The Inability of Podocytes to Proliferate: Cause, Consequences, and Origin

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ABSTRACT

This study presents a theoretical analysis of the problems related to the inability of podocytes to proliferate. The basis of these problems is the very high rate of glomerular filtration. Podocytes do not in general die by apoptosis or necrosis but are lost by detachment from the glomerular basement membrane (GBM) as viable cells. Podocytes situated on the outside of the filtration barrier and attached to the GBM only by their foot processes are permanently exposed to the flow dynamic forces of the high filtration rate tending to detach them from the GBM. The major challenge seems to consist of the high shear stresses on the foot processes within the filtration slits due to filtrate flow. Healthy podocytes are able to resist this challenge, injured podocytes are not, and may undergo foot process detachment, leading to a gap in the podocyte cover of the GBM. This represents a mortal event. Like a dam break, such a leak cannot be repaired. The ongoing exposure to filtrate flow prevents any attempt to close the gap, thus preventing any regeneration including cell proliferation. An improvement of this precarious situation consists of healing by scarring that may involve only one lobule of the glomerulus, permitting the remaining lobules to maintain filtration. An answer to the question of which waste product requires such a high filtration rate for its excretion may be in the huge quantity of circulating peptides, a problem that dates far back in evolution.

KEYWORDS
glomerular filtration, tensile stress, shear stress, repair of podocyte injuries, excretion of circulating peptides

A renal glomerulus contains a unique type of cell, the podocyte, that, on the one hand, is quite resistant to ischemic and toxic challenges and generally do not die by apoptosis or necrosis, but are lost by detachment of viable cells (Vogelmann et al., 2003; Petermann et al., 2004; Kriz et al., 2013). On the other hand, lost podocytes cannot be replaced by proliferation nor is there definite evidence that they may be replaced by an ingress of progenitors.

Significant efforts have been undertaken to clarify the capacity of progenitors to replace lost podocytes (Pippin et al., 2014; Romoli et al., 2018). In individual cases, authors have successfully shown by lineage tracing studies that progenitor-derived fully developed podocytes intermingle with original resident podocytes. However, so far, the route of podocyte ingress and evidence of the migration itself have not been shown. In contrast, in long-term
in vivo studies in zebrafish, it was found that podocytes are stationary cells and do not move on the glomerular basement membrane (GBM), even if challenged to close areas of bare GBM after podocyte detachment (Endlich et al., 2014; Endlich et al., 2017; Siegerist et al., 2017). Moreover, there is yet no solution to the puzzle of why viable podocytes that are lost by detachment from the GBM need to be replaced by immigrating cells: why do viable detaching podocytes not start a de novo reintegration onto the GBM? Thus, the question is Why is the replacement of lost podocytes impossible—either by local proliferation or by immigration of progenitors?

THE UNIQUE CHALLENGE TO PODOCYTES

Podocytes are an integral part of the filtration barrier and the challenges to them have to be considered in the context of that barrier. Podocytes are firmly attached to the GBM. They seem to be able to adapt, even acutely, to any changes in the area and configuration of the GBM. Podocytes attach to the GBM exclusively by foot processes (FPs) or foot process equivalents called basal ridges (Ichimura et al., 2015). Thus, the entire outer aspect of the GBM is completely covered by FPs bridged by the slit diaphragm forming a completely interconnected homogenous cell layer (Fig. 1). GBM and FPs together may be considered as a giant blanket that covers the entire tuft. Subdivisions that may be ascribed to individual podocytes do not exist.

The two human kidneys produce a filtrate of 180 L/day, that is, a huge fluid flow that has to pass through the filtration surface, and ultimately be channeled to the Bowman’s space through the filtration slits between the FPs. The immense challenge of this flow becomes fully clear when we relate this volume to the amount of tissue, in which filtration occurs. The kidneys are perfused by blood flow of 1.25 L/min, that is, about 400 mL/min blood or 200 mL/min plasma per 100 g renal tissue. Since the vast majority of this blood has to pass through the glomeruli, which makes up about 2% of renal tissue, these high flows pass through 2 g of glomerular tissue driven by the trans-glomerular blood pressure. Since about 20% of plasma is steadily squeezed through the filtration barrier as an ultrafiltrate, 20 mL of fluid is filtered by 1 g of glomerular tissue in every minute, 20-fold its volume. In another way of calculating it, that is, dividing 180 L filtrate/day by two million glomeruli results in 62.5 nL per minute for each glomerulus. Taking a tuft diameter of 150 μm, we obtain a single glomerular volume of 1.8 mL, thus about a 30-fold volumetric flow of the filtrate. These numbers highlight the challenge of the glomerulus to channel the enormous amount of filtrate from inside to outside.

This process leads to two distinct mechanical strains on the filtration barrier, first tensile stress derived from the hydrostatic pressure difference across the barrier (the driving force for filtration) and, second, the shear stress due to filtrate flow (Fig. 1).
THE CHALLENGE OF TENSILE STRESS

The hydrostatic pressure difference across the barrier may reach, even under normal conditions more than 30 mm Hg (Steinhausen et al., 1990) an enormously high value for capillaries. Increases above this value, as in glomerular hypertension, have traditionally been seen as presenting a major challenge to the podocytes. Reducing blood pressure is an essential component of effective treatments that slow the progression of chronic kidney disease. It has been widely believed that the beneficial effect of reducing blood pressure results from the decrease in the tensile stress on podocytes.

Podocytes have been considered as a kind of pericyte, actively counteracting the pressure-derived expansion of the GBM by the contractile tone of their FPs (Kriz et al., 1994). This view has turned out to be wrong. Cell culture studies have shown that podocytes exposed to stretch do not reinforce contractile structures—rather they reduce their stress fibers, a behavior that is fundamentally different from that of cultured mesangial cells (Harris et al., 1992; Endlich et al., 2001). Recently by super-resolution microscopy, Suleiman et al. (2017) have shown that FPs do not contain any myosin (myosin IIA), thus the actin fibers in FPs are not part of a contractile system. Instead, the complex cytoskeleton of FPs serves as the basis for the attachment of FPs to the GBM and the maintenance of their interdigitating pattern, including their adaption to changes in the area of the underlying GBM (Kriz, Lemley 2017). Moreover, the fact that the major route of podocyte loss consists of their detachment from the GBM as viable cells is not compatible with a pericyte function.

The dominant structure capable of generating wall tension to counteract expansion of the capillary under distending pressure would seem to be the GBM (Haraldsson et al., 2008) As a cross-linked filamentous network, the GBM is expected to display a nonlinear elasticity (strain stiffening (Janmey and Miller, 2011) meaning that its distensibility progressively decreases with increasing distension and finally reaches a limit. Thus, the expansion of a glomerular capillary has an upper limit (Kriz and Lemley, 2017a; Kriz and Lemley, 2017b; Kriz, 2018). Stress and wall tension of the GBM will increase further with increasing pressures but without any further expansion, that is, without further expansile challenge to the podocytes. Podocytes, being situated downstream of the GBM, seem to be effectively protected from excessive increases in pressure. Thus, the challenge presented by tensile stress can hardly be the factor that prevents cell proliferation.

THE CHALLENGE BY SHEAR STRESS

The importance of shear stress produced by filtrate flow on the podocyte as an essential parameter of the filtration process was introduced in renal research by Karl-Hans and Nicole Endlich in 2006 (Friedrich et al., 2006) and later more specifically in 2012 (Endlich and Endlich, 2012). Since then, the exposure of podocytes to the shear stress created by filtrate flow has been increasingly acknowledged as the most important challenge to the attachment of podocytes to the GBM. It has become clear that the loss of podocytes by detachment from the GBM as viable cells is ultimately due to the flow dynamic forces of filtration.

The strength of the shear stress depends on the flow rate and the geometry of the slit channel; the narrower the channel or the higher the flow velocity, the greater the shear stress. Filtrate flow exerts shear stress at two sites within the glomerulus: on the lateral walls of the FPs within the filtration slits and on the podocyte cell bodies within Bowman’s space. Taking into account a total glomerular filtrate flow of 30 nL/min (in the rat) the shear stress through 30 nm-wide slits (with a total slit area of 12,000 mm²) has been calculated to be as high as 8 Pa, acting on the lateral walls of the FPs at the level of the slit diaphragm (Endlich and Endlich, 2012). Much lower values of shear stress (~0.05 Pa) have been calculated to act on podocyte cell bodies by filtrate flow through Bowman’s space.

Even if the calculation of the magnitude of shear stress to podocytes produced by filtrate flow must be taken as only approximate, shear stress of filtrate flow represents a major mechanical stress to podocytes tending to detach them from the GBM. Unequivocal evidence for the decisive role of shear stress in the detachment of podocytes has been presented in cases in which podocytes have come to lie within the opening to the proximal tubule. These podocytes are exposed to the shear stress of the total filtrate in a comparatively narrow channel that finally leads to their detachment (Kriz and Lemley, 2015; Kriz, Lemley 2017; Kriz, 2018).

In the context of the present question, the relevance of shear stress on the FPs by the flow of filtrate through the filtration slits is of major importance. As shown in Figure 2, the filtrate flow through the endothelial pores pushes the endothelium toward the GBM. In contrast, filtrate flow through the filtration slits pushes the FPs away from the GBM tending to detach them from the GBM. In an analysis of the effects of the flow dynamic forces (Kriz, Lemley 2017) of filtrate flow through the filtration slits, it was shown that the shear stresses on FPs have a
centrifugal component that is counteracted by the integrin-mediated connections of the FPs to the GBM, and a sideward-directed component that is counteracted by the slit diaphragm mechanically interconnecting the two adjacent FPs (Fig. 2). Failure of these counterforces will lead to detachment of FPs, finally to viable cells being swept away with the filtrate flow. The latter most likely being the major way of losing podocytes.

The attachment of the FPs by integrins and dystroglycans to the GBM as well as the interconnection of adjacent FPs by the slit diaphragm (SD) seem to be mechanically strong. Under physiological and even under perturbed flow conditions (glomerular hypertension, hyper-filtration) the system does not seem to be compromised. It needs a preceding weakening of the podocytes, the slit membrane or the attachment to the GBM (by genetic, toxic, inflammatory factors or likely also by excessive podocyte hypertrophy) for the system to fail, resulting in the disconnection of individual FPs from the GBM followed by a gap in the podocyte cover of the GBM. This must be considered as a mortal event.

A defect in the podocyte cover of the GBM will lead to local uncontrolled high fluid flows (as well as protein leakage), which may be compared with the triggering leak in a dam break. There is no evidence that such a gap may ever be repaired, that two podocytes can approach each other and close the gap by forming an intercellular junction during ongoing filtration. In contrast, a defect in the podocyte cover of the GBM seems to inevitably proceed to the detachment of the concerned podocytes. It makes little sense to consider the loss of a single podocyte since podocytes always have neighbors and the neighbors have

**Figure 2**  Schematics. (A) Showing three glomerular capillaries, their attachment to the mesangium and their cover by a podocyte. The hydrostatic pressure gradient across the filtration barrier (symbolized by a long red arrow) is counteracted (1) by mesangial cells (short red arrows) that insert to the GBM maintaining its folding pattern including the niches that house the capillaries and (2) by the elastic resistance of the GBM that limits the expansion of the capillary lumens reaching an endpoint. (B) Showing the three-layered filtration barrier with the porous endothelium, the GBM and the filtration slits between the FPs bridged by the slit diaphragm (SD). The filtrate flow (hatched lines) pushes the endothelium toward the GBM, in contrast, it pushes the FPs away from the GBM tending to detach them. (C) Showing a filtration slit. The shear stress of filtrate flow to the FPs (curved small red arrows) has a centrifugal component (X) counteracted by integrin-mediated attachment to the GBM and a sideward-directed component (Y) that is counteracted by the interconnection to the opposite FP by the SD. A and B: original drawings; C modified after Kriz, Lemley (2017)
further neighbors that are necessarily included in the detachment process, which finally will affect all podocytes of a lobule.

The detachment of podocytes is a gradual process possibly lasting for weeks or even months (Fig. 3). It seems to be part of a program that subjects an entire glomerular lobule into a scarring process terminating in focal segmental glomerulosclerosis (FSGS). It consists of various mechanisms that, depending on the kind of initial damage, may be involved in various combinations and sequences. They include: (1) foot process effacement; in its initial stage foot process effacement represents a protective strategy aiming at preventing detachment, in its completed stage it becomes an essential part in the program of healing by scarring (Kriz et al., 2013), (2) thickening, wrinkling, and compacting of the GBM by effaced portions of podocytes (in contrast to FPs, effaced podocyte portions of podocytes are contractile having acquired myosin (Suleiman et al., 2017) and of mesangial cells (Kriz et al., 2014), (3) restricting the podocyte-depleted areas of GBM by spreading of effaced portions on the GBM even if a complete closure is impossible, (4) retarding the detachment of podocytes by forming of intercellular junctions between the cell bodies or primary processes to adjacent podocytes that still have widespread contact to the GBM (Kriz et al., 2014), (5) collapse of capillaries possibly by the withdrawal of VEGF stimulation of the endothelium, (6) junctional attachment of podocytes to the parietal epithelium, starting the formation of a tuft adhesion to Bowman’s capsule (Kriz and Le Hir, 2005), (7) immigration of parietal epithelial cells that entrap the concerned lobule excluding it from Bowman’s space and thus from the other lobules (Kriz and Le Hir, 2005; Miesen et al., 2017), (8) production of matrix within the affected lobule, turning it into a segmental scar, that is, healing by scarring to FSGS (Smeets et al., 2009; Miesen et al., 2017).

This complex process seems to keep the areas of bare GBM small, avoiding bulk flows of filtrate and excessive protein loss through large areas of unprotected GBM, even if not always with complete success. Finally, the damaged lobule is removed from the glomerulus as a segmental scar (FSGS) permitting the remaining glomerular lobules to continue with filtration (at least for some time).

In conclusion, shear stress resulting from the high filtrate flow seems to be the decisive reason why a gap in the podocyte cover of the GBM cannot be repaired.

The permanent exposure of podocytes to the filtrate flow prevents the closing of a gap, thus preventing any regeneration including cell proliferation. This leads to the question which waste product requires such a high filtration rate for its excretion, why has nature developed such a precarious situation?

**FIGURE 3** Detachment of a podocyte. A single podocyte (highlighted in violet) in an advanced stage of detachment from the GBM (shown in yellow) that has separated from former adjacent podocytes occupying the entire area between seven capillary loops. Its shape is greatly changed with many pseudocysts (asterisks). For its major part, it attaches to the GBM by effaced cytoplasmic portions. At some sites (red dots), there are gaps in the podocyte cover of the GBM. Note that the capillaries 4, 5, and 6 are partially collapsed associated with wrinkled portions (arrowheads) of the GBM. The connection to neighboring podocytes is effected by tight junctions (arrows). Filtration slits have fully disappeared. Unpublished TEM from rat kidney after excessive growth stimulation (Kriz et al., 2014). Bar: 5 μm

WHICH WASTE PRODUCT OF METABOLISM NEEDS SUCH A HIGH FILTRATION RATE TO BE EXCRETED?

Why mammals, in general, need such high filtration rates, specifically in humans 180 L/day, represents an enigma. Traditionally, this phenomenon has been regarded as an evolutionary heritage from early vertebrates, fishes that lived in freshwater and had to excrete the water that continually permeated into their bodies (Smith, 1953). Nature
has been thought to have conserved this feature so that mammals have adapted the functions to excrete their waste products and to maintain body fluid homeostasis on this basis. This view can hardly be maintained.

As discussed above, the high filtrate flow seems to represent the major mechanical stress on the filtration barrier. To counteract this stress, nature has developed a unique cell type, the podocyte, however, at the price of serious drawbacks: podocytes are unable to proliferate, thus cannot be replaced when lost. This is in distinct contrast to proximal tubule cells, for example. This leads to the conclusion that the high filtration rate must be an indispensable precondition for the excretion of some waste products. Surprisingly, we do not really know for which waste product.

The most widely presumed candidate requiring high excretion rates is nitrogenous end products, especially urea with a concentration of 5 mmol/L in the plasma and up to 500 mmol/L in concentrated urine (Bankir and Trinh-Trang-Tan, 2000). This argumentation is not conclusive when considering that 50% of the filtered urea is already reabsorbed in the proximal tubule. Moreover, even if not proven to exist in mammals, nature has developed active urea transporters (Bankir, 2014).

In my view, a more reasonable cause for the high filtration rates in mammals is the excretion of circulating peptides. It is rarely appreciated that a giant number of peptide breakdown products is present in the plasma, peptides that need to be excreted. Measured by mass spectrometry in the hemofiltrate of patients with chronic kidney disease approximately 5,000 different peptides were found (Richter et al., 1999). Fifty-five percent were fragments from plasma proteins (fibrinogen A 13%, albumin 10%, h2-microglobulin 8.5%, cystatin C 7%, and fibrinogen B 6%). Seven percent represented peptide hormones, growth factors, and cytokines. Thirty-three percent belonged to protein families such as complement factors, enzymes, enzyme inhibitors, and transport proteins. Five percent were unknown peptides. A substantial fraction of all these peptides is filtered into the primary urine and then removed by endocytosis and degraded within the vacuolar apparatus of the proximal tubule (Schuh et al., 2018).

This hypothesis links the high filtration rate to the high re-absorptive capacity of the proximal tubule. Seventy percent of the filtered fluid is reabsorbed in the proximal tubule together with most of the corresponding ions, the handling of which (apart from phosphate) is comparatively unprecise, unrelated to the actual needs of excretion. The specific functions of the proximal tubule consist of the reabsorption of glucose and amino acids, thus taking back valuable compounds that would otherwise be lost, and specifically the excretion of xenobiotics (Koepsell, 2013) and the receptor-mediated endocytosis and degradation of the filtered peptides, thus clearing the plasma of potentially toxic substances. No waste products other than the circulating peptides seem to be obvious that would require such a high filtrate rate to be adequately excreted.

THE NEPHROCYTE

The coupling of these functions—filtration and lysosomal degradation—developed early in evolution and is exemplified in the nephrocytes of insects. Nephrocytes combine a filter system almost identical to that in mammals with an endocytotic lysosomal system in the same cell (Fig. 4; Helmstadter et al., 2017). With every heartbeat, a fraction of the hemolymph is filtered into the basal labyrinthine channels, where peptides are reabsorbed by endocytosis and degraded by lysosomes. During diastole, the filtrate is returned into the hemolymph compartment. Most surprising in this process is the fact that the filtration barrier in nephrocytes contains a layer of foot process equivalents interconnected by a slit diaphragm, which are made up of components identical to the FPs and the slit diaphragm in mammals. The pressure gradients underlying the filtration of the hemolymph are likely extremely low supporting our view that flow and shear stress represent the rheological challenge in the filtration process, not pressure and tensile stress.

UREMIC TOXINS

There is a myriad of solutes that accumulate in the plasma in chronic kidney disease (Glorieux et al., 2015), many of them are considered as uremic toxins though the evidence for this is not always clear (Tanaka et al., 2015). Whether their accumulation is due to decreased filtration rates or due to other filtration-independent reasons is also not always clear. An overview by Fujii et al. (2018) distinguishes three groups: (1) Small watersoluble compounds, such as urea, uric acid, creatinine, and asymmetric dimethylarginine, (2) a large group of peptides with a molecular weight higher than 500 Da such as ANP, Interleukins, and PTH among many others, and (3) protein-bound compounds with a molecular weight above 500 Da including advanced glycosylation end products, Indoxyl-sulfate, p-cresyl sulfate among others. Thus, the accumulation of the second and third groups of compounds may readily be suggested to result from insufficient filtration and degradation in the proximal tubule.
Patients on maintenance dialysis suffer from a substantial morbidity and mortality risk. The contribution of incomplete clearance of toxic peptides by dialysis is not clear. In comparison with conventional high-flux membranes, the use of protein-permeant membranes in dialysis has resulted in greater clearances of low molecular weight proteins and small protein-bound solutes but at the cost of some albumin loss into the dialysate (Ward, 2005). In a more recent study, Latosinska et al. (2018) clearly showed that dialyzers with a higher permeability profile (Revaclear 400) enabled more efficient removal of cell-activating and toxic substances from the blood of patients on hemodialysis than a conventional dialyzer (MCO-CI). The dialysate of the former was clearly less toxic to cultured proximal tubular cells than that cleared by the latter. This benefit could be due to any of the entire spectrum of proteins/peptides including receptors, enzymes, enzyme modulators, immunity proteins, and signaling molecules among others.

Peritoneal dialysis is widely considered as superior to hemodialysis (Dulaney and Hatch Jr, 1984), at least in the
first years as long as the peritoneum maintains its normal structure and filter functions. In this regard, the removal of so-called “middle molecules” is considered to be one of the most beneficial features. Among them, natriuretic peptides, which accumulate in the plasma in chronic kidney disease and may be a factor in cardio-renal-comorbidity, are more effectively lowered by peritoneal dialysis than by hemodialysis (Santos-Araujo et al., 2015; Chao et al., 2018). Thus, the effective excretion of circulating peptides represents an essential part of renal clearance.

CONCLUSIONS

The efficient clearance of ubiquitous circulating peptides may be a major reason for the existence of high glomerular filtration rates in mammals. These high filtration rates are well matched with the capacity of the proximal tubule to clear the filtered fluid of peptides by endocytosis and subsequent lysosomal degradation together with the reabsorption of most of the filtered fluid.

The crucial problem seems to consist of how to channel the enormous fluid flows during filtration from the inside to the outside of the filtration barrier. The filtration slits between podocyte FPs appear to be specifically equipped to counteract the enormous shear stress associated with the high flow rates. The permanent exposure of the filtration barrier to flow dynamic forces likely accounts for the fact that lost podocytes cannot be replaced by any mechanism. Loss of these channels, that is, the formation of a gap in this pattern of filtration slits, will result in local uncontrolled filtrate flows across the filtration barrier. This may be compared to the triggering leak in a dam break that cannot be repaired but will proceed to more severe damage and to the detachment of the neighboring podocytes.

Seen from an evolutionary point of view the development of a filtration barrier necessitated a cell that tolerates the permanent exposure to the flow dynamic forces of filtration at the price that it cannot be replaced in case it fails and is lost by detachment. This basic condition underlies the inability of nephrons to regenerate. Teleologically reasoned, to improve this precarious situation nature has equipped mammals with a rich surplus of nephrons as a reserve (Bertram et al., 2011).

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