Altering peritoneal membrane function: removing the GAG?

Donald J. Fraser¹ and Nicholas Topley²

¹Institute of Nephrology and ²Department of Infection, Immunity and Biochemistry, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK

Correspondence and offprint requests to: Donald J. Fraser; E-mail: fraserdj@cf.ac.uk

Peritoneal dialysis (PD) is a highly effective and convenient mode of renal replacement therapy. The success of PD depends on maintaining the structural and functional integrity of the peritoneal membrane. The outer (serosal) part of the peritoneal membrane consists of a monolayer of mesothelial cells, which provide a low-friction surface, allowing internal organs to move relative to one another. The membrane acts as a selective permeability barrier, regulating the passage of water and solutes between the intravascular compartment and the peritoneal cavity. Duration of PD is often limited by peritoneal membrane failure, associated with increased solute transport, ultrafiltration dysfunction and with characteristic degenerative changes in the peritoneal membrane, including mesothelial cell loss, accumulation of sub-mesothelial extracellular matrix and vasculopathy (Figure 1) [1].

The role of glycosaminoglycans (GAG) in peritoneal membrane function and failure has not been extensively studied, although their potential roles are the subject of recent excellent reviews [2,3]. GAG are long, unbranched polysaccharides. The majority of GAG-containing molecules, including decorin and versican, are proteoglycans, which consist of GAG chains attached to a protein core (Figure 2). Hyaluronan is an important exception, consisting of a simple repeating disaccharide. GAG have an extensive ability to bind water, leading to highly hydrated molecules that lend themselves to various structural roles in connective tissues [4]. However, GAG otherwise vary widely in structure and function. Mesothelial cells cultured in vitro synthesize and secrete GAG [5], and GAG are found in PD effluent fluid following dialysis exchange, particularly relatively small proteoglycans such as decorin and bikunin [5]. The physical properties of GAG suggest that they may play a role in maintaining the integrity of the mesothelial monolayer, by providing a hydrated and low friction surface, allowing internal organs to move relative to one another, and avoiding adhesion formation. To date, however, there is a paucity of data on the expression of GAG within the peritoneal membrane.

In this issue, Osada et al. [6] have examined the expression of proteoglycans in peritoneal membrane biopsies from peritoneal dialysis patients and from normal controls. They examined the expression of decorin, versican and hyaluronan in samples from eight patients at the initiation of PD, five long-term PD patients who had peritonitis for more than one month, and compared these data to expression patterns in three normal subjects.

Decorin has a molecular weight of approximately 100 kD. It is widely expressed in connective tissue, where it binds particularly to type I collagen, and plays an important role in ECM organisation, such that mice null for decorin exhibit abnormalities of collagen fibre formation, and have fragile skin [7]. Decorin also regulates signalling pathways, for example, by down regulating epidermal growth factor receptor [8], and by binding to the prototypic profibrotic cytokine, transforming growth factor beta-1 (TGF-β) and inhibiting its bioactivity [9]. In the current study, decorin expression was highest in peritoneal membrane samples from normal individuals, lower at onset of PD and lowest in long-term PD patients. In long-term PD patients with active peritonitis, decorin was not detectable. The major interest in decorin as a potential anti-fibrotic molecule has arisen largely from studies demonstrating that, secondary to its inhibitory action on TGF-β signalling, it is effective in limiting renal injury in rodent glomerulonephritis when injected [10] or systemically over-expressed [11]. Therefore, one possible consequence of loss of decorin expression in long-term PD might be enhanced TGF-β signalling, suggesting that such a loss of decorin expression might play a causative role in driving peritoneal fibrosis. Indeed, in a murine model of chronic PD fluid infusion, over-expression of decorin limited collagen accumulation, although it is important to note that, in this study at least, this did not lead to any significant changes in peritoneal ultrafiltration [12].

Hyaluronan is a linear GAG that can vary in size from as little as 5 kD to as much as 20 000 kD. It acts as the major lubricant within synovial fluid, and is widely expressed in other connective tissues and extracellular matrices [13]. Interactions of many hyaluronan-binding proteins are important in modelling the extracellular matrix (ECM) in various locations in the body [13]. Through interaction with its major cell surface receptors, including CD44 and RHAMM, hyaluronan also plays a key role in cellular movement and proliferation, in response to injury and inflammation [14], and in malignancy [15]. In the current study, hyaluronan was weakly expressed in normal subjects and at initiation of PD, more readily detectable in biopsies from long-term PD patients, and uniformly strongly present (as evidenced by increased staining) in biopsies from PD patients.
Fig. 1. Pictorial representation of the time course of changes in the peritoneal membrane during peritoneal dialysis. Alterations driven by continuous exposure to dialysis solutions, episodic infection and local chronic peritoneal inflammation lead to extracellular matrix changes (protein, proteoglycan deposition) and vascular alterations (angiogenesis and vasculopathy). Key cellular events are epithelial to mesenchymal transition (of mesothelial cells to myofibroblasts) and the activation of resident peritoneal fibroblast populations. The contribution of alterations to GAG in these processes remain to be fully defined. Images presented courtesy of the peritoneal biopsy registry.

Fig. 2. Structures of versican, decorin, and hyaluronan. Versican and decorin consist of a core protein with attached polysaccharide and oligosaccharide chains. Hyaluronan is a linear polysaccharide. Chondroitin/dermatan sulphate chains consist of up to 100 sugar molecules, with variable sulphation patterns. Hyaluronan is a linear polymer of up to 50 000 sugar molecules, which are unsulphated.
patients with ongoing infection. Many proteins bind extracellular HA (the so-called hyaladherins) and modify its function, and cellular responses to HA may vary depending on expression of HA receptors. Variation in the HA chain length can also have profound effects on cellular response to HA, with high-molecular weight HA implicated in cellular proliferation and healing, while low-molecular weight HA may be profoundly pro-inflammatory [16]. The findings of Osada et al. (NDT insert reference) are intriguing, therefore, and suggest that further studies will be required on the molecular nature of peritoneal membrane HA to draw definitive conclusions about its role in normal peritoneal function, and any contribution alteration in its expression might have in the processes that regulate peritoneal fibrogenesis and membrane dysfunction.

Versican exceeds 1000 kD in size and is highly hydrated. It is widely expressed, interacts with hyaluronan and plays a role in maintaining the structure of the extracellular matrix (ECM) [17,18]. Versican is increased in expression in inflammatory and malignant conditions, where its interaction with adhesion molecules appears to play a key role in the homing of inflammatory leukocytes [18], and may be a key component of metastatic progression [19]. In the current study, versican staining was undetectable in normal subjects, and increasingly heavy in biopsies from patients at PD initiation, long-term PD patients, with and without infection. Versican staining was noted predominantly in areas of fibrosis, the elastic lamina of the peritoneum, vascular walls and perivascular regions. It is possible that versican is involved in PD-associated vasculopathy, adoption of a profibrotic phenotype by mesothelial cells, and in recruitment of non-resident inflammatory cells. Consistent with these potential roles, Osada et al. noted an association between versican staining intensity and macrophage influx, alpha-smooth muscle actin (α-SMA) intensity and matrix metalloproteinase-2 (MMP-2) expression.

This study raises many important questions concerning the role of GAG in peritoneal function and dysfunction. It is tempting to speculate that loss of decorin leads to abnormal collagen fibril morphology and skin fragility. Nephrol Dial Transplant 2007; 27(Suppl 2): S104–S109

References

Conflict of interest statement. None declared.

(See related article by S. Osada et al. Alterations in proteoglycan components and histopathology of the peritoneum in uremic and peritoneal dialysis (PD) patients. Nephrol Dial Transplant 2009; 24: 3504–3512.)


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