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Chapter 2

The Mesothelial to Mesenchymal Transition a Pathogenic and Therapeutic Key for Peritoneal Membrane Failure

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1. Introduction

Peritoneal dialysis (PD) is a form of renal replacement therapy that is growing progressively, possibly because of the freedom it offers to the patients and the undoubted improvement in the PD technique. Parallel the PD-related complications have also increased. In PD, the peritoneal membrane (PM) is exposed to bio-incompatible dialysis solutions, rich in glucose, which can cause peritoneal injury when associated with peritoneal incidents like repeated episodes of peritonitis or hemoperitoneum [1]. Progressive fibrosis, angiogenesis and ultimately, ultrafiltration failure, are some characteristics of the so-called sclerotic peritonitis syndromes (SPS) [2].

Several pathologic factors, such as inflammatory mediators, high glucose content, the presence of glucose degradation products, and low pH can induce peritoneal mesothelial cells (MCs) to lose certain epithelial characteristics, and they progressively acquire a fibroblast-like phenotype soon after initiation of PD [3]. This so-called mesothelial-to-mesenchymal transition (MMT) serves as a trigger for peritoneal fibrosis and angiogenesis, via up-regulation of transforming growth factor-β (TGF-β1 and vascular endothelial growth factor (VEGF), respectively. As such, MMT is considered an important potential therapeutic target in sclerotic peritonitis syndromes [4]. Encapsulating peritoneal sclerosis (EPS) is a severe form of peritoneal fibrosis characterized by intestinal encapsulation through the formation of excessive matrix components that subsequently may lead to obstruction of the intestinal tract [5]. Although rare, EPS is a serious complication of PD for which no specific and definitive
treatment exists [6]. However, peritoneal rest, steroids, immunosuppressive agents and Tamoxifen have been used previously as therapeutic approaches with divergent results [4]. Herein, we review in detail the effect of PD liquids and other peritoneal accidents like peritonitis and hemoperitoneum on the MCs physiology, the transdifferentiation in fibroblast-like cells (MMT), its clinical correlation with data from peritoneal and morphologic function (peritoneal biopsies), the initiation and perpetuation of peritoneal fibrosis (SPS) and his eventual rise to EPS. We also purpose therapeutic alternatives, ranging from the improvement in the biocompatibility of the liquids of DP, the use of drugs available on the market today, or even the use of molecular strategies, as blockades or stimulation of genes involved in the peritoneal damage.

2. Morphologic and phenotypic MCs characterization

The mesothelium is a continuous superficial layer of MCs formed by flattened, polygonal, mononuclear, squamous epithelial cells. This monolayer shows remarkable fibrinolytic properties and is thought to be involved in the prevention of fibrous adhesion formation in the peritoneum. MCs cells have vast biosynthetic capacity and secrete phospholipids and phosphotidylcholine in the form of lamellar bodies that provide a lubricating surface for the movement of abdominal viscera [7]. Besides this function, the mesothelium also modulates peritoneal microcirculation by secreting vasodilators (eg, prostaglandin E2 and nitric oxide), as well as vasoconstrictors (eg, endothelin) [8]. The luminal aspect of MCs plasmalemma has numerous cytoplasmic extensions called “microvilli” which play a significant role in the transperitoneal transfer of anionic macromolecules such as proteins. Microvilli are extremely sensitive and easily lost due to injury [9].

MCs can be isolated from healthy omentum donors of elective abdominal surgeries and the effluent from patients with PD. The analysis of the effluent drained peritoneal MCs has allowed us to assess the health status of peritoneal. The purity of effluent and omentum-derived MC cultures are determined by the expression of standard mesothelial markers: IC-M, cytokeratins, and calretinin. MCs cultures remain stable, without any evident sign of senescence, for at least two to three passages [10, 11].

The analysis of cytokeratins and E-cadherin expression, that are typical epithelial markers and highly expressed in MC, is important to determine more precisely the nature of effluent-derived cells. High expression of cytokeratins and E-cadherin is only observed in omentum-derived MC, whereas effluent-derived cells show a progressive reduction in the expression of these molecules, although even fibroblast-like MC may maintain a small population of positive cells (Figure 1). In mixed populations the expression of cytokeratins and E-Cadherin is normally bimodal. Fibroblasts are completely negative for these two markers. Previous studies had characterized the cobblestone-like MC from effluents as indistinguishable from omentum-derived MC. However, already in this early stage a loss of apico-basolateral polarity as well as down-regulation of cytokeratins and E-Cadherin is observed ex vivo, even though cells still show a morphologically epithelioid appearance [10-12].
Figure 1. Morphology and gene expression of MCs. Panel "A" shows a culture of MCs isolated from omentum donor. Cells show the typical cobblestone phenotype. Panel "B" shows MCs isolated from PD effluent with transitional phenotype, and panel "C" shows a fibroblastoid phenotype these cells were isolated and cultured from the PD effluent. The genetic pattern of each phenotype is described below.

The morphological changes and down-regulation of cytokeratin and E-Cadherin in effluent-derived MC are indicative of an MMT. MMT is a complex and generally reversible process that starts with the disruption of intercellular junctions and loss of apical–basolateral polarity, typical of epithelial cells, which are then transformed into fibroblast-like cells with increased migratory, invasive and fibrogenic features. The objective of this process is to repair tissue wounds by promoting the recovery of ancestor capabilities of epithelial cells. Cell migration, production of extracellular matrix and induction of neoangiogenesis are the main activities [11, 12]. This process is conducted by the transforming growth factor-β (TGF-β) and the representative cell form is the myofibroblast (Figure 2). TGF-β synthesis may be stimulated by glucose, and infections, via peritoneal leucocyte-derived factors. TGF-β has been found to be up-regulated in peritoneal inflammatory processes and its over-expression has been correlated to worse PD outcomes [13]. Moreover, the injection of an adenovirus vector that transferred active TGF-β1 in rat and mice peritoneum induces myofibroblastic conversion of MC. [14, 15]. TGF-β is a growth factor that has been implicated as the causal agent in fibrosis of different tissues and organs [16].
3. MMT signalling

Figure 3 shows the signaling cascade of MMT which begins with the activation of TGF-β which is considered the master molecule in peritoneal injury during PD. Activation of TGF-β receptors triggers smads-dependent and smads-independent signaling. Smads depending pathway include integrin-linked kinase, GSK-3β, β-catenin, Lef-1/Tcf and AP gene cascade. Smads independing include RhoAp160ROCK and H-Ras/Raf/ERK pathways [17-32].

4. Clinical implication of MMT in PM failure

We have described three major morphologies of MCs cultures from PD effluents: cobblestone-like, similar to omentum-derived MC, transitional and fibroblast-like MC which remained stable for at least two to three cell passages. After analyzing more than two hundred MC cultures with growth capacity, from more than 100 PD patients, we determined that the frequencies of the different effluent-derived MC cultures are approximately 53 percent for...
cobblestone-like, 24 percent for transitional, and 17 percent for fibroblast-like MC. The prevalence of non-epitheliod MC cultures (transitional or fibroblast-like) is associated with the time the patients have been subjected to PD and with the episodes of acute or recurrent peritonitis or hemoperitoneum [3, 10, 11]. We have also described a less frequent (less than 6 percent) cell culture with mixed morphologies [3, 10]. Effluent mesothelial cells were isolated from 37 PD patients and analyzed for mesenchymal conversion. Mass transfer coefficient for creatinine (Cr-MTC) was used to evaluate peritoneal function. VEGF concentration was

Figure 3. TGF-β signaling. Glucose, low pH from PD fluids, advanced glycation end products (AGEs), glucose degradation products (GDPs), peritonitis and haemoperitoneum stimulate TGF-β synthesis, and possibly FGF which in turn triggers the healing processes that ultimately lead to tissue fibrosis and angiogenesis. The increase in total VEGF production might increase the VEGF-C levels, which are directly implicated in lymphogenesis. TGF-β receptor I phosphorylates Smad 2 and 3 inducing their association with the common partner Smad 4, and then they translocate into the nucleus, where they control the expression of TGF-β-responsive genes, such as that encoding integrin-linked kinase (ILK). The activation of up-regulated ILK by β1 integrins results in strong phosphorylation of Akt and glycogen synthase kinase-3 (GSK-3). Phosphorylated-Akt triggers NF-kB activation, which in turn induces the expression of Smad 7, an inhibitory Smad molecule that interferes with the phosphorylation of Smad 2 and 3, and of snail, a key regulator of MMT. The transcription factor snail regulates MMT by inhibiting the expression of E-cadherin, and by inducing growth arrest and survival, which confer selective advantage to migrating trans-differentiated cells. The phosphorylation of GSK-3 by ILK results in its inhibition and subsequent stabilization of β-catenin, released from the adherens junction, and of AP-1. Stabilized β-catenin, in conjunction with Lef-1/Tcf, may se induce MMT, and AP-1 activates MMP-9 expression inducing the invasion of ECM. One of the main Smad-independent signalling cascades triggered by TGF-β receptor I ligation, includes the RhoA/RoCK pathway that regulates cytoskeleton remodelling and cellular migration/invasion. In addition, RhoA induces the expression of α-SMA in a ROCK-independent manner. Another signal transduction stimulated by TGF-β is the H-Ras/Raf/ERK pathway, which is also necessary for the induction of snail expression and MMT.
measured by using standard procedures. Patients whose drainage contained nonepithelioid mesothelial cells had greater serum VEGF levels than those with epithelial-like mesothelial cells in their effluent. VEGF production ex vivo by effluent mesothelial cells correlated with serum VEGF level. In addition, Cr-MTC correlated with VEGF levels in culture and serum. Cr-MTC also was associated with mesothelial cell phenotype. VEGF expression in stromal cells, retaining mesothelial markers, was observed in peritoneal biopsy specimens from high-transporter patients. These results suggest that mesothelial cells that have undergone epithelial-to-mesenchymal transition are the main source of VEGF in PD patients and therefore may be responsible for a high peritoneal transport rate [3].

In a clinical study performed by our group, we studied the peritoneal anatomical changes during the first months on PD, and to correlate them with peritoneal functional parameters. We studied 35 stable PD patients for up to 2 years on PD, with a mean age of 45.37 years. Seventy-four percent of patients presented loss of the mesothelial layer, 46% fibrosis and 17% in situ evidence of MMT (submesothelial cytokeratin staining), which increased over time. All patients with MMT showed myofibroblasts, while only 36% of patients without MMT had myofibroblasts. The myofibroblasts represent a dynamic population of cells showing functional and phenotypic diversity. During the last years, numerous different molecules have been reported to be expressed by tissue fibroblasts including peritoneal ones [10]. The origin of tissue fibroblasts has been largely overlooked, so that their lineage is not fully elucidated. There is now evidence supporting that fibro-myofibroblasts might originate from different sources. Firstly, they may differentiate from resident tissue stem cells or fibroblasts. Secondly, they can originate from nearby epithelial cells through a process known as MMT. Finally, the bone marrow and circulating cells may be responsible for the production of fibro-myofibroblasts circulating in the blood stream to their final tissue destination [33].

In PD, emergent evidence points that fibroblasts may arise from local conversion of epithelial cells by MMT or from CD34 + cells (fibrocytes) of the bloodstream after being recruited from bone marrow. In the case of renal fibrosis models, it has been shown that 36% of new fibroblasts derive from MMT, 15% from bone marrow and the rest comes from local proliferation of resident fibroblasts. In PD-related fibrosis, we have demonstrated the expression of mesothelial markers in stromal spindle-like cells, suggesting that they stemmed from local conversion of MC. In contrast, we did not observe a significant contribution of CD34+ cells from bone marrow to the submesothelial fibroblast population in the fibrotic peritoneal tissue [33].

In regard to angiogenesis, the number of peritoneal vessels did not vary when we compared different times on PD. Vasculopathy was present in 17% of the samples. Functional studies were used to define the peritoneal transport status. Patients in the highest quartile of mass transfer area coefficient of creatinine (Cr-MTAC) showed significantly higher MMT prevalence but similar number of peritoneal vessels. In the multivariate analysis, the highest quartile of Cr-MTAC remained as an independent factor predicting the presence of MMT after adjusting for fibrosis [34]. These findings indicate that MMT is a frequent morphological change in the peritoneal membrane. These myofibroblastic cells with submesothelial localization may arise from local conversion of MC during the repair responses and the high solute transport status is associated with MMT.
5. Are MMT, SPS and EPS part of the same process?

From MMT to SPS. Peritoneal fibrosis (or sclerosis) is a term that comprises a wide spectrum of peritoneal structural alterations, ranging from mild inflammation to severe sclerosing peritonitis and its most complicated manifestation, encapsulating peritonitis sclerosis (EPS) [6, 35, 36]. Simple sclerosis (SS), an intermediate stage of peritoneal fibrosis, is the most common peritoneal lesion found in the patients after few months on PD, and could represent the initial phase of sclerosing peritonitis syndrome (SPS). Rubin et al [5] described a normal thickness of the peritoneum of ŘŖ μm, but after a few months on PD could reach up to ŚŖ μm (SS). The SP is a progressive sclerosis that is characterized by a dramatic thickening of the peritoneum (up to 4000 μm) and is accompanied by inflammatory infiltrates, calcification, neo-vascularization and dilatation of blood and lymphatic vessels, being the thickening the most commonly used pathological criterion for differential diagnosis [6, 35, 36].

The importance of establishing a connection between MMT, SPS and EPS is the potential therapeutic and preventive effect of blocking this axis. Also emerging evidence suggests that partial or total blockade of the MMT prevents early stages of PM fibrosis and angiogenesis and preserves the PM function. Moreover, current studies show TGF-Ά is probably the most important molecule in the PM failure development, so act on a single molecule, the TGF-Ά, facilitates therapeutic approach. In fact we have shown that blockade of TGF-Ά significantly attenuated PM failure induced by PD fluids.

One of the biggest problems to establish the definitive connection between SPS and EPS is that the EPS animal model has not been fully and properly developed. While in our mice PD model in 4 or more weeks reaches the typical changes induced by PD fluids on humans, the peritoneal fibrosis model with chlorhexidine results artificial and extremely aggressive. The experimental development of an appropriate EPS model is mandatory. Possibly the most appropriate EPS mice model would be to maintain long-term (months) in PD according to our model of SPS. Once accepted this limitation, the current data suggest that MMT and SPS are part of the process. We have analyzed serially PM pieces of mice in PD at baseline, ŗś and řŖ days and we found a linear correlation between time on PD, the thickness of the PM and the number of MCs cytokeratin (+) and FSP-ŗ (+) in the area submesothelial. This phenomenon was accompanied by progressive loss of the mesothelial monolayer which indicates an important participation of the MMT in the development of peritoneal fibrosis (our unpublished results). Using a TGF-Ά adenovirus model, we found early MMT at Ś day after stimuli intraperitoneal injection that was correlated with PM fibrosis [14]. Similar finding was found by others [15]. Clinically, in MCs serially isolated and cultured from PD effluents, the MMT was present progressively over time in PD and is associated with solute transport disorders and ultrafiltration failure [37]. In PM biopsies from 35 PD stable patients performed during the first 2 years on PD, we demonstrated that the first morphological change in peritoneum that appears as a consequence of PD is submesothelial thickening partially caused by the MMT. This phenotype change is associated with an increase in peritoneal solute transport independent of the number of capillaries present in the tissue [1, 3]. Reaching this point, the following questions arise, as follows: could have peritoneal fibrosis without MMT?, or more specifically,
could have MMT without the participation of TGF-β? Experimental data by us [14] and others [15] indicate that blocking MMT in different degrees result in a significantly attenuation of structural and functional changes of PM. Using the adenovirus (TGF-β) and our PD mice model, the double submesothelial staining for cytokeratin (+) and FSP1 (+) was positive in approximately 37% of activated fibroblasts, indicating its epithelial origin [14]. However, the peritoneal fibrosis is inhibited in more than 50% indicating that direct inhibition of TGF-β with anti-TGF-β peptides inhibited other effects of this molecule as the activation of regional fibroblasts. Promising results have also obtained acting on immune system [38], on AGEs accumulation [39] or on renin-angiotensin system (ACE, AR-II, Paricalcitol) and BMP-7 which also modulate directly or indirectly the TGF-β [40]. These arguments lead us to conclude that TGF-β is a key in the initiation and possibly perpetuation of an uncontrolled MMT, which leads to fibrosis and SPS.

From SPS to EPS. The next question is as follows: at which point the SPS becomes an irreversible process to become EPS? The “two-hit” hypothesis explains the EPS as the result of the PD injury. Two factors are required for the onset of EPS: a predisposing factor, such as peritoneal deterioration from persistent injury caused by peritoneal dialysis (the first “hit”), and an initiating factor, such as inflammatory stimuli superimposed on the chronically injured peritoneum (the second “hit”). Peritoneal deterioration (consisting of mesothelial denudation, interstitial fibrosis, vasculopathy, and angiogenesis) leads to an increased tendency toward plasma exudations that contain fibrin and coagulation factors. The fibrins in the exudates contribute to the intestinal adhesions and formation of fibrin capsule. Inflammatory stimuli caused by infectious peritonitis are superimposed on the damaged peritoneum and act as an initiating factor to trigger the onset of EPS. Inflammatory cytokines also induce activation and proliferation of the peritoneal fibroblasts, promoting peritoneal fibrosis and intestinal adhesions. The relationship between the extent of the first and second “hits” can be demonstrated. The extent of peritoneal damage (the first “hit”) increases with the duration of peritoneal dialysis [41, 42].

The onset of EPS depends on the total intensity of both lesions: peritoneal damage and inflammatory stimuli. For the onset of EPS, the total intensity must be greater than a given threshold. The extent of the inflammatory stimuli (the second “hit”) are required for the onset of EPS [41, 42].

In both cases (acute and chronic peritoneal injury), the TGF-β is activated with subsequent initiation and perpetuation of MMT and its deleterious effects (fibrosis, angiogenesis, etc.). However, it is very difficult to establish the point of no return in peritoneal lesions clinically because patients with type-I PM failure usually recover functionality and possibly tissue damage with rest peritoneal [43]. In experimental animals, data about fibrosis reversibility are not available. Unfortunately, the initial degree of PM fibrosis has been determined in very few cases (peritoneal biopsies not available). Finally a genetic component cannot be ruled [44, 45].

From MMT to EPS. In both, experimental animals [14, 46] and human peritoneal biopsies from patients within 2 years in PD [34], it seems clear that MMT is an early phenomenon able to determine the degree of peritoneal fibrosis and the future of the PM. But no information about MMT in patients with long term in PD or diagnosis of EPS is available. It is possible that MMT
may be an initial phenomenon and few signs of it are in severe stages of fibrosis. However, in bridles and postsurgical adhesions, we have found MMT signs (unpublished data by us), and Bowel adherences may represent an intermediate degree between the SPS and EPS (our unpublished data by us), which encourages to conduct studies aimed to find MMT peritoneum with EPS.

These findings represent important evidence linking both processes, but indirect evidence may also be marked. In human studies [3, 11] and in experimental animals [47], our studies demonstrated a direct relationship between MMT and time on PD. Similarly, the several studies showed a parallel between EPS and time on PD [2, 48]. Another important fact is that peritoneal function studies also show a parallel between high frequency of MMT ofMCs, high Cr-MTC, and low ultrafiltration. Indeed we observed a higher frequency of mesothelial fibroblastoid phenotype in patients with type Cr-MTC >11 mL/min [3]. Furthermore, as is well known, patients with EPS even displayed these with EPS showed similar functional PM deterioration [35, 49, 50]. Another indirect association between these two events is peritonitis. Yañez-Mo and coworkers [11] found that the frequency of nonepithelioidMC was associated with episodes of peritonitis, this means that peritonitis leads to the MMT. In the case of the EPS, there are some studies in the literature that correlate it with peritonitis events. Previous studies suggest that peritonitis may predispose to EPS, especially if this is caused by *Staphylococcus aureus*, fungi, and/or *Pseudomonas* [9, 51]. There is also an association between persistent infections such as tuberculosis peritonitis and EPS [52]. Although peritonitis and EPS are highly associated in several studies it is also known that, especially in a long-term case, EPS may occur without peritonitis. Moreover, patients that have suffered from more events of peritonitis have a higher incidence of MMT and EPS, which suggest again that these processes are related. Finally, we have analyzed more than 10 peritoneal biopsies from patients with EPS where we had found a significant amount of mesothelial cells (CK +) in the peritoneal submesothelial area, which indicates that despite the significant denudation of the peritoneal MCs monolayer.

6. The MMT as therapeutic target

Based on the concept, that MMT, fibrosis and angiogenesis may be part of the same process of peritoneal membrane failure, therapeutic approaches may be addressed to prevent either MMT of the MC or its deleterious effects such as ECM synthesis and/or VEGF production. In this context, *in vitro* and *ex vivo* cultures of MC may be useful for testing pharmacological agents with potential effects on MMT of the MC. Two molecules with expectedpreventive effect on the MMT of MC are hepatocyte growth factor (HGF) and bone morphogenic protein-7 (BMP-7). It has been demonstrated that these molecules are able to inhibit and reverse MMT and renal fibrosis in animal models. [53-54]. Other strategies that would open new avenues of therapeutic intervention to prevent or reverse MMT of MC may include the inhibition of ILK, RhoA-ROCK or Akt-mediated signaling cascades [25-33, 55]. In this context, the administration of the ROCK inhibitor Y-27632 resulted in suppression of α-SMA expression and renal interstitial fibrosis in a mouse model of ureteral obstruction. [55]
We performed our studies using testing different drugs or anti-MMT strategies. We have developed a PD mouse model, this consist in the intra-abdominal catheter implantation with a subcutaneous chamber localized in the top of mouse back. Afterwards, we injected a daily intra-peritoneal injection of PD solution at least for 4 weeks. In-vitro we used MCs isolated from omentum and from PD peritoneal effluent. We managed to inhibit the MMT and its adverse effects from using Rapamycin [56]. With Rapamycin got a specific inhibition of fibrosis and the vessels formation specifically lymphatic vessels (56, 57, our unpublished results). Rosiglitazone showed an inhibitory effect on the accumulation of submesothelial AGEs, also anti-inflammatory action mediated by T-cells was observed [39]. Similarly, celecoxib inhibited the peritoneal fibrosis by an anti-cox2 effect [38]. MMT also was prevented by tamoxifen. This drug inhibited the peritoneal fibrosis and increased MCs fibrinolytic capacity [47]. Clinically, tamoxifen also improved survival in patients diagnosed of EPS [58]. Paricalcitol acted on
smads cascade inhibiting the MMT (our unpublished results). Finally, we were able to inhibit specifically TGF-β with anti-TGF-β specific peptides demonstrating the role of TGF-β in the initiation and perpetuation of MMT [14]. In this context, other promising substances are pentoxifylline, dipyridamole, and emodin [59-61]. Figure 4 summarizes the sites where we may act by blocking the MMT or adverse effects. Some of these drugs and / or therapeutic strategies have been described by our group.

7. Conclusion

Recent findings suggest that in the peritoneum new fibroblast-like cells arise from local conversion of MMT during the repair responses that take place in long-term PD. These trans-differentiated MC may invade the submesothelial tissue and may contribute to peritoneal fibrosis and angiogenesis, which ultimately lead to peritoneal membrane failure. MMT appears as the central point in the pathogenesis of peritoneal damage associated to PD. Current data support a connection between MMT and SPS. However, the jump from SPS to EPS and the connection between MMT and EPS have not been fully established. MMT can be a therapeutic target the blockade of which could benefit especially in initial stages of the process.

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