INF2 Is Another Piece of the Jigsaw Puzzle for FSGS

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Inf2 is a protein that is conserved across mouse, rat, dog, cows, and humans. It is a member of the Dbl family of Rho-activating kinases. It is a negative regulator of RhoA and is expressed in most cells, with the highest expression in blood vessels. It has been shown to be important in the development of the cardiovascular system.

Inf2 is also important in the function of podocytes. It is important in maintaining the integrity of the slit diaphragm, which is the protein structure that forms the filter of the glomerulus. When Inf2 is not present or is not functioning properly, the slit diaphragm becomes leaky, allowing protein to leak into the urine. This is the hallmark of FSGS.

In this era of molecular medicine, we have also witnessed significant progress in understanding the genetic basis of disease. By positional cloning, nephrin, IQGAP-1, podocin, and CD2AP have been shown to cause a severe form of congenital nephrotic syndrome. These studies have identified many genes that are involved in the pathogenesis of FSGS.

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 childhood. By contrast, dominant mutations in ACTN4, TRPC6, and INF2 associate with milder disease with later onset proteinuria and ESRD in the third and fourth decades of life.

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 colleagues have mapped a gene to chromosome 14 that is associated with familial FSGS.

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recessive gene locus for steroid-responsive FSGS to chromosome 2p with evidence of genetic heterogeneity, and Gbadegisin et al. have recently mapped another dominant locus for familial FSGS to the same region.

Until recently, the discovery of rare monogenic disease genes 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 Generation sequencing). Indeed, the application of whole exome or genome sequencing in combination with a genome-wide linkage scan can provide a powerful approach in disease gene discovery. Furthermore, genome-wide gene copy variation represents another complementary approach. 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.

When more pieces of the jigsaw puzzle for FSGS are filled in, this knowledge can provide a strong foundation for future development of comprehensive molecular diagnostic testing and mechanism-based therapeutics. Meanwhile, molecular diagnostics 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 diagnostics 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.

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DISCLOSURES

None.

REFERENCES


See related article, “Mutations in INF2 Are a Major Cause of Autosomal Dominant Focal Segmental Glomerulosclerosis,” on pages 239–245.

### Macrophages in Kidney Repair and Regeneration

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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. 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.2 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. When the investigators adoptively transferred M1-primed macrophages to the kidney early after injury and then tracked them,