Focal segmental glomerulosclerosis (FSGS) is even more complex, as it refers to a morphological pattern that can not only be present in its primary variants, but also occur as a consequence of secondary insults and as a common final pattern of glomerular obliteration.

FSGS is a morphological pattern of glomerular injury primarily directed at the podocyte and defined by the presence of sclerosis in parts (segmental) of some (focal) glomeruli, as observed by light microscopy of a renal biopsy. However, the name itself is misleading. Morphometric analysis of complete glomeruli from renal biopsies obtained from patients with FSGS shows that the volume of the sclerotic lesions averages just 12.5% of the entire glomerular volume. Moreover, as remarked by Sethi et al.2 renal biopsies with <15 glomeruli cannot exclude FSGS with confidence. This is further complicated by the well-known fact that the inner (deep) juxtaglomerular glomeruli are preferentially affected in the early phases of primary FSGS. A biopsy specimen containing only cortical glomeruli may underestimate the frequency of FSGS lesions in the whole kidney. In order to maximise accuracy, the diagnostic caseload should be comprised of consecutive sections selected from 12-15 routinely cut serial sections and should contain a minimum of 8 glomeruli.

Another point frequently overlooked is that the electron microscopy-observed changes are the initial phase of the pathological process; only with time will the characteristic sclerotic lesion develop. This can explain the absence of FSGS lesions in an initial biopsy while a second biopsy, performed months or even years later, clearly demonstrates lesions of FSGS. The bottom line is that the lesion of FSGS observed by light microscopy, which is how FSGS is defined, is not really segmental and is only rarely truly focal in its distribution. While FSGS is not a very common cause of nephrotic syndrome (NS) in the elderly,2 some of these patients may present with NS and an FSGS as the only apparent lesion in optical microscopy. Finally, evaluation of non-sclerosed glomeruli by electron microscopy can be helpful in identifying a primary podocytopathy, and can support the use of immunosuppressive therapy in the setting of widespread foot process effacement.

FSGS caused by mutations in nephrin (NPHS1), podocin (NPHS2), CD2-associated protein (CD2AP), phospholipase C epsilon-1 (PLCe1), and myosin le (MYO1E) is characterised by an autosomal recessive pattern of inheritance. As a rule, the onset of disease occurs in childhood. In contrast, mutations in ACTN4, TRPC6, and INF2 cause autosomal dominant FSGS. In most patients, onset of disease is in adulthood, and many patients do not develop a full-blown nephrotic syndrome. FSGS can also be caused by mutations in genes that encode proteins that are expressed not only in the podocytes but also, or even more so, in other tissues and cell types. In these syndromic forms of FSGS the extrarenal manifestations are most prominent and often diagnostic, and in some of these diseases FSGS may be the only or the presenting manifestation, thus mimicking isolated FSGS. Well-known examples are mutations in the transcription factor Wilms tumour 1 (WT1) and certain mitochondrial mutations.9

**GENETIC CAUSES OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS**

FSGS is a major cause of chronic kidney disease in children and adults. It can occur as a primary disorder (called primary acquired FSGS) as a consequence of genetic mutations in podocyte-specific or slit diaphragm proteins (also called primary genetic FSGS), or as a secondary disorder. In recent years, much of the progress obtained in unravelling the pathophysiological events in FSGS has been focussed primarily on the identification of genetic mutations of membrane and podocyte slit diaphragm proteins and on immune factors, but the real identity of the
primary acquired variant apparently caused by circulating permeability factors remains elusive. In this regard, the role of these permeability factors in the pathogenesis of proteinuria has also shown progress in recent years, although the results are not entirely convincing and appear to lack specificity for a unique type of glomerular disease, as has been found in other glomerular diseases such as minimal change disease and membranous nephropathy.6 Lately, the soluble factor urokinase-type plasminogen activator receptor (suPAR) has become one of the most studied permeability factors with a potential pathophysiologic involvement in FSGS. It is reported to be responsible for the contraction of podocytes and their eventual detachment from the glomerular basement membrane, which denudes it and causes proteinuria in the majority of primary acquired cases of FSGS.7

Abnormally high circulating levels of suPAR have been associated with the pathogenesis of acquired primary FSGS, since approximately two-thirds of patients with acquired FSGS have increased circulating suPAR levels. suPAR then binds to and activates αvβ3 integrin in podocytes by a lipid-dependent mechanism,8 leading to alterations in the morphology and dynamics of the metabolism of podocytes and foot process effacement, detachment and podocyturia, finally resulting in proteinuria and the beginning of glomerulosclerosis, nephrotic syndrome, and renal insufficiency.9,10 According to Li et al.11 steroid responsiveness may be related to the levels of suPAR in some primary FSGS cases. The authors propose a suPAR concentration of 3,400 pg/ml to be used as an optimal cut-off value for corticosteroid therapy.12

What is the cellular origin of this increased membrane urokinase-type plasminogen activator receptor (uPAR) and circulating suPAR in FSGS? Wei et al.13 suggest that neutrophils and monocytes may be culprits, but another possibility is circulating T cells, since there is an association between T cell activation and systemic proteinuria. In turn, and as mentioned above, not all cases of idiopathic acquired FSGS display increased circulating levels of suPAR. This is another confirmation that histological FSGS is not a disease but a form of kidney damage characterized by common histopathological features with different pathophysiologival pathways.14 In other words, FSGS is a morphological description that is denoting podocyte injury; it is a lesion and not a disease.15

With regard to suPAR and FSGS, this concept is not shared by others who question whether elevated levels of suPAR are indeed pathogenic or are merely markers of a split uPAR (CD87) molecule. Moreover, proteinuria does not occur in other clinical settings in which suPAR is elevated.16,17 An elevated concentration of suPAR is not a specific marker of FSGS as levels can also be high in patients with other glomerulopathies, as well as in patients without glomerular derangement. In addition, elevated suPAR levels are not always encountered in recurrences of FSGS following transplantation.18,19 Finally, some authors suggest that it is the presence of suPAR in urine that is the real cause of primary acquired FSGS.20

Various molecules can activate uPAR, including urokinase-type plasminogen activator (uPA), plasminogen, chymotrypsin, various metalloproteinases, and some elastases.21-23 Studies are generally based on the action of these molecules on uPAR but, as suPAR slightly shares the same molecular structure as uPAR, these proteases are also likely to cleave suPAR fragments. Furthermore, suPAR or uPAR are capable, once activated, of catalysing the conversion of plasminogen to plasmin, which is an important molecule in fibrinolytic processes and in the degradation of several extracellular molecules. In the recycling and degradation of the extracellular matrix, in cell activation, migration, contraction, vasculogenesis, and in vitronectin degradation.24-26 This phenomenon may occur in plasma, on the podocyte surface, or in renal distal tubular cells.27-29 It is noteworthy that patients with NS present with elevated serum levels of plasminogen and plasmin, and after being filtered, urinary plasminogen is converted to plasmin by podocyte or distal renal tubular epithelial uPA/uPAR.

At this distal location, plasmin has been reported to function as a regulator of water and sodium absorption, which is a key event in the pathogenesis of oedema, and also as a mediator in calcium tubular transport.30-32 It is known that uPAR is needed to activate the integrin αvβ3 in podocytes, which promotes cell motility and activation of small GTPases that control cell polarization and spreading. When integrin activation is activated, the podocyte contracts and proteinuria ensues. However, it is believed that suPAR has inhibitory properties on adhesion and uPAR-dependent migration but not on cell contraction. Thus, it would be able to interact with αvβ3 integrin, vitronectin, or plasmin.33,34

### PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS: PATHOPHYSIOLOGY: B7-1

A new and provocative proposal recently came onto the scene when expression of the B7-1 molecule on podocytes was found to be present in patients with primary FSGS.35 B7-1 is a 55 kDa membrane-associated protein that, in the glomerulus, is exclusively in podocytes, although it can also be found in renal tubules.20,24 It is better known for its role in the immune system as a co-stimulatory receptor involved in T cell activation.36 Activation of B7-1 by purinergic in cultured podocytes was found to attenuate expression of nephrine and results in foot process effacement and retraction.37 The ability of B7-1 to modulate internal filters capacity also shares similar characteristics when lipopolysaccharide (LPS) is injected into mice, which results in increased B7-1 expression and proteinuria; proteinuria does not occur in B7-1 knockout mice.38 Therefore, the immune stimulatory role of B7-1 within the glomerulus would support the idea that it may modulate immune-mediated injury to podocytes.39

T cells require two signals to become activated. The first signal comes from the interaction between the antigen-presenting cell (APC) and the T cell receptor via the major histocompatibility complex. This signal alone leads to anergy or tolerance.40 The second signal is named the co-stimulatory or accessory signal, and is mediated via interactions between CD28 expressed on CD4+ and CD8+ T cells by abatacept, or CD86 expressed on the surface of T cells and the lymphocyte activation antigens B7-1 or B7-2 (also known as CD86) expressed on the surface of APCs.41 B7-1 modulates the activity of responding CD4+ and CD8+ T cells by alternatively binding to the surface glycoprotein CD28 co-stimulator, which is constitutively expressed on the surface of naive and activated T cells, or the cytotoxic T lymphocyte-associated protein 4 (CTLA 4) co-inhibitor, which is inducibly expressed on both CD4+ and CD8+ T cells upon activation. As mentioned above, podocytes do not express the B7-1 molecule on their extracellular membrane in normal conditions. However, various rodent models of glomerular diseases are associated with an upregulation of B7-1 in podocytes.42-44 In this respect, the podocyte would act as an APC to T cells, which would then activate other T cell populations as well as B cell populations, triggering antibody synthesis and also potentially influencing the synthesis or release of suPAR from leucocytes. These findings and speculations may portend relevant implications for the role the second signal should be playing at the initial steps of the immune response involved in glomerulopathies.

In this regard, there are at least two implications related to the podocyte expression of B7-1. First, the APC role of podocytes in abnormal conditions; second, B7-1+ podocytes have a reduced capacity to attach to the surrounding matrix (the glomerular basement membrane) through β integrin.45,46 Whereas in T cells B7-1 acts by binding to CD28 or CTLA-4 through its extracellular domains, in podocytes the cytoplasmic tail of B7-1 is necessary and sufficient to block β-integrin activation by competing with talin for β-integrin binding.47-50 B7-1+ podocytes change their morphological characteristics and their function, promoting podocyte transformation, B7-1 activation, and the expression of B7-1 integrin and leading to detachment of their foot processes from the glomerular basement membrane, podocyturia, and proteinuria.51 This is a result of the interaction between T cells and podocytes through B7-1 and B7-2. The inhibition of β-integrin activation in podocytes by abatacept could be a potential mechanism that could explain the underlying antiproteinuric action of this drug.52 B7-1 can be detected and measured in the urine and may be a potential biomarker of podocyte injury, but, as mentioned above, its origin could be either urinary or tubular.48,53 Urinary B7-1 mRNA was found to be enhanced in patients with minimal change disease in remission or those in healthy control patients.54 Data from a second study by the same group showed that urinary B7-1 was increased in patients with minimal change disease in relapse compared with patients with minimal-change disease in remission or those with FSGS.55 Additionally, the level of urinary B7-1 mRNA was found to be enhanced in patients with at least one chemical abnormality in a series of healthy patients.56 Promising data describing the utility of urinary B7-1 as a biomarker of
podocyte pathology have been reported; however, the fact that B7-1 can also be derived from tubular epithelium reduces confidence in its specificity. Moreover, immunohistochemical detection of B7-1 technically difficult using paraffin-embedded tissue samples. This highlights the need for the development of improved techniques for routine widespread use.

Recently, Yu et al. administered abatacept in one or two intravenous doses of 10 mg/kg to four patients with recurrent FSGS after kidney transplantation and to one patient with primary FSGS. The patients with recurrent FSGS underwent concurrent plasmapheresis. The conclusions from this study must be taken with utmost caution as only five patients were included. Nonetheless, the results were interesting, and encouraging; these patients experienced a remission that lasted 10-48 months. As the therapy was beneficial, B7-1 staining of kidney biopsy samples from patients with glomerular disease was assessed and podocyte B7-1 expression was observed. In the non-transplant setting, Yu et al. administered abatacept 10 mg/kg on Day 1, 15, and 30, and monthly thereafter, was associated with partial remission and proteinuria decrease at 12 months. Several hypotheses for this response could be proposed. Firstly, abatacept is capable of modulating the immune response by affecting B7-1 and CD28 co-stimulation, which in turn could decrease leukocyte-derived circulating factors, such as suPAR, and consequently protect the barrier function by the urokinase receptor. To my knowledge, abatacept is a specific treatment for FSGS. It is technically difficult using paraffin-embedded tissue samples. Nonetheless, the results were interesting, and encouraging; these patients experienced a remission that lasted 10-48 months. As the therapy was beneficial, B7-1 staining of kidney biopsy samples from patients with glomerular disease was assessed and podocyte B7-1 expression was observed. In the non-transplant setting, Yu et al. administered abatacept 10 mg/kg on Day 1, 15, and 30, and monthly thereafter, was associated with partial remission and proteinuria decrease at 12 months. Several hypotheses for this response could be proposed. Firstly, abatacept is capable of modulating the immune response by affecting B7-1 and CD28 co-stimulation, which in turn could decrease leukocyte-derived circulating factors, such as suPAR, and consequently protect the barrier function by the urokinase receptor.

Abatacept 10 mg/kg on Day 1, 15, and 30, and monthly thereafter was associated with partial remission and proteinuria decrease at 12 months. Several hypotheses for this response could be proposed. Firstly, abatacept is capable of modulating the immune response by affecting B7-1 and CD28 co-stimulation, which in turn could decrease leukocyte-derived circulating factors, such as suPAR, and consequently protect the barrier function by the urokinase receptor. To my knowledge, abatacept is a specific treatment for FSGS. Nonetheless, the results were interesting, and encouraging; these patients experienced a remission that lasted 10-48 months. As the therapy was beneficial, B7-1 staining of kidney biopsy samples from patients with glomerular disease was assessed and podocyte B7-1 expression was observed. In the non-transplant setting, Yu et al. administered abatacept 10 mg/kg on Day 1, 15, and 30, and monthly thereafter, was associated with partial remission and proteinuria decrease at 12 months. Several hypotheses for this response could be proposed. Firstly, abatacept is capable of modulating the immune response by affecting B7-1 and CD28 co-stimulation, which in turn could decrease leukocyte-derived circulating factors, such as suPAR, and consequently protect the barrier function by the urokinase receptor. To my knowledge, abatacept is a specific treatment for FSGS. Nonetheless, the results were interesting, and encouraging; these patients experienced a remission that lasted 10-48 months. As the therapy was beneficial, B7-1 staining of kidney biopsy samples from patients with glomerular disease was assessed and podocyte B7-1 expression was observed. In the non-transplant setting, Yu et al. administered abatacept 10 mg/kg on Day 1, 15, and 30, and monthly thereafter, was associated with partial remission and proteinuria decrease at 12 months. Several hypotheses for this response could be proposed. Firstly, abatacept is capable of modulating the immune response by affecting B7-1 and CD28 co-stimulation, which in turn could decrease leukocyte-derived circulating factors, such as suPAR, and consequently protect the barrier function by the urokinase receptor. To my knowledge, abatacept is a specific treatment for FSGS. Nonetheless, the results were interesting, and encouraging; these patients experienced a remission that lasted 10-48 months. As the therapy was beneficial, B7-1 staining of kidney biopsy samples from patients with glomerular disease was assessed and podocyte B7-1 expression was observed. In the non-transplant setting, Yu et al. administered abatacept 10 mg/kg on Day 1, 15, and 30, and monthly thereafter, was associated with partial remission and proteinuria decrease at 12 months. Several hypotheses for this response could be proposed. Firstly, abatacept is capable of modulating the immune response by affecting B7-1 and CD28 co-stimulation, which in turn could decrease leukocyte-derived circulating factors, such as suPAR, and consequently protect the barrier function by the urokinase receptor. To my knowledge, abatacept is a specific treatment for FSGS. Nonetheless, the results were interesting, and encouraging; these patients experienced a remission that lasted 10-48 months. As the therapy was beneficial, B7-1 staining of kidney biopsy samples from patients with glomerular disease was assessed and podocyte B7-1 expression was observed. In the non-transplant setting, Yu et al. administered abatacept 10 mg/kg on Day 1, 15, and 30, and monthly thereafter, was associated with partial remission and proteinuria decrease at 12 months. Several hypotheses for this response could be proposed. Firstly, abatacept is capable of modulating the immune response by affecting B7-1 and CD28 co-stimulation, which in turn could decrease leukocyte-derived circulating factors, such as suPAR, and consequently protect the barrier function by the urokinase receptor.