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The Mechanism of Peritoneal Fibrosis in Peritoneal Dialysis

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Abstract

Peritoneal fibrosis (PF) is a common morphological change in peritoneal dialysis (PD) patients. With the progression of PF, peritoneal membrane function is impaired, which leads to ultrafiltration failure. Furthermore, PF is an essential precursor condition for the development of encapsulating peritoneal sclerosis (EPS), which is the most serious complication of PD. Epithelial-mesenchymal transition (EMT) of peritoneal mesothelial cells (PMCs) plays a crucial role in PF. Transforming growth factor-β_1 (TGF-β_1) was thought to be the main regulator of EMT in PMCs. High glucose, hypertonicity, low pH, glucose degradation products and advanced glycation end-products in PD solution were suggested to induce TGF-β_1 production. In addition, chronic inflammation mediated by infiltration of immune cells and peritoneal angiogenesis also play pivotal roles for the progression of PF.

Introduction

Peritoneal dialysis (PD) is a useful renal replacement therapy for end-stage renal disease (ESRD). However, long-term PD leads to peritoneal damage and subsequently to peritoneal fibrosis (PF) [1-3]. PF is associated with ultrafiltration failure, which leads to discontinuation of the PD by the patient [1-3]. Furthermore, PF is a major risk factor for the development of encapsulating peritoneal sclerosis (EPS), which is the most serious complication of PD and considered to be one of the reasons why PD is avoided in ESRD patients [4,5]. The mechanisms of the initiation and progression of PF have been increasingly understood through numerous studies involving basic and clinical research.

The mechanism of PF

Mechanisms such as epithelial-to-mesenchymal transition (EMT) of peritoneal mesothelial cells (PMCs), chronic inflammation and vascularization are thought to be involved in the initiation and progression of PF (Figure 1).

EMT of PMCs

EMT is a biological process in which an epithelial cell that interacts with basement membrane is altered into a cell with a mesenchymal phenotype that has enhanced migratory capacity, invasiveness and increased production of extracellular matrix [6]. PMCs express epithelial markers such as E-cadherin, cytokeratin and intercellular adhesion molecule 1 (ICAM-1). During the process of EMT, these epithelial markers are downregulated and mesenchymal markers such as α-smooth muscle actin, vimentin and fibronectin are upregulated, leading to a change into mesenchymal-like PMCs [7-11]. The expression of type I collagen and the migratory capacity are enhanced in these transformed PMCs [9,12]. Several clinical studies reported that peritoneal tissue samples obtained from PD patients showed the existence of elongated fibroblast-like cells expressing epithelial markers such as cytokeratin and ICAM-1 in the fibrotic tissue of the submesothelial compact zone [9,13]. These results suggested that PMCs changed their phenotype to mesenchymal-like cells via EMT and migrated to the submesothelial zone. Transforming growth factor-β_1 (TGF-β_1) plays a central role in EMT of PMCs [9,14-16]. When TGF-β_1 binds to its receptors, the signal is transmitted through Smad and non-Smad pathways and then upregulates transcription factor Snail, which is a key regulator of EMT, resulting in the phenotypic changes of PMCs [11,17-19].

Chronic inflammation

Among inflammatory cells, macrophages are the most abundant in PD effluents and are considered to play a central role in intraperitoneal chronic inflammation [20,21]. Macrophage infiltration was observed histologically in association with PF [22]. The concentrations of tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6, which behaved as proinflammatory cytokines mainly produced by macrophages, were reported to be elevated in PD effluent in PF [23-27]. These cytokines can promote fibroblast proliferation and type I collagen synthesis [28,29].
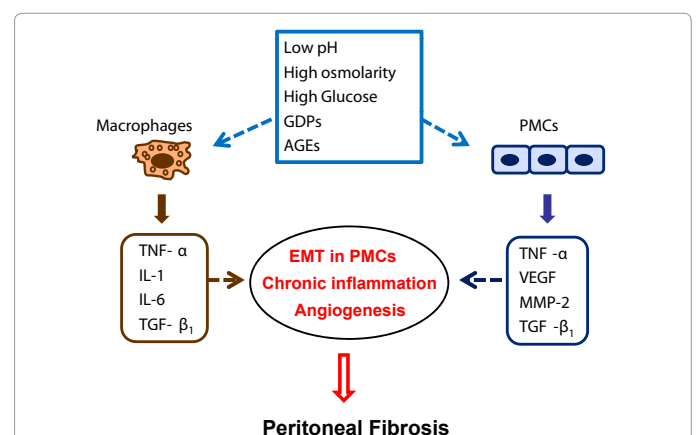

Figure 1: The mechanisms of peritoneal fibrosis. When stimulated by various factors, peritoneal mesothelial cells (PMCs) and macrophages produce various proinflammatory cytokines and growth factors. These products induce epithelial-mesenchymal transition (EMT) in PMCs, chronic inflammation in the peritoneal cavity and angiogenesis. These processes promote fibroblast proliferation and collagen synthesis, which lead to the progression of peritoneal fibrosis (PF). GDPs: glucose degradation products, AGEs: advanced glycation end-products, TNF-α: tumor necrosis factor-alpha, IL: interleukin, TGF-β_1: transforming growth factor-beta1, VEGF: vascular endothelial growth factor, MMP-2: matrix metallopeptidase 2, PMCs: peritoneal mesothelial cells, EMT: epithelial-mesenchymal transition.

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Infiltrated macrophages also contribute to TGF-β_1 production on peritoneum in PD [30]. Recently, it was reported that the concentration of CC chemokine ligand 18 (CCL18) which was secreted mainly by macrophages in the spent dialysate was high in the PD patients with decreased peritoneal membrane functions, and in those who later developed EPS [31,32]. These results suggested that CCL18 may be directly related to development of PF and EPS. These line of results suggested that chronic inflammation mainly induced by macrophages contributed to the development of PF. A recent study showed that PF was attenuated, at least in part, through the recruitment of regulatory T cells and the augmentation of an anti-inflammatory cytokine, IL-10 [33]. These results suggested that there are certain roles of lymphocytes other than macrophages on PF. Further studies will be needed to elucidate the role of immune cells for PF.

Peritoneal angiogenesis

Peritoneal vascular density in PD patients has been reported to be increased in association with increased severity of PF [34]. Submesothelial angiogenesis in a large vascular surface area resulted in elevation of small solute transport, enhancement of glucose absorption and dissipation of the glucose-driven osmotic pressure leading to the reduction of water removal [1,3]. Vascular endothelial growth factor (VEGF) acts as a key regulator of angiogenesis, vascular permeability and endothelial cell survival [35]. VEGF was reported to be upregulated by local hypoxia and also possibly by inflammation [36,37]. Local production of VEGF in PMCs was reported to play a central role in peritoneal angiogenesis during PD [38]. Several studies showed that the inhibition of peritoneal angiogenesis by anti-VEGF neutralizing antibody prevented the progression of PF [39-42]. These lines of evidence suggested that angiogenesis promoted the development of PF.

Fibrogenic factors

Several fibrogenic factors were reported to contribute to the development of PF in PD.

Glucose degradation products (GDPs)

As a dialysate-side factor, high glucose content is an important fibrogenic factor of the peritoneum on PD. High glucose induces the production of TGF-β_1 [7]. Furthermore, glucose degradation products (GDPs) such as methylglyoxal, glyoxal, formaldehyde and 3-deoxyglucosone (3-DG) from glucose are thought to be factors that strongly induce PF. The glucose is degraded to GDPs during heat sterilization and storage. GDPs have been reported to inhibit proliferation and induce EMT on PMCs via upregulation of TGF-β_1 signaling [11,43]. GDPs also promote cytokine release and superoxide radical generation of macrophages and blood polymorphonuclear cells leading to peritoneal injury. Intraperitoneal administration of dialysate including GDP leads to PF in animal models [11]. Furthermore, GDPs are precursors of advanced glycation end-products (AGEs), which are important inducers of PF as described below [44].

Advanced glycation end-products (AGEs)

AGEs are formed by non-enzymatic glycation between reducing sugars and proteins, lipids and nucleic acids [45]. AGEs are considered to take part in the remodeling and fibrosis of the peritoneum when they interact with their receptors. The receptor of AGE (RAGE) was expressed by PMCs in the submesothelial layer. The accumulation of AGEs is recognized in peritoneal mesothelial and submesothelial layers in PD patients, especially with low ultrafiltration [7,46,47]. In PD patients, since highly concentrated glucose solution is infused into the peritoneal cavity in the long term, the formation of AGEs from GDPs in the peritoneum could be accelerated [48,49]. In subnephrectomized rats, AGEs accumulation was observed in fibrotic peritoneum along with the expression of TGF-β_1, and the administration of anti-RAGE antibody was found to prevent PF as well as the upregulation of TGF-β_1 [50]. Furthermore, PF was not promoted by the exposure to GDP-containing PD fluid in RAGE-deficient mice [51]. These lines of evidence suggested that PF was dependent, at least in part, on AGEs–RAGE interaction.

Hypertonicity of dialysate

Hypertonicity of dialysate is also considered to be a factor that induces PF. Osmotic agents such as glucose, mannitol and glycerol inhibit the growth and stimulate the secretion of lactate dehydrogenase, which reflects cytotoxicity and TGF-β_1 production to induce EMT in PMCs [7]. Low-pH dialysis solution also induced PMC damage [52]. Intraperitoneal injection of acidic dialysate induced PF in animal models [53]. It was reported that neutral pH and low-GDP dialysate was less inductive of the progression of PF than conventional dialysate in an animal model [54]. Several clinical studies showed that neutral PD solution with low GDP is superior to conventional solution in terms of biocompatibility and survival in PD patients [44,55,56].

Other fibrogenic factors

As a patient-side factor, long-term PD treatment is the most representative risk factor for PF. Peritoneal thickness has been reported to increase depending on the duration of PD [46]. Repeated exposure to dialysis fluid with the factors mentioned below might be one of the main causes of PF. The complication of diabetes mellitus is liable to promote PF progression [46]. The mechanism for this may be related mainly to the accumulation of AGEs in diabetic patients. Some clinical studies have revealed that low residual renal function is also associated with high risk of EPS, suggesting that uremia has some influence on the progression of PF [2,46]. Not only long-term PD patients but also predialysis uremic patients show increased peritoneal thickness [46]. The accumulation of AGEs is considered to promote peritoneal thickening with fibrosis in a uremic condition [46].

Potential strategy for the prevention and treatment of PF

Since TGF-β_1 plays a central role in the pathogenesis of PF, it can be a good target for the prevention and treatment of PF. Blockade of TGF-β_1 signaling using anti-TGF-β_1 neutralizing antibody inhibited EMT-like changes in cultured PMCs [7]. Smad7 is a molecule that inhibits TGF-β_1 signaling. Smad7 gene transfer to the peritoneum attenuated PF induced by high-glucose-containing dialysis fluid in an animal model [57]. Similarly, it was reported that the administration of TGF-β_1-blocking peptide attenuated the PF in an animal model [58]. These lines of evidence suggested that the therapy that targets TGF-β_1 signaling may be a powerful option in the treatment of PF. Several studies reported therapies targeting the AGEs and RAGE for the treatment of PF. An anti-AGEs reagent, benfotiamine, suppressed the progression of PF partly through the reduction of AGEs accumulation [59]. The administration of anti-RAGE antibody suppressed TGF-β_1 production in the peritoneum and attenuated PF [50]. These lines of evidence suggested that therapy that targets AGEs and RAGE may be a powerful option in the treatment of PF.

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