INF2 Is Another Piece of the Jigsaw Puzzle for FSGS

York Pei
Divisions of Nephrology and Genomic Medicine, Department of Medicine, University Health Network and University of Toronto, Toronto, Ontario, Canada

doi: 10.1681/ASN.2010121293

Idiopathic FSGS is a syndrome of both immunologic and nonimmunologic etiologies often leading to ESRD.1–2 It is recognized typically by the presence of nephrotic syndrome in association with several varieties of glomerular lesions on light and electron microscopy, which individually are not very specific.3 Up to 40% of patients with FSGS experience a complete remission of their proteinuria in response to treatment with immunosuppressive drugs and have an excellent renal prognosis.2 By contrast, unresponsive patients with high-grade proteinuria are at significant risk for renal progression. There is no reliable means to differentiate between the immune and nonimmune forms of FSGS. Consequently, there is much uncertainty as to the use of immunosuppressive agents (when, if at all, and how much) in FSGS among the clinicians who have to balance the risk of unwanted toxicities from aggressive treatment in patients who might not respond versus the risk for ESRD with inadequate treatment in patients who would.

In this era of molecular medicine, we have also witnessed significant progress in understanding the genetic basis of disease with the hope that this new knowledge will improve diagnostic recognition and mechanism-based therapeutics. To this end, FSGS is also being redefined at the molecular level. By positional cloning, nephrin (NPHS1) was the first gene shown to cause a severe form of congenital nephrotic syndrome.4 Using the same strategy, three recessive (NPHS2, CD2AP, and PLCE1)5–7 and three dominant (ACTN4, TRPC6, and INF2)8–11 disease genes to date have been identified as causes of nonsyndromic forms of familial FSGS. These studies highlight the central role of podocyte dysfunction in the molecular pathogenesis of proteinuric disorders.12,13 Specifically, we now know that nephrin, podocin, CD2AP, the protein products of NPHS1, NPHS2, and CD2AP, respectively, are the main structural elements of the glomerular slit diaphragm.12 TRPC6, encoded by TRPC6, is a calcium channel localized in the membrane lipid complex with podocin that regulates the mechanosensation of the slit diaphragm.10 PLCE1, encoded by PLCE1, is a phospholipase that interacts with nephrin and IQGAP-1, a podocyte cell junction–associated protein.7 By contrast, altered actin bundling seems to play a pathogenic role in familial FSGS associated with ACTN4 mutations.8

To this we now add the recent discovery that mutations of INF2 also cause a form of familial FSGS.11 Inverted formin 2 (INF2) is a member of the diaphanous formin subfamily of actin-regulating proteins that sever actin filaments and accelerate actin polymerization and depolymerization.14 Characteristic of the diaphanous formins, INF2 is regulated by autoinhibition through interaction of an N-terminus diaphanous inhibitory domain and a C-terminus diaphanous autoregulatory domain. Interestingly, all of the missense mutations reported by Brown et al.11 in their families with FSGS and confirmed by Boyer et al.15 in this issue of JASN are located within the diaphanous inhibitory domain region. More recently, a preliminary report by Akilesh et al.16 suggested that a mutation of ARHGAP24, which encodes a negative regulator of Rho GTPases implicated in actin remodeling, cell polarity, and cell migration, may also cause familial FSGS. Collectively, the latter findings on ACTN4, INF2, and ARHGAP24 suggest an important role of cytoskeletal dynamics in the normal maintenance of podocyte function.

What are the clinical correlates of these disease mutations? In general, recessive mutations in NPHS2, CD2AP, and PLCE1 associate with more severe disease with earlier onset proteinuria and ESRD presenting in infancy and throughout childhood, although some milder cases have also been noted.5–7,13 By contrast, dominant mutations in ACTN4, TRPC6, and INF2 associate with milder disease with later onset proteinuria in the second decade and ESRD in the third and fourth decades of life.8–11,13,15 On renal biopsy, both minimal change lesions and FSGS may be found in different affected members from the same family.13,17 With the exception of NPHS2 and INF2, which account for up to approximately 40% and approximately 15% of childhood- and adult-onset familial FSGS, respectively, all of the other disease gene mutations account for only a small fraction of familial FSGS.5–13,15 Similarly, with the exception of NPHS2, which may account for 6 to 17% of sporadic childhood-onset FSGS, all of the other disease gene mutations are quite rare in sporadic FSGS.5–13,15

Looking forward, what can we expect to see in future studies of familial FSGS? It is likely that multiple rare disease genes with large effect size will be discovered in studies of familial FSGS. For example, Ruf and colleagues18,19 have mapped a
recessive gene locus for steroid-responsive FSGS to chromosome 2p with evidence of genetic heterogeneity, and Gbadege-
sin et al.20 have recently mapped another dominant locus for familial FSGS to the same region.

Until recently, the discovery of rare monogenic disease
genese remained a tedious task requiring mutation screening
gene by gene in linkage regions that may contain many genes.
However, this task may be facilitated by the recent availability of
massive parallel DNA sequencing (also termed Next Gener-
ation sequencing).21 Indeed, the application of whole exome or
genome sequencing in combination with a genome-wide link-
age scan can provide a powerful approach in disease gene dis-
cover.22,23 Furthermore, genome-wide gene copy variation represents another complementary approach.24 In
parallel, population-based genome-wide association studies are also promising for detecting polygenes with modest effect
size, as exemplified by the success of a recent admixture study in
identifying a susceptibility/modifier locus for FSGS linked to
MYH9/APOL1 in black individuals.25,26

When more pieces of the jigsaw puzzle for FSGS are filled in,
this knowledge can provide a strong foundation for future develop-
ment of comprehensive molecular diagnostic testing and
mechanism-based therapeutics. Meanwhile, molecular diag-
nostics for FSGS can be readily adapted for testing individuals who are
at risk for familial FSGS when a specific disease-causing mutation
is known. This information may also provide useful guidance to
the clinician in deciding whether a course of immunosuppressive
drug treatment is appropriate. Otherwise, clinical molecular diag-
nostics for FSGS should be used with extreme care especially for
sporadic cases and only in instances in which there is no ambiguity
in interpreting the pathogenicity of the putative mutations; that is,
truncating mutations and highly conserved missense mutations supported by a functional studies.

ACKNOWLEDGMENTS

This work is supported by a grant from the Kidney Foundation of
Canada to Y.P.

DISCLOSURES

None.

REFERENCES

1. Falk R, Jennette C, Nachman P: Primary glomerular disease. In: The
Company, 2000, pp 1263–1332
2. Korbet S: Treatment of primary focal segmental glomerulosclerosis.
3. D'Agati V, Fogo A, Bruijin J, Jennette J: Pathological classification of
focal segmental glomerulosclerosis: A working proposal. Am J Kidney
Dis 43: 368–382, 2004
H, Ruotsalainen V, Morita T, Nissinen M, Herva R, Kashtan C, Peltonen
L, Holmberg C, Olsen A, Tryggvason K: Positionally cloned gene for a
novel glomerular protein—nephrin—is mutated in congenital ne-
Dahan K, Gubler MC, Niaudet P, Antignac C: NPHS2, encoding the
glomerular protein podocin, is mutated in autosomal recessive ste-
A: CD2-associated protein haploinsufficiency is linked to glomerular
Hennes HC, Goyal M, Wharram BL, Schachter AD, Mudermusa S,
Drummond I, Kerjaschki D, Waldherr R, Dietrich A, Ozalit F, Bakkalo-
glu A, Cleper R, Basel-Vanagaite L, Pohli M, Griebel M, Tsygkin AN,
Soylu A, Müller D, Söri CS, Bunney TD, Katan M, Liu J, Attanasio M,
O’toole JF, Hasselbacher K, Mucha B, Otto EA, Arisk R, Kispert A,
Kelley GG, Smrika AV, Guðemmann T, Holzma B, Nürnberg P,
Hildebrandt F: Positional cloning uncovers mutations in PLEC1 re-
 sponsible for a nephrotic syndrome variant that may be reversible. Nat
Genet 38: 1397–1405, 2006
Rodriquez-Pérez JC, Allen PG, Beggs AH, Pollak MR: Mutations in
ACTN4, encoding α-actinin-4, cause familial focal segmental glomer-
9. Winn M, Conlon P, Lynn K, Farrington MK, Creazzo T, Hawkins AF,
Daskalakis N, Kwan SY, Ebersviller S, Burchette JL, Pericak-Vance MA,
Howell DN, Vance JM, Rosenberg PB: A mutation in the TRPC6 cation
channel causes familial focal segmental glomerulosclerosis. Science
308: 1801–1804, 2005
D, Kalluri R, Mundel P, Smith PL, Clapham DE, Pollak MR: TRPC6 is a
glomerular slt diaphragm-associated channel required for normal ren-
Higgs H, Henderson J, Pollak M: Mutations in the forming gene INF2
12. Mundel P, Reiser J: Proteinuria: An enzymatic disease of the podo-
systematic approach for genetic testing and a review of associated
14. Chhabra E, Higgs H: INF2 is a WASP homology 2 motif-containing
formin that severs actin filaments and accelerates both polymeriza-
C, Joly D, Rieu P, Mohsin N, Hennedouche T, Moal V, Gubler MC,
Brouin M, Griebel M, Antignac C: Mutations in INF2 are a major cause
of autosomal dominant focal segmental glomerulosclerosis. J Am Soc
Ruffling in Podocytes and Is a New Candidate Gene for Focal Seg-
mental Glomerulosclerosis [Abstract F-P01880]. Presented at the an-
nual meeting of the American Society of Nephrology, 2010
Graham F, Bembe M, Quares J, Pericak-Vance M, Vance J: Clinical
and genetic heterogeneity in familial focal segmental glomeruloscle-
18. Fuchshuber A, Gribouval O, Ronner V, Kroiss S, Karle S, Brandis M,
Hildebrandt F, APN Study Group: Clinical and genetic evaluation of
familial steroid-responsive nephrotic syndrome in childhood. J Am
E, Hildebrandt F: Identification of the first gene locus (SSNS1) for
Macrophages in Kidney Repair and Regeneration

Jeremy S. Duffield
Laboratory of Inflammation Research, Renal Division, and Center for Lung Biology, Department of Medicine, Institute of Stem Cell and Regenerative Medicine, University of Washington, Seattle, Washington

Published online ahead of print. Publication date available at www.jasn.org.

Appreciation of a central role for recruited monocyte-derived macrophages to repair organs after injury is gaining considerable momentum. In the past 2 years, monocyte-derived tissue leukocytes have been identified as orchestrators of repair in skin, muscle, gut, brain, and heart. Macrophages, however, exhibit considerable plasticity in their phenotype and can polarize into functional states that additionally contribute to tissue injury or fibrosis. These functional states have become known as M1 for pro-injurious functions and M2 for wound-healing functions, but this nomenclature belies the complexity of macrophage diversity. The phenotypic switch that is central to macrophage-directed repair and the effectors of this repair merit further study.

In kidney diseases, monocyte-derived tissue effector cells, known as macrophages, have a bad reputation along with neutrophils as drivers of tissue injury and fibrosis.1 Although this is certainly true and therapies that target injurious macrophages and injurious mechanisms of the innate immune system that wreak havoc inappropriately in our organs are greatly welcomed, it seems that proinflammatory macrophages and neutrophils are the exception that proves the rule.1,2

What is the rule? The innate immune system serves to police our organs and promote repair and regeneration without causing injury. Only in overwhelming circumstances such as infection or severe tissue injury do macrophages activate sterilizing and injurious programs. Macrophages are particularly adept at clearing debris, extracellular matrix, immune complexes, and dead cell products of tissue injury and most of the time perform such tasks silently.3 The same sort of macrophages also seem to have the capacity to release almost every cytokine and growth factor described in the literature. Coordinated release of many of these factors promotes organized tissue regeneration including basement membrane synthesis, cell proliferation, cell migration, and dampening of the inflammatory response.

In some circles, reparative monocyte-derived cells with avidity for microvascular repair are known as endothelial progenitor cells (EPCs). EPCs are now widely described to promote capillary repair and restoration by a number of mechanisms, including canalization of new capillary tracts, temporary (days to weeks) replacement of endothelial cells in areas of denuded capillary basement membrane, new capillary basement membrane synthesis, cytokine release that promotes endothelial cell proliferation, and adoption of pericyte functions.4,5

But can the endogenous reparative functions of macrophages be harnessed for good in the kidney? It seems so. Lee et al.3 in this issue of JASN set out to test whether deliberate manipulation of inflammatory monocyte/macrophages alters the course of injury and repair in kidney ischemia reperfusion injury (IRI). In loss-of-function studies, the authors specifically ablate monocytes and macrophages using a toxic drug encapsulated within liposomes. Ablation at the onset of injury was protective, whereas ablation during the repair phase was deleterious. In gain-of-function studies, they adoptively transferred into the circulation macrophages that were recruited to the injured kidney. Macrophages primed with IFN-γ to adopt an M1 or injurious phenotype exacerbated injury, but adoptively transferred macrophages primed to exhibit a wound-healing phenotype lacked this capacity. Typical macrophage M1 markers such as nitric oxide synthase 2 were found in early kidney injury, whereas typical macrophage M2 markers such as the mannose receptor were detected during the repair phase. The investigators adoptively transferred M1-primed macrophages to the kidney early after injury and then tracked them,