CHAPTER 6

Epithelial toMesenchymal Transition of Mesothelial Cells as a Mechanism Responsible for Peritoneal Membrane Failure in Peritoneal Dialysis Patients

Abelardo Aguilera, Luiz S. Aroeira, Marta Ramírez-Huesca, José A. Jiménez-Heffernan, Rafael Selgas and Manuel López-Cabrera*

Abstract

Peritoneal dialysis (PD) is an alternative to hemodialysis for the treatment of end-stage renal disease and is based on the use of the peritoneum as a semi-permeable membrane for water and solutes. Peritoneal membrane fibrosis (or sclerosis) is one of the most frequent complications of PD that includes a wide spectrum of peritoneal structural changes, ranging from mild inflammation to severe sclerosing peritonitis and encapsulating-sclerosing peritonitis. In parallel with fibrosis, the peritoneum shows a progressive increase of capillary number (angiogenesis) and vasculopathy, which are involved in increased small solute transport across the peritoneal membrane and ultrafiltration failure. Local production of vascular endothelial growth factor (VEGF) during PD appears to play a central role in the processes leading to peritoneal angiogenesis and functional decline. The most important factors of the PD solutions responsible of peritoneal deterioration are glucose and glucose degradation products, which stimulate transforming growth factor-β (TGF-β) and VEGF production by mesothelial cells (MC). TGF-β is a potent pro-fibrotic factor and inducer of epithelial-mesenchymal transition (EMT) of the MC.

This review discusses the mechanism implicated in peritoneal structural alteration and points to EMT of MC as protagonist and starter of peritoneal membrane injury through the increase of submesothelial fibroblast population. Possible mechanisms of regulation and new targets for inhibition of EMT or its deleterious effects are proposed.

Introduction

Peritoneal dialysis (PD) is a form of renal replacement that has increased during the last years, in parallel to its complications. Currently, prolonged survival on PD has been reached due to technological advances, prevention and early diagnosis of uremic complications. One of the most important issues in PD is the long-term preservation of the peritoneal membrane function.

*Corresponding Author: Manuel López-Cabrera—Unidad de Biología Molecular, Hospital Universitario de la Princesa, Diego de León, 62, 28006-Madrid, Spain. Email: mlopez.hilpr@salud.madrid.org

The peritoneal membrane is lined by a monolayer of mesothelial cells (MC) that have characteristics of epithelial cells and act as a permeability barrier across which ultrafiltration and diffusion take place. Unfortunately, long-term exposure to hyperosmotic, hyperglycemic and low pH of dialysis solutions and repeated episodes of peritonitis or hemoperitoneum cause injury of the peritoneum, which progressively becomes denuded of MC and undergoes fibrosis and neovascularization.\(^1\) Such structural alterations are considered the major cause of ultrafiltration failure.\(^1,2\)

Two main reasons have led to PD-induced sclerosis to become a subject of active research: first, the high frequency of mild degree peritoneal sclerosis (50 and 80%),\(^3,4\) and second the severity and poor prognosis of the so-called encapsulating-sclerosing peritonitis (ESP).\(^4,5\) Fortunately, the frequency of ESP is low (0.5–4.3 cases per 1000 patients per year).\(^5,6\) The severity of ESP and the lack of adequate and proved alternative therapeutic management deserve special attention. However, fibrosis is not the unique structural alteration of the peritoneal membrane induced by PD. In parallel with this alteration, the peritoneum shows a progressive increase of capillary number (angiogenesis) and vasculopathy, which is also related to type-I membrane failure, characterized by elevated transport of water and small solutes.\(^7\) In this context, it has been proposed that local production of vascular endothelial growth factor (VEGF), a potent pro-angiogenic cytokine, during PD plays a central role in processes leading to peritoneal angiogenesis and functional decline.\(^8\)

The pathophysiology of peritoneal functional impairment during long-term PD has remained elusive for long time. Recently, we have demonstrated that, soon after PD is initiated, peritoneal MC from dialysis effluents show a progressive loss of epithelial phenotype and acquire fibroblast-like characteristics.\(^9\) In addition, by immunohistochemical studies of peritoneal biopsies from PD patients, we demonstrated the expression of the mesothelial markers in stromal α-smooth muscle actin (αSMA)-positive myofibroblasts,\(^9,10\) suggesting that these cells stemmed from local conversion of MC. All these biochemical and morphological changes of the MC are reminiscent of those that take place during the EMT, also called trans-differentiation. EMT 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 pseudopodial protrusions and increased migratory, invasive, and fibrogenic features.\(^11\) MC have been considered, for long time, as mere victims of the peritoneal injury during long-term PD, whereas peritoneal stromal fibroblasts have been classically considered as the main cells responsible of the structural and functional peritoneal alterations.\(^9\)

Our most recent findings show a clear association between EMT of MC, synthesis of VEGF, secretion of extracellular matrix components (ECM) and type-I peritoneal membrane failure (our unpublished results). Nowadays, there is no treatment for the progressive thickening and angiogenesis of peritoneal membrane associated with PD. The observation that EMT of MC is a key process in the initiation of peritoneal fibrosis and angiogenesis, opens new insights for therapeutic intervention. The therapeutic treatments may be designed toward either the direct prevention of EMT of the MC or its deleterious effects such as ECM synthesis and/or VEGF production.

**Peritoneal Fibrosis**

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 ESP.\(^3,5\) 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 (SP).\(^2\) Rubin et al\(^12\) described a normal thickness of the peritoneum of 20 μm, but after a few months on PD could reach up to 40 μm (SS). The SP is a progressive sclerosis that is characterized by a dramatic thickening of