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POROELASTIC MODELLING REVEALS THE COOPERATION BETWEEN TWO MECHANISMS FOR ALBUMINURIA

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ABSTRACT

Albuminuria occurs when albumin leaks abnormally into the urine. Its mechanism remains unclear. A gel-compression hypothesis attributes the glomerular barrier to compression of the glomerular basement membrane (GBM) as a gel layer. Loss of podocyte foot processes (FPs) would allow the gel layer to expand circumferentially, enlarge its pores and leak albumin into the urine. To test this hypothesis, we develop a poroelastic model of the GBM. It predicts GBM compression in healthy glomerulus and GBM expansion in the diseased state, essentially confirming the hypothesis. However, by itself, the gel compression and expansion mechanism fails to account for two features of albuminuria: the reduction in filtration flux and the thickening of the GBM. A second mechanism, the constriction of flow area at the slit diaphragm downstream of the GBM, must be included. The cooperation between the two mechanisms produces the amount of increase in GBM porosity expected *in vivo* in a mutant mouse model, and also captures the two *in vivo* features of reduced filtration flux and increased GBM thickness. Finally, the model supports the idea that in the healthy glomerulus, gel compression helps maintain a roughly constant filtration flux under varying filtration pressure.

METHODOLOGY

The function of the kidney relies on microvascular filtration units known as glomeruli (Fig. 1a). To clarify mechanism of albuminuria, a gel compression hypothesis[1] has been proposed to explain the change of permeability between a healthy GBM and a diseased one. We have built the following model to testify the hypothesis. In view of recent studies of the mechanics of basement membranes[2,3], we represent the GBM as a poroelastic gel layer composed of an elastic network and aqueous solvent. we omit the endothelial cells owing to their limited contribution to the size selective filtration, and focus on the GBM and FPs. Fig. 1(b) depicts a quarter of the glomerular capillary, and the computational domain is an annular sector delineated by the two arcs Γ_1 and Γ_2. The filtration flow is driven by the pressure difference between P_1 at Γ_1 and $P = 0$ in the urinary space downstream of the FPs. The flow inside the lumen is inertialess Stokes flow along the radial direction. The GBM is a layer of poroelastic gel, with initially constant fluid and solid volume fractions. As the GBM is deformed by the flow, its volume fraction may vary in time and along the radial direction.

The details of the poroelastic theory and numerical method can be find in our previous studies[4,5].

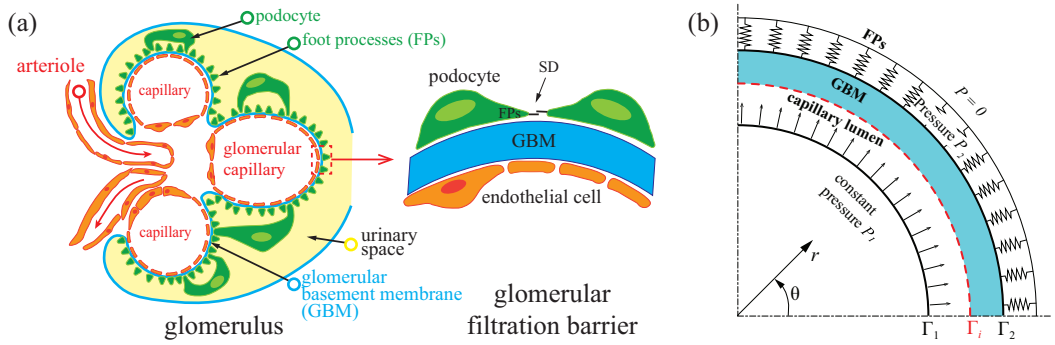

Figure 1: (a) Schematics showing the glomerular filtration barrier in the kidney. Each glomerulus encloses a network of capillaries through which the blood is filtered. The capillary wall consists of a fenestrated endothelium on the inside, a glomerular basement membrane (GBM) and podocytes on the outside. The liquid filtrate passes through the endothelium and the GBM, and flows out through the slit diaphragm (SD) between the foot processes (FPs) of the podocytes into the urinary space. (b) The computational domain is between the arcs Γ_1 and Γ_2. The red dashed line Γ_i represents the interface between the blood in the capillary lumen and the GBM. The filtration is driven by a constant pressure P_1 on Γ_1 and the flow direction is indicated by the array of arrows. The buttressing effect of the FPs is represented by elastic springs pushing on the exit of the domain Γ_2.

To reflect the morphological changes due to FP effacement, we focus on two features. The first is the weakening of the buttress force on the downstream surface of the GBM. The second is the effect of shortened and narrowed SD on restricting the filtration flux. We model the FP buttressing force by elastic springs that resist normal displacement of the GBM's outer surface Γ_2 with a radial normal stress by an elastic coefficient E. The viscous flow across the SD requires a pressure drop which is assumed to be proportional to the local fluid velocity with a friction coefficient μ_D. For the diseased state, E should decrease while μ_D would increase according to the experimental observation[6].

RESULTS

We present here only the most salient results of the study, and a more comprehensive description can be found in our recent paper[7]. Fig. 2 compares the steady-state shape of GBM for the healthy glomerulus and for a diseased glomerulus with softened E and elevated μ_D. The values of E and μ_D for healthy and diseased state have been determined from experimental literature and our own modeling. We can observe the dilation of the capillary and the more porous GBM in the diseased state. These are primarily caused by the softening of FP and also consistent with the gel compression hypothesis and experimental observation by Butt *et al.*[6]. Additionally, we found the thickening of GBM and lower filtration flux. We attribute these two characteristics to the shorting SD, represented by an elevated μ_D. Both were observed in the experiment, but were not explained by the gel compression hypothesis alone. Most interestingly, the shorting SD increases the porosity of the GBM further, which could lead to more serious albuminuria. In summary, the softening FPs and the shortening SD both contribute to the albuminuria.

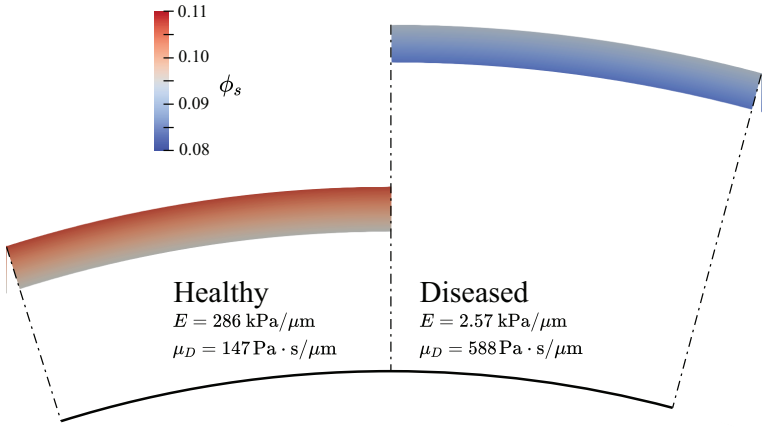

Figure 2: Combined effects of reducing the buttressing modulus E and raising the SD friction coefficient μ_D. Comparison of the GBM morphology and the volume fraction ϕ_s contours.

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