It leads to alterations in cell growth and cellular dysfunction (100–102). The p38 MAPK is critical for the production of nuclear factor-kappa B (NF-κB)-dependent inflammatory cytokines, including TNF-α, IL-8, and IL-6 (103). Increased p38 MAPK activity has been demonstrated in mesothelial cells cultured under high glucose conditions (100). The use of p38 MAPK inhibitors may be an attractive strategy in the PD setting due to their ability to reduce the synthesis and signaling of proinflammatory cytokines. Indeed, p38 MAPK inhibitors have been found to reduce the production of TNF-α, IL-6, and IL-10 (104,105).

Reactive Oxygen Species (ROS)–Protein Kinase C: Protein kinase C (PKC) is a family of serine/threonine

kinases that regulate cell functions, including proliferation, cell cycle, differentiation, cell migration, and apoptosis (106). High glucose has been shown to trigger PKC activation as well as elevation of ROS, which in turn may result in MAPK activation via PKC (107,108). This implies that ROS are not only downstream but also upstream signaling molecules to PKC (109). Both high glucose and ROS activate PKC transcription factors such as NF-κB as well as the upregulation of TGF-β and ECM genes in cultured mesothelial cells (89,109). *In vitro* studies showed that inhibition of PKC can both prevent high glucose-induced intracellular ROS generation and inhibit NF-κB activation in mesangial cells (110).

Tyrosine Kinase Receptors: Tyrosine kinases are central components of cell signaling in processes such as apoptosis, proliferation, migration, and differentiation (111). Receptors of the tyrosine kinase pathways include VEGF, platelet-derived growth factor, FGF-2, and colony stimulating factor-1, the latter being involved in the differentiation, proliferation, and activation of macrophages. Inhibition of tyrosine kinase receptors is one of the most promising new anticancer strategies (112). These inhibitors block endothelial cell migration, new blood vessel formation, and the early phase of fibrosis (113,114), which may reduce tissue remodeling in PD.

Receptor for AGE (RAGE): Most PDFs contain GDPs, which are identified as toxic compounds and lead to the formation of AGEs, contributing to the toxicity of PDF (115). RAGE is the best-characterized signal transduction receptor for AGEs. Stimulation of RAGE results in mesothelial cell activation, which may promote local inflammation and is thus implicated in the peritoneal injury seen in long-term PD patients (116). Ligand binding of AGE to RAGE results in activation of signal transduction pathways, including NF-κB and MAPKs (117). In RAGE-deficient mice, fibrosis, angiogenesis, inflammatory cell influx, and TGF-β upregulation were inhibited upon treatment with high-GDP PD solution (118). Inhibition of AGE-RAGE interaction with anti-RAGE antibodies did not prevent peritoneal angiogenesis but did prevent upregulation of TGF-β and development of submesothelial fibrosis (119). Both *in vitro* and *in vivo* blocking of AGE-RAGE interaction by soluble RAGE or anti-RAGE antibodies reduces the cellular alterations secondary to RAGE activation (116). The fact that inhibition of the AGE-RAGE interaction reduces peritoneal changes stresses the importance of AGEs in peritoneal membrane damage and their potential as therapeutic targets.

Janus Kinase 2 (JAK2), Signal Transducers, and Activators of Transcription (STAT; JAK-STAT): Exposure of mesangial cells to high glucose concentrations activates the growth-promoting enzyme JAK2 and its latent STAT factors (120). JAK-STAT signaling is activated by several hormones, cytokines, and growth factors and participates in cell proliferation, differentiation, survival, and apoptosis (121). Upon exposure to high glucose, the JAK-STAT pathway is activated by AII and responds to intracellular ROS, leading to TGF-β expression (122,123). Incubation of mesangial cells with specific JAK2 or STAT1 inhibitors prevented the high glucose-induced synthesis of TGF-β and fibronectin, implicating direct linkages between JAK2, STAT, and glucose-induced overproduction of TGF-β in mesangial cells (120).

PERITONEAL REST AND REVERSIBILITY

Activation of peritoneal cells, mediators, and pathways results in functional and structural changes in peritoneal membranes in long-term PD. Some of these changes can be reversed by peritoneal rest. Peritoneal rest by switching temporarily to hemodialysis can help restore ultrafiltration (124,125). Also, switching from chronic ambulant PD to daytime ambulatory PD with a nocturnal "empty belly" has been reported to improve ultrafiltration (126). Apart from these clinical implications, the reversibility of both morphological and functional alterations in the peritoneal membrane by peritoneal rest was shown in animal studies (127,128).

Peritoneal rest of more than 4 weeks restored ultrafiltration capacity as well as peritoneal permeability to glucose and total protein (127,128). Moreover, the thickness of the parietal peritoneum was reduced and omental and mesenterial vessel density was restored (127,128). Furthermore, peritoneal rest reversed the increased mast cell density and milky spot response and recovered PD-induced mesothelial damage (128). These data suggest that PD-induced changes in the peritoneal membrane are generally reversible after peritoneal rest, as shown in the rat model.

SUMMARY AND CONCLUSION

In long-term PD, uremia, peritonitis, and permanent exposure to PDF result in morphological and functional changes in the peritoneal membranes. The ultrafiltration loss seen in PD patients is caused in part by the bioincompatibility of PDF. Novel PDFs offer an improvement in biocompatibility and further development of biocompatible fluids will probably lead to better preservation of the peritoneal membrane. However, the addition of a specific (pathway) inhibitor will most likely be needed to prevent peritoneal damage and improve ultrafiltration. Figure 3 shows possibilities for therapeutic interventions on the different levels that contribute to

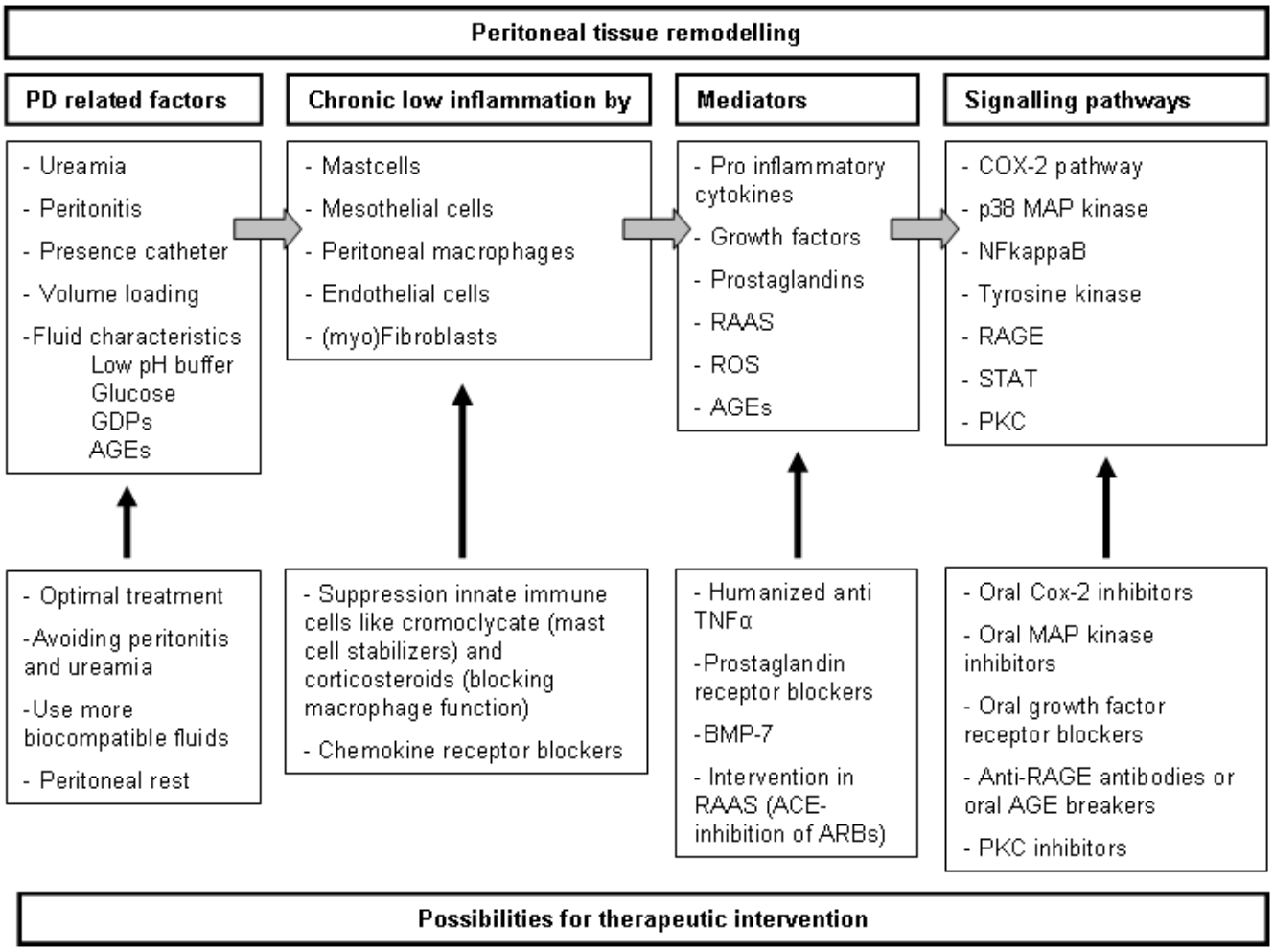

Figure 3 — Effects of long-term peritoneal dialysis (PD) on the peritoneal membrane and factors mediating these morphological and functional changes, and possibilities for therapeutic interventions. GDPs = glucose degradation products; AGEs = advanced glycation end products; RAAS = renin–angiotensin–aldosterone system; ROS = reactive oxygen species; TNF-α = tumor necrosis factor-alpha; BMP-7 = bone morphogenic protein 7; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; COX = cyclo-oxygenase; MAP = mitogen-activated protein; NF-kappaB = nuclear factor-kappa B; RAGE = receptor for AGE; STAT = signal transducers and activators of transcription; PKC = protein kinase C.

PD-related changes. Inhibitors of pathways involved in angiogenesis, such as the COX-2 or the tyrosine kinase pathway, are thought to be promising strategies in preventing ultrafiltration failure. We therefore foresee a combination therapy using most biocompatible fluids along with specific inhibitors involved in peritoneal tissue remodeling to be the most effective approach in future PD.

DISCLOSURE

The authors have no conflicts of interest.

ACKNOWLEDGMENTS

This work was supported by grant #C05-2142 of the Dutch Kidney Foundation.

REFERENCES

1. Hekking LH, van den Born J. Feasibility of mesothelial transplantation during experimental peritoneal dialysis and peritonitis. *Int J Artif Organs* 2007; 30(6):513–19.
2. Schilte MN, Loureiro J, Keuning ED, ter Wee PM, Celie JWAM, Beelen RH, *et al*. Long-term intervention with heparins in a rat model for peritoneal dialysis. *Perit Dial Int* 2009; 29(1):26–35.
3. Zareie M, Hekking LH, Welten AG, Driesprong BA, Schadee-Eestermans IL, Faict D, *et al*. Contribution of lactate buffer, glucose and glucose degradation products to peritoneal injury *in vivo*. *Nephrol Dial Transplant* 2003; 18(12): 2629–37.
4. Zareie M, De Vriese AS, Hekking LH, ter Wee PM, Schalkwijk CG, Driesprong BA, *et al*. Immunopathological changes in a uraemic rat model for peritoneal dialysis. *Nephrol Dial*

Transplant 2005; 20(7):1350–61.
5. Yanez-Mo M, Lara-Pezzi E, Selgas R, Ramirez-Huesca M, Dominguez-Jimenez C, Jimenez-Heffernan JA, *et al*. Peritoneal dialysis and epithelial-to-mesenchymal transition of mesothelial cells [Published correction appears in *N Engl J Med* 2005; 353(26):2827]. *N Engl J Med* 2003; 348(5):403–13.
6. Hekking LH, Zareie M, Driesprong BA, Faict D, Welten AG, de Greeuw I, *et al*. Better preservation of peritoneal morphologic features and defense in rats after long-term exposure to a bicarbonate/lactate-buffered solution. *J Am Soc Nephrol* 2001; 12(12):2775–86.
7. Fusshoeller A. Histomorphological and functional changes of the peritoneal membrane during long-term peritoneal dialysis. *Pediatr Nephrol* 2008; 23(1):19–25.
8. Zareie M, Keuning ED, ter Wee PM, Schalkwijk CG, Beelen RH, van den Born J. Improved biocompatibility of bicarbonate/lactate-buffered PDF is not related to pH. *Nephrol Dial Transplant* 2006; 21(1):208–16.
9. Di Paolo N, Sacchi G, Garosi G, Sansoni E, Bargagli L, Ponzo P, *et al*. Omental milky spots and peritoneal dialysis—review and personal experience. *Perit Dial Int* 2005; 25(1): 48–57.
10. Beelen RHJ, Oosterling SJ, van Egmond M, van den Born J, Zareie M. Omental milky spots in peritoneal pathophysiology (spots before your eyes). *Perit Dial Int* 2005; 25(1): 30–2.
11. Lai KN, Tang SC, Leung JC. Mediators of inflammation and fibrosis. *Perit Dial Int* 2007; 27(Suppl 2):S65–71.
12. Michels WM, Zweers MM, Smit W, Korevaar J, Struijk DG, van Westrhenen R, *et al*. Does lymphatic absorption change with the duration of peritoneal dialysis? *Perit Dial Int* 2004; 24(4):347–52.
13. Chan TM, Yung S. Studying the effects of new peritoneal dialysis solutions on the peritoneum. *Perit Dial Int* 2007; 27(Suppl 2):S87–93.
14. Jorres A, Bender TO, Finn A, Witowski J, Frohlich S, Gahl GM, *et al*. Biocompatibility and buffers: effect of bicarbonate-buffered peritoneal dialysis fluids on peritoneal cell function. *Kidney Int* 1998; 54(6):2184–93.
15. Flessner MF, Credit K, Henderson K, Vanpelt HM, Potter R, He Z, *et al*. Peritoneal changes after exposure to sterile solutions by catheter. *J Am Soc Nephrol* 2007; 18(8): 2294–302.
16. Wieczorowska-Tobis K, Polubinska A, Schaub TP, Schilling H, Wisniewska J, Witowski J, *et al*. Influence of neutral-pH dialysis solutions on the peritoneal membrane: a long-term investigation in rats. *Perit Dial Int* 2001; 21(Suppl 3): S108–13.
17. Mortier S, Faict D, Lameire NH, De Vriese AS. Benefits of switching from a conventional to a low-GDP bicarbonate/lactate-buffered dialysis solution in a rat model. *Kidney Int* 2005; 67(4):1559–65.
18. Musi B, Braide M, Carlsson O, Wieslander A, Albrektsson A, Ketteler M, *et al*. Biocompatibility of peritoneal dialysis fluids: long-term exposure of nonuremic rats. *Perit Dial Int* 2004; 24(1):37–47.
19. Honda K, Nitta K, Horita S, Yumura W, Nihei H, Nagai R, *et al*. Accumulation of advanced glycation end products in the peritoneal vasculature of continuous ambulatory peritoneal dialysis patients with low ultra-filtration. *Nephrol Dial Transplant* 1999; 14(6):1541–9.
20. Kim CD, Kwon HM, Park SH, Oh EJ, Kim MH, Choi SY, *et al*. Effects of low glucose degradation products peritoneal dialysis fluid on the peritoneal fibrosis and vascularization in a chronic rat model. *Ther Apher Dial* 2007; 11(1):56–64.
21. Lee EA, Oh JH, Lee HA, Kim SI, Park EW, Park KB, *et al*. Structural and functional alterations of the peritoneum after prolonged exposure to dialysis solutions: role of aminoguanidine. *Perit Dial Int* 2001; 21(3):245–53.
22. Zareie M, Tangelder GJ, ter Wee PM, Hekking LH, van Lambalgen AA, Keuning ED, *et al*. Beneficial effects of aminoguanidine on peritoneal microcirculation and tissue remodelling in a rat model of PD. *Nephrol Dial Transplant* 2005; 20(12):2783–92.
23. Mortier S, De Vriese AS, Lameire N. Recent concepts in the molecular biology of the peritoneal membrane—implications for more biocompatible dialysis solutions. *Blood Purif* 2003; 21(1):14–23.
24. Williams JD, Craig KJ, Topley N, Von Ruhland C, Fallon M, Newman GR, *et al*. Morphologic changes in the peritoneal membrane of patients with renal disease. *J Am Soc Nephrol* 2002; 13(2):470–9.
25. Combet S, Ferrier ML, Van Landschoot M, Stoenoiu M, Moulin P, Miyata T, *et al*. Chronic uremia induces permeability changes, increased nitric oxide synthase expression, and structural modifications in the peritoneum. *J Am Soc Nephrol* 2001; 12(10):2146–57.
26. Verger C, Luger A, Moore HL, Nolph KD. Acute changes in peritoneal morphology and transport properties with infectious peritonitis and mechanical injury. *Kidney Int* 1983; 23(6):823–31.
27. Tekstra J, Visser CE, Tuk CW, Brouwer-Steenbergen JJ, Burger CW, Krediet RT, *et al*. Identification of the major chemokines that regulate cell influxes in peritoneal dialysis patients. *J Am Soc Nephrol* 1996; 7(11):2379–84.
28. Lewis S, Holmes C. Host defense mechanisms in the peritoneal cavity of continuous ambulatory peritoneal dialysis patients. 1. *Perit Dial Int* 1991; 11(1):14–21.
29. Peterson PK, Gaziano E, Suh HJ, Devalon M, Peterson L, Keane WF. Antimicrobial activities of dialysate-elicited and resident human peritoneal macrophages. *Infect Immun* 1985; 49(1):212–18.
30. Bauermeister K, Burger M, Almanasreh N, Knopf HP, Schumann RR, Schollmeyer P, *et al*. Distinct regulation of IL-8 and MCP-1 by LPS and interferon-gamma-treated human peritoneal macrophages. *Nephrol Dial Transplant* 1998; 13(6):1412–19.
31. Topley N. The cytokine network controlling peritoneal inflammation. *Perit Dial Int* 1995; 15(7 Suppl):S35–9.
32. Lee SK, Kim BS, Yang WS, Kim SB, Park SK, Park JS. High glucose induces MCP-1 expression partly via tyrosine

kinase-AP-1 pathway in peritoneal mesothelial cells. *Kidney Int* 2001; 60(1):55–64.
33. Topley N, Mackenzie R, Jorres A, Coles GA, Davies M, Williams JD. Cytokine networks in continuous ambulatory peritoneal dialysis: interactions of resident cells during inflammation in the peritoneal cavity. *Perit Dial Int* 1993; 13(Suppl 2):S282–5.
34. Dobbie JW, Anderson JD, Hind C. Long-term effects of peritoneal dialysis on peritoneal morphology. *Perit Dial Int* 1994; 14(Suppl 3):S16–20.
35. Hekking LH, Zweers MM, Keuning ED, Driesprong BA, de Waart DR, Beelen RH, *et al*. Apparent successful mesothelial cell transplantation hampered by peritoneal activation. *Kidney Int* 2005; 68(5):2362–7.
36. Mutsaers SE, Whitaker D, Papadimitriou JM. Mesothelial regeneration is not dependent on subserosal cells. *J Pathol* 2000; 190(1):86–92.
37. Witowski J, Korybalska K, Wisniewska J, Breborowicz A, Gahl GM, Frei U, *et al*. Effect of glucose degradation products on human peritoneal mesothelial cell function. *J Am Soc Nephrol* 2000; 11(4):729–39.
38. Horiuchi T, Miyamoto K, Miyamoto S, Fujita M, Sano N, Minamiyama K, *et al*. Image analysis of remesothelialization following chemical wounding of cultured human peritoneal mesothelial cells: the role of hyaluronan synthesis. *Kidney Int* 2003; 64(6):2280–90.
39. Witkowicz J. Mesothelial cell transplantation. *Pol Arch Med Wewn* 2008; 118(5):307–13.
40. Margetts PJ, Bonniaud P, Liu L, Hoff CM, Holmes CJ, West-Mays JA, *et al*. Transient overexpression of TGF-{beta}1 induces epithelial mesenchymal transition in the rodent peritoneum. *J Am Soc Nephrol* 2005; 16(2):425–36.
41. Aroeira LS, Aguilera A, Selgas R, Ramirez-Huesca M, Perez-Lozano ML, Cirugeda A, *et al*. Mesenchymal conversion of mesothelial cells as a mechanism responsible for high solute transport rate in peritoneal dialysis: role of vascular endothelial growth factor. *Am J Kidney Dis* 2005; 46(5): 938–48.
42. Zhang J, Oh KH, Xu H, Margetts PJ. Vascular endothelial growth factor expression in peritoneal mesothelial cells undergoing transdifferentiation. *Perit Dial Int* 2008; 28(5):497–504.
43. Vargha R, Endemann M, Kratochwill K, Riesenhuber A, Wick N, Krachler AM, *et al*. *Ex vivo* reversal of *in vivo* transdifferentiation in mesothelial cells grown from peritoneal dialysate effluents. *Nephrol Dial Transplant* 2006; 21(10): 2943–7.
44. Aguilera A, Aroeira LS, Ramirez-Huesca M, Perez-Lozano ML, Cirugeda A, Bajo MA, *et al*. Effects of rapamycin on the epithelial-to-mesenchymal transition of human peritoneal mesothelial cells. *Int J Artif Organs* 2005; 28(2): 164–9.
45. Alscher DM, Braun N, Biegger D, Fritz P. Peritoneal mast cells in peritoneal dialysis patients, particularly in encapsulating peritoneal sclerosis patients. *Am J Kidney Dis* 2007; 49(3):452–61.
46. Jimenez-Heffernan JA, Bajo MA, Perna C, Del Peso G, Larrubia JR, Gamallo C, *et al*. Mast cell quantification in normal peritoneum and during peritoneal dialysis treatment. *Arch Pathol Lab Med* 2006; 130(8):1188–92.
47. Metcalfe DD, Baram D, Mekori YA. Mast cells. *Physiol Rev* 1997; 77(4):1033–79.
48. Katsanos GS, Anogeianaki A, Orso C, Tete S, Salini V, Antinolfi PL, *et al*. Mast cells and chemokines. *J Biol Regul Homeost Agents* 2008; 22(3):145–52.
49. Norrby K. Mast cells and angiogenesis. *APMIS* 2002; 110(5):355–71.
50. Zareie M, Fabbrini P, Hekking LH, Keuning ED, ter Wee PM, Beelen RH, *et al*. Novel role for mast cells in omental tissue remodeling and cell recruitment in experimental peritoneal dialysis. *J Am Soc Nephrol* 2006; 17(12):3447–57.
51. Brouty-Boye D, Pottin-Clemenceau C, Doucet C, Jasmin C, Azzarone B. Chemokines and CD40 expression in human fibroblasts. *Eur J Immunol* 2000; 30(3):914–19.
52. Chang HY, Chi JT, Dudoit S, Bondre C, van de Rijn M, Botstein D, *et al*. Diversity, topographic differentiation, and positional memory in human fibroblasts. *Proc Natl Acad Sci U S A* 2002; 99(20):12877–82.
53. Aroeira LS, Aguilera A, Sanchez-Tomero JA, Bajo MA, Del Peso G, Jimenez-Heffernan JA, *et al*. Epithelial to mesenchymal transition and peritoneal membrane failure in peritoneal dialysis patients: pathologic significance and potential therapeutic interventions. *J Am Soc Nephrol* 2007; 18(7):2004–13.
54. Jorres A, Ludat K, Lang J, Sander K, Gahl GM, Frei U, *et al*. Establishment and functional characterization of human peritoneal fibroblasts in culture: regulation of interleukin-6 production by proinflammatory cytokines. *J Am Soc Nephrol* 1996; 7(10):2192–201.
55. Nakagawa H, Ikesue A, Hatakeyama S, Kato H, Gotoda T, Komorita N, *et al*. Production of an interleukin-8-like chemokine by cytokine-stimulated rat NRK-49F fibroblasts and its suppression by anti-inflammatory steroids. *Biochem Pharmacol* 1993; 45(7):1425–30.
56. Larsen CG, Anderson AO, Oppenheim JJ, Matsushima K. Production of interleukin-8 by human dermal fibroblasts and keratinocytes in response to interleukin-1 or tumour necrosis factor. *Immunology* 1989; 68(1):31–6.
57. Flessner MF. Sterile solutions and peritoneal inflammation. *Contrib Nephrol* 2006; 150:156–65.
58. Harris SG, Padilla J, Koumas L, Ray D, Phipps RP. Prostaglandins as modulators of immunity. *Trends Immunol* 2002; 23(3):144–50.
59. Okada H, Inoue T, Kanno Y, Kobayashi T, Watanabe Y, Ban S, *et al*. Selective depletion of fibroblasts preserves morphology and the functional integrity of peritoneum in transgenic mice with peritoneal fibrosing syndrome. *Kidney Int* 2003; 64(5):1722–32.
60. Dragomir E, Manduteanu I, Voinea M, Costache G, Manea A, Simionescu M. Aspirin rectifies calcium homeostasis, decreases reactive oxygen species, and increases NO production in high glucose-exposed human endothelial cells.

J Diabet Complications 2004; 18(5):289–99.
61. Mantovani A, Bussolino F, Dejana E. Cytokine regulation of endothelial cell function. *FASEB J* 1992; 6(8):2591–9.
62. Zareie M, van Lambalgen AA, De Vriese AS, Van Gelderop E, Lameire N, ter Wee PM, *et al*. Increased leukocyte rolling in newly formed mesenteric vessels in the rat during peritoneal dialysis. *Perit Dial Int* 2002; 22(6):655–62.
63. Mortier S, Faict D, Gericke M, Lameire N, De Vriese A. Effects of new peritoneal dialysis solutions on leukocyte recruitment in the rat peritoneal membrane. *Nephron Exp Nephrol* 2005; 101(4):e139–45.
64. Devuyst O, Nielsen S, Cosyns JP, Smith BL, Agre P, Squifflet JP, *et al*. Aquaporin-1 and endothelial nitric oxide synthase expression in capillary endothelia of human peritoneum. *Am J Physiol* 1998; 275(1 pt 2):H234–H242.
65. Gesualdo L, Pertosa G, Grandaliano G, Schena FP. Cytokines and bioincompatibility. *Nephrol Dial Transplant* 1998; 13(7):1622–6.
66. Margetts PJ, Kolb M, Yu L, Hoff CM, Holmes CJ, Anthony DC, *et al*. Inflammatory cytokines, angiogenesis, and fibrosis in the rat peritoneum. *Am J Pathol* 2002; 160(6): 2285–94.
67. Haslinger B, Mandl-Weber S, Sellmayer A, Sitter T. Hyaluronan fragments induce the synthesis of MCP-1 and IL-8 in cultured human peritoneal mesothelial cells. *Cell Tissue Res* 2001; 305(1):79–86.
68. Breborowicz A, Korybalska K, Grzybowski A, Wieczorowska-Tobis K, Martis L, Oreopoulos DG. Synthesis of hyaluronic acid by human peritoneal mesothelial cells: effect of cytokines and dialysate. *Perit Dial Int* 1996; 16(4):374–8.
69. Ha H, Yu MR, Choi HN, Cha MK, Kang HS, Kim MH, *et al*. Effects of conventional and new peritoneal dialysis solutions on human peritoneal mesothelial cell viability and proliferation. *Perit Dial Int* 2000; 20(Suppl 5):S10–18.
70. De Vriese AS, Stoenoiu MS, Elger M, Devuyst O, Vanholder R, Kriz W, *et al*. Diabetes-induced microvascular dysfunction in the hydronephrotic kidney: role of nitric oxide. *Kidney Int* 2001; 60(1):202–10.
71. Margetts PJ, Kolb M, Galt T, Hoff CM, Shockley TR, Gauldie J. Gene transfer of transforming growth factor-beta1 to the rat peritoneum: effects on membrane function. *J Am Soc Nephrol* 2001; 12(10):2029–39.
72. Margetts PJ, Gyorffy S, Kolb M, Yu L, Hoff CM, Holmes CJ, *et al*. Antiangiogenic and antifibrotic gene therapy in a chronic infusion model of peritoneal dialysis in rats. *J Am Soc Nephrol* 2002; 13(3):721–8.
73. Beavis MJ, Williams JD, Hoppe J, Topley N. Human peritoneal fibroblast proliferation in 3-dimensional culture: modulation by cytokines, growth factors and peritoneal dialysis effluent. *Kidney Int* 1997; 51(1):205–15.
74. Cina D, Patel P, Bethune JC, Thoma J, Rodriguez-Lecompte JC, Hoff CM, *et al*. Peritoneal morphological and functional changes associated with platelet-derived growth factor B. *Nephrol Dial Transplant* 2009; 24(2):448–57.
75. Ogata S, Yorioka N, Kiribayashi K, Naito T, Kuratsune M, Nishida Y. Viability of, and basic fibroblast growth factor secretion by, human peritoneal mesothelial cells cultured with various components of peritoneal dialysis fluid. *Adv Perit Dial* 2003; 19:2–5.
76. Ogata S, Naito T, Yorioka N, Kiribayashi K, Kuratsune M, Kohno N. Effect of lactate and bicarbonate on human peritoneal mesothelial cells, fibroblasts and vascular endothelial cells, and the role of basic fibroblast growth factor. *Nephrol Dial Transplant* 2004; 19(11):2831–7.
77. Roubin R, Benveniste J. Formation of prostaglandins, leukotrienes and PAF-acether by macrophages. *Comp Immunol Microbiol Infect Dis* 1985; 8(2):109–18.
78. Topley N, Petersen MM, Mackenzie R, Neubauer A, Stylianou E, Kaever V, *et al*. Human peritoneal mesothelial cell prostaglandin synthesis: induction of cyclooxygenase mRNA by peritoneal macrophage-derived cytokines. *Kidney Int* 1994; 46(3):900–9.
79. Douma CE, de Waart DR, Zemel D, Struijk DG, Krediet RT. Prostaglandin inhibition by intraperitoneal indomethacin has no effect on peritoneal permeability during stable CAPD. *Nephrol Dial Transplant* 2001; 16(4):803–8.
80. Pool JL. Direct renin inhibition: focus on aliskiren. *J Manag Care Pharm* 2007; 13(8 Suppl B):21–33.
81. Duman S. The renin-angiotensin system and peritoneal dialysis. *Perit Dial Int* 2004; 24(1):5–9.
82. Ruiz-Ortega M, Ruperez M, Lorenzo O, Esteban V, Blanco J, Mezzano S, *et al*. Angiotensin II regulates the synthesis of proinflammatory cytokines and chemokines in the kidney. *Kidney Int Suppl* 2002; 82:S12–22.
83. Fujiyama S, Matsubara H, Nozawa Y, Maruyama K, Mori Y, Tsutsumi Y, *et al*. Angiotensin AT(1) and AT(2) receptors differentially regulate angiopoietin-2 and vascular endothelial growth factor expression and angiogenesis by modulating heparin binding-epidermal growth factor (EGF)-mediated EGF receptor transactivation. *Circ Res* 2001; 88(1):22–9.
84. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm* 2007; 13(8 Suppl B):9–20.
85. Hatakeyama H, Miyamori I, Fujita T, Takeda Y, Takeda R, Yamamoto H. Vascular aldosterone. Biosynthesis and a link to angiotensin II-induced hypertrophy of vascular smooth muscle cells. *J Biol Chem* 1994; 269(39): 24316–20.
86. Juknevicius I, Segal Y, Kren S, Lee R, Hostetter TH. Effect of aldosterone on renal transforming growth factor-beta. *Am J Physiol Renal Physiol* 2004; 286(6):F1059–F1062.
87. Nakamoto H, Imai H, Fukushima R, Ishida Y, Yamanouchi Y, Suzuki H. Role of the renin-angiotensin system in the pathogenesis of peritoneal fibrosis. *Perit Dial Int* 2008; 28(Suppl 3):S83–7.
88. Ersoy R, Celik A, Yilmaz O, Sarioglu S, Sis B, Akan P, *et al*. The effects of irbesartan and spironolactone in prevention of peritoneal fibrosis in rats. *Perit Dial Int* 2007; 27(4):424–31.
89. Ha H, Lee HB. Effect of high glucose on peritoneal

mesothelial cell biology. *Perit Dial Int* 2000; 20(Suppl 2): S15–18.
90. Ha H, Lee HB. Reactive oxygen species and matrix remodeling in diabetic kidney. *J Am Soc Nephrol* 2003; 14(8 Suppl 3):S246–9.
91. Rhyu DY, Yang Y, Ha H, Lee GT, Song JS, Uh ST, *et al*. Role of reactive oxygen species in TGF-beta1-induced mitogen-activated protein kinase activation and epithelial-mesenchymal transition in renal tubular epithelial cells. *J Am Soc Nephrol* 2005; 16(3):667–75.
92. Xia L, Wang H, Munk S, Kwan J, Goldberg HJ, Fantus IG, *et al*. High glucose activates PKC-{zeta} and NADPH oxidase through autocrine TGF-{beta}1 signaling in mesangial cells. *Am J Physiol Renal Physiol* 2008; 295(6): F1705–F1714.
93. Noh H, Kim JS, Han KH, Lee GT, Song JS, Chung SH, *et al*. Oxidative stress during peritoneal dialysis: implications in functional and structural changes in the membrane. *Kidney Int* 2006; 69(11):2022–8.
94. Williams CS, Mann M, DuBois RN. The role of cyclooxygenases in inflammation, cancer, and development. *Oncogene* 1999; 18(55):7908–16.
95. Hilario MO, Terreri MT, Len CA. Nonsteroidal anti-inflammatory drugs: cyclooxygenase 2 inhibitors. *J Pediatr (Rio J)* 2006; 82(5 Suppl):S206–12.
96. Gately S, Li WW. Multiple roles of COX-2 in tumor angiogenesis: a target for antiangiogenic therapy. *Semin Oncol* 2004; 31(2 Suppl 7):2–11.
97. Shanmugam N, Gaw Gonzalo IT, Natarajan R. Molecular mechanisms of high glucose-induced cyclooxygenase-2 expression in monocytes. *Diabetes* 2004; 53(3):795–802.
98. Saed GM, Munkarah AR, Diamond MP. Cyclooxygenase-2 is expressed in human fibroblasts isolated from intraperitoneal adhesions but not from normal peritoneal tissues. *Fertil Steril* 2003; 79(6):1404–8.
99. Fabbrini P, Schilte MN, Zareie M, ter Wee PM, Keuning ED, Beelen RH, *et al*. Celecoxib treatment reduces peritoneal fibrosis and angiogenesis and prevents ultrafiltration failure in experimental peritoneal dialysis. *Nephrol Dial Transplant* 2009; [in press].
100. Xu ZG, Kim KS, Park HC, Choi KH, Lee HY, Han DS, *et al*. High glucose activates the p38 MAPK pathway in cultured human peritoneal mesothelial cells. *Kidney Int* 2003; 63(3):958–68.
101. Mittelstadt PR, Salvador JM, Fornace AJ Jr, Ashwell JD. Activating p38 MAPK: new tricks for an old kinase. *Cell Cycle* 2005; 4(9):1189–92.
102. Ambrosino C, Nebreda AR. Cell cycle regulation by p38 MAP kinases. *Biol Cell* 2001; 93(1–2):47–51.
103. Ryan S, McNicholas WT, Taylor CT. A critical role for p38 MAP kinase in NF-kappaB signaling during intermittent hypoxia/reoxygenation. *Biochem Biophys Res Commun* 2007; 355(3):728–33.
104. Kaminska B. MAPK signalling pathways as molecular targets for anti-inflammatory therapy—from molecular mechanisms to therapeutic benefits. *Biochim Biophys Acta* 2005; 1754(1–2):253–62.
105. Badger AM, Bradbeer JN, Votta B, Lee JC, Adams JL, Griswold DE. Pharmacological profile of SB 203580, a selective inhibitor of cytokine suppressive binding protein/p38 kinase, in animal models of arthritis, bone resorption, endotoxin shock and immune function. *J Pharmacol Exp Ther* 1996; 279(3):1453–61.
106. Carter CA, Kane CJ. Therapeutic potential of natural compounds that regulate the activity of protein kinase C. *Curr Med Chem* 2004; 11(21):2883–902.
107. Ha H, Lee HB. Reactive oxygen species as glucose signaling molecules in mesangial cells cultured under high glucose. *Kidney Int Suppl* 2000; 77:S19–25.
108. Wu WS. The signaling mechanism of ROS in tumor progression. *Cancer Metastasis Rev* 2006; 25(4):695–705.
109. Lee HB, Yu MR, Song JS, Ha H. Reactive oxygen species amplify protein kinase C signaling in high glucose-induced fibronectin expression by human peritoneal mesothelial cells. *Kidney Int* 2004; 65(4):1170–9.
110. Ha H, Yu MR, Choi YJ, Kitamura M, Lee HB. Role of high glucose-induced nuclear factor-kappaB activation in monocyte chemoattractant protein-1 expression by mesangial cells. *J Am Soc Nephrol* 2002; 13(4):894–902.
111. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. *J Pharmacol Exp Ther* 2005; 315(3):971–9.
112. Cabebe E, Wakelee H. Sunitinib: a newly approved small-molecule inhibitor of angiogenesis. *Drugs Today (Barc)* 2006; 42(6):387–98.
113. Osusky KL, Hallahan DE, Fu A, Ye F, Shyr Y, Geng L. The receptor tyrosine kinase inhibitor SU11248 impedes endothelial cell migration, tubule formation, and blood vessel formation *in vivo*, but has little effect on existing tumor vessels. *Angiogenesis* 2004; 7(3):225–33.
114. Neef M, Ledermann M, Saegesser H, Schneider V, Widmer N, Decosterd LA, *et al*. Oral imatinib treatment reduces early fibrogenesis but does not prevent progression in the long term. *J Hepatol* 2006; 44(1):167–75.
115. Welten AG, Schalkwijk CG, ter Wee PM, Meijer S, van den Born J, Beelen RJ. Single exposure of mesothelial cells to glucose degradation products (GDPs) yields early advanced glycation end-products (AGEs) and a proinflammatory response. *Perit Dial Int* 2003; 23(3):213–21.
116. Boulanger E, Grossin N, Wautier MP, Taamma R, Wautier JL. Mesothelial RAGE activation by AGEs enhances VEGF release and potentiates capillary tube formation. *Kidney Int* 2007; 71(2):126–33.
117. Schwenger V. GDP and AGE receptors: mechanisms of peritoneal damage. *Contrib Nephrol* 2006; 150:77–83.
118. Schwenger V, Morath C, Salava A, Amann K, Seregin Y, Deppisch R, *et al*. Damage to the peritoneal membrane by glucose degradation products is mediated by the receptor for advanced glycation end-products. *J Am Soc Nephrol* 2006; 17(1):199–207.
119. De Vriese AS, Flyvbjerg A, Mortier S, Tilton RG, Lameire NH. Inhibition of the interaction of AGE-RAGE prevents hyperglycemia-induced fibrosis of the peritoneal mem-

brane. *J Am Soc Nephrol* 2003; 14(8):2109–18.
120. Wang X, Shaw S, Amiri F, Eaton DC, Marrero MB. Inhibition of the JAK/STAT signaling pathway prevents the high glucose-induced increase in TGF-beta and fibronectin synthesis in mesangial cells. *Diabetes* 2002; 51(12):3505–9.
121. Hebenstreit D, Horejs-Hoeck J, Duschl A. JAK/STAT-dependent gene regulation by cytokines. *Drug News Perspect* 2005; 18(4):243–9.
122. Marrero MB, Banes-Berceli AK, Stern DM, Eaton DC. Role of the JAK/STAT signaling pathway in diabetic nephropathy. *Am J Physiol Renal Physiol* 2006; 290(4):F762–F768.
123. Amiri F, Shaw S, Wang X, Tang J, Waller JL, Eaton DC, *et al*. Angiotensin II activation of the JAK/STAT pathway in mesangial cells is altered by high glucose. *Kidney Int* 2002; 61(5):1605–16.
124. Rodrigues A, Cabrita A, Maia P, Guimaraes S. Peritoneal rest may successfully recover ultrafiltration in patients who develop peritoneal hyperpermeability with time on continuous ambulatory peritoneal dialysis. *Adv Perit Dial* 2002; 18:78–80.
125. de Alvaro F, Castro MJ, Dapena F, Bajo MA, Fernandez-Reyes MJ, Romero JR, *et al*. Peritoneal resting is beneficial in peritoneal hyperpermeability and ultrafiltration failure. *Adv Perit Dial* 1993; 9:56–61.
126. Zhe XW, Tian XK, Cheng L, Wang T. Effects of peritoneal resting on peritoneal fluid transport kinetics. *Perit Dial Int* 2007; 27(5):575–9.
127. Kim YL, Kim SH, Kim JH, Kim SJ, Kim CD, Cho DK, *et al*. Effects of peritoneal rest on peritoneal transport and peritoneal membrane thickening in continuous ambulatory peritoneal dialysis rats. *Perit Dial Int* 1999; 19(Suppl 2): S384–7.
128. Zareie M, Keuning ED, ter Wee PM, Beelen RH, van den Born J. Peritoneal dialysis fluid-induced changes of the peritoneal membrane are reversible after peritoneal rest in rats. *Nephrol Dial Transplant* 2005; 20(1):189–93.