The Pathogenesis of Focal Segmental Glomerulosclerosis

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Focal segmental glomerulosclerosis (FSGS) is a histologic pattern of injury on kidney biopsy that can arise from a diverse range of causes and mechanisms. Although primary and secondary forms are described based on the underlying cause, there are many common factors that underlie the development of this segmental injury. In this review, we will describe the currently accepted model for the pathogenesis of classic FSGS and review the data supporting this model. Although the podocyte is considered the major target of injury in FSGS, we will also highlight the contributions of other resident glomerular cells in the development of FSGS.

Key Words: Focal segmental glomerulosclerosis, Podocyte, Parietal epithelial cell, Proteinuria, Glomerular disease

Introduction

Focal segmental glomerulosclerosis (FSGS) is not because of a specific glomerular disease but rather refers to a morphologic/histologic pattern of injury recognized on kidney biopsy that is characterized by sclerotic (fibrotic) lesions in glomeruli that are focal (<50% of all glomeruli affected on light microscopy) and segmental (<50% of the glomerular tuft affected). This pathologic pattern has been further classified by the Columbia group according to specific pathologic light microscopic findings (tip lesion, cellular, collapsing, perihilar, and not otherwise specified) that might have diagnostic and prognostic utility (see review in this issue written by D'Agati and colleagues).[1] Many consider collapsing glomerulopathy to be a separate entity with a very different pathogenesis. This review will focus on the pathogenesis of the more classic forms of FSGS. Clinicians also commonly classify FSGS according to known etiologic factors as a guide to deciding which patients to offer immunosuppression (Table 1). Patients with primary FSGS (no known cause identified to date) often present acutely with severe nephrotic syndrome, whereas secondary forms of FSGS (causes known) typically have a more chronic presentation. There is significant overlap in these clinical presentations, and the development of the sclerotic FSGS lesion in the glomerulus may have common pathophysiological mechanisms. In this review, we will focus on the pathogenesis of the segmental glomerular lesions and analyze the experimental and clinical data supporting this view.

Morphological Studies Place Podocytes at the Center of FSGS

Seminal morphologic studies in experimental animals, by Wilhelm Kriz in the 1990's, laid the groundwork for the current view of pathogenesis for classic FSGS (also called the not otherwise specific variant of FSGS).[2,3] These studies, confirmed in human FSGS that recurs after kidney transplant,[4] have shown that podocyte injury exemplified by cell body attenuation, foot process effacement, pseudocyst formation, and microvillous transformation is the earliest feature of FSGS. In human FSGS, these electron microscopic findings may be seen weeks to months before the development of visible lesions by light microscopy. If the podocyte does not recover from this initial/early injury, the resultant cell death and/or detachment leads to a reduction in podocyte number and a mismatch between podocyte coverage and the underlying glomerular basement membrane (GBM) surface area, leading to "uncovered" bare areas of GBM (Fig 1). Possibly because of the loss of structural support by overlying podocytes at these sites, the capillary loop may bulge toward Bowman capsule (BC) (ballooning), and an early connection (cell bridge) forms between the cells lining BC (the parietal epithelial cells [PECs]) and the podocyte-deprived areas of GBM. Taken together, these studies highlight that the initiating events in classic FSGS are in podocytes. Their contribution to the evolution of the FSGS lesion is well known (and will be discussed subsequently), but other resident glomerular cells participate in the underlying pathogenesis of this lesion.

The glomerular PECs forming the cell bridge can deposit matrix between these bridging cells to form a fibrous attachment (tuft adhesion) between the glomerular tuft and BC (Figs 2 and 3). The tuft adhesion is considered the earliest feature of FSGS seen on light microscopy in human biopsies. A suggested consequence of the adherence of PECs to the naked areas of GBM is the formation of gaps in the parietal epithelium into which glomerular filtrate from attached capillary loops can traverse (misdirected filtration). This leads to stripping of PECs off the Bowman basement membrane (BBM), the formation of proteinaceous pseudocrescents, and the spreading of filtrate along the tubular basement membrane (peritubular filtrate spreading) resulting in tubular atrophy. Accumulation of proteinaceous material in the adherent capillary loop (hyalinosis), the deposition of extracellular matrix, and the accumulation of intracapillary foam cells (lipid-laden macrophages) lead to obliteration of capillary loops, the characteristic lesion of segmental sclerosis.

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Financial Disclosure: The authors declare that they have no relevant financial interests.

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1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2014.05.009

Mesangial expansion because of increased matrix is commonly noted. In FSGS, the sclerosis is by definition segmental and other portions of the glomerular tuft appear normal, although this lesion may progress to global glomerulosclerosis over time. Taken together, FSGS involves several glomerular cell types and other structures, all which will be considered in the overall pathogenesis of this glomerular lesion in this review.

Initiating Mechanisms of Podocyte Injury

With the rapid advances in molecular biology over the last 2 decades, let us now review some of the data supporting this "podocyte depletion model" of FSGS.

Podocyte injury is the earliest morphologic feature of FSGS, which has led to the current paradigm that classic FSGS is primarily a podocyte disorder, at least initially. A wide range of genetic and acquired cellular causative insults have been identified (Table 1). Hyperglycemia and insulin signaling, mechanical stress, angiotensin II, calcium signaling, viral infection, toxins, oxidants, and immunologic injury are all well described. A wide range of disease states can, therefore, lead to the development of the FSGS pattern of injury reflecting the difficulties of classification of this group of disparate conditions. Because of space limitations, we shall highlight 3 of several potential factors that can predispose to the development of the FSGS lesion.

CLINICAL SUMMARY

- Multiple etiologies may lead to the lesion of FSGS.
- A reduction in podocyte number is associated with the development of FSGS.
- Replenishment of podocyte number may repair glomerular injury and prevent the development of FSGS.

Genetic Causes of FSGS: Defects in Constitutive Podocyte Proteins

Genetic studies of familial FSGS have identified multiple disease-causing genes that are primarily expressed in the podocyte. Many of these gene products encode critical structural podocyte elements including the slit diaphragm (nephrin, podocin, CD2AP, TRPC6, GLEPP1, MYO1E), actin cytoskeleton (α-actinin 4, formin, myosin IIA, ARHGAP24, ARHGDIA), or foot process-GBM interaction (LAMB2, ITGA3). Notably, the clinical presentation in each of these disorders is variable. For example, mutations in genes encoding proteins of the slit diaphragm often lead to early-onset disease, whereas gene disorders of the actin cytoskeleton more commonly lead to disease onset in adulthood, suggesting the requirement of additional podocyte insults to generate this condition. Notably, most of these hereditary podocytopathies are resistant to immunosuppression.[5]

Genetic variation in the *APOL1* gene in African-American patients is a major risk factor for the development of FSGS and hypertensive nephrosclerosis and correlates with the rate of progression of both diabetic and nondiabetic kidney disease.[6] The exact mechanisms leading to podocyte injury are yet to be determined; however, ApoL1 is expressed by the podocyte.[7] Notably, these kidney disease-associated ApoL1 variants lyse *Trypanosoma brucei rhodesiense*, and a survival benefit of this polymorphism in Africans (similar to sickle cell trait and malaria) likely contributes to the high rate of kidney disease in this population.

Circulating Permeability Factors

A circulating permeability factor has long been implicated in primary FSGS. The major pieces of evidence supporting this include: (1) primary FSGS can recur very rapidly after kidney transplantation, (2) injection of plasma or plasma fractions from patients with FSGS into rats causes proteinuria, (3) sera from patients with FSGS increase albumin permeability in an isolated glomerulus model ex vivo, and (4) a transient nephrotic syndrome has been transmitted to a newborn from a mother with FSGS (reviewed in McCarthy and colleagues[8]). The soluble urokinase plasminogen activator receptor (suPAR) is a recent candidate. Podocytes adhere tightly to the GBM via interactions between the actin cytoskeleton, integrins α3β1 and αvβ3, and the GBM components laminin 521 and type IV collagen. Wei and others[9] showed that enhanced αvβ3 integrin signaling within podocytes is associated with foot process effacement and the development of proteinuria. They showed that û3 integrin signaling may be activated by both membrane-bound urokinase-type plasminogen activator receptor (uPAR) on podocytes and circulating (soluble) uPAR fragments (suPAR).[10] In uPAR null mice, chronic suPAR overexpression or administration resulted in a glomerulopathy with foot process effacement, proteinuria, and other features of FSGS, which could be ameliorated with an uPAR-specific monoclonal antibody. Although there are questions over the suPAR bioassay, several, but not all, studies have confirmed high levels of suPAR in patients with FSGS (reviewed in Jefferson and Alpers[11]).

Glomerulomegaly and Mechanical Stretch: Podocyte and GBM Mismatch

The podocyte with its contractile actin cytoskeleton plays a critical role in counteracting the hemodynamic forces encountered by the glomerular capillary. According to the Brenner hypothesis of glomerular hyperfiltration, chronic glomerular hypertension leads to progressive glomerular injury that can be ameliorated with blockade of the renin-angiotensin system.[12] In experimental models, chronic hypertension can lead to FSGS, possibly because of the mechanical stretch of podocytes.[13] *In vitro*, mechanical stretch has been shown to lead to podocyte injury with activation of a local renin-angiotensin system,[14] and overexpression of the AT1 receptor within the podocyte causes glomerulosclerosis.[15] Notably, angiotensin inhibition is still renoprotective in models of FSGS where the AT1 receptor has been specifically deleted from podocytes, suggesting other beneficial effects of angiotensin blockade.[16]