Distinct roles for the complement regulators factor H and Crry in protection of the kidney from injury

Jennifer Laskowski[1], Brandon Renner[1], Moglie Le Quintrec[2], Sarah Panzer[3], Jonathan P. Hannan[1], Danica Ljubanovic[4], Marieta M. Ruseva[5], Dorin-Bogdan Borza[6], Alexandra H. Antonioli[1], Matthew C. Pickering[5], V. Michael Holers[1] and Joshua M. Thurman[1]

[1]*Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA;* [2]*Department of Nephrology and Renal Transplantation, Lapeyronnie Hospital, Montpellier, France;* [3]*Department of Medicine, University of Wisconsin Madison, Madison, WI, USA;* [4]*Department of Pathology, University Hospital Dubrava, Zagreb, Croatia;* [5]*Centre for Complement and Inflammation Research, Imperial College, UK; and* [6]*Department of Microbiology and Immunology, Meharry Medical College, Nashville, TN, USA*

Mutations in the complement regulatory proteins are associated with several different diseases. Although these mutations cause dysregulated alternative pathway activation throughout the body, the kidneys are the most common site of injury. The susceptibility of the kidney to alternative pathway-mediated injury may be due to limited expression of complement regulatory proteins on several tissue surfaces within the kidney. To examine the roles of the complement regulatory proteins factor H and Crry in protecting distinct renal surfaces from alternative pathway mediated injury, we generated mice with targeted deletions of the genes for both proteins. Surprisingly, mice with combined genetic deletions of factor H and Crry developed significantly milder renal injury than mice deficient in only factor H. Deficiency of both factor H and Crry was associated with C3 deposition at multiple locations within the kidney, but glomerular C3 deposition was lower than that in factor H alone deficient mice. Thus, factor H and Crry are critical for regulating complement activation at distinct anatomic sites within the kidney. However, widespread activation of the alternative pathway reduces injury by depleting the pool of C3 available at any 1 location.

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Correspondence: *Joshua M. Thurman, Division of Nephrology and Hypertension, B-115, 1775 Aurora Court, M20-3103, Aurora, Colorado 80045, USA. E-mail: Joshua.Thurman@ucdenver.edu*

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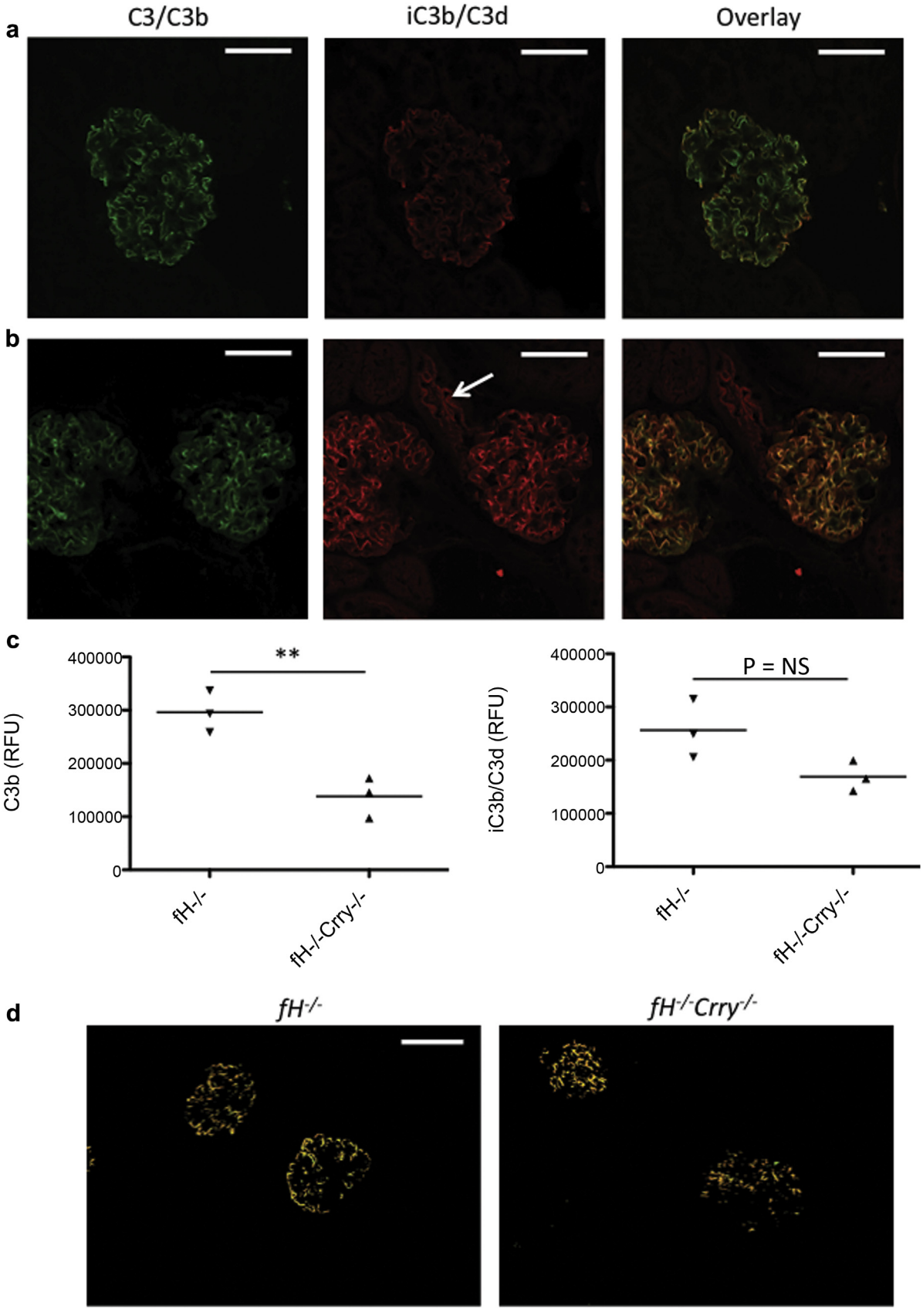
The complement system is an important part of the innate immune system. It defends the host against pathogens and also facilitates the clearance of injured cells and immune complexes.[1] Uncontrolled activation of the complement system can cause inflammatory injury, however, and a group of regulatory proteins controls complement activation on host tissues.[2] Every cell in the body expresses 1 or more of these regulatory proteins, and soluble regulatory proteins (factor H for the alternative pathway and C4 binding protein for the classical pathway) circulate at high concentrations in plasma. There is redundancy in the control of the complement cascade, and most tissue surfaces are protected by ≥1 regulatory protein. Nevertheless, a large number of diseases are associated with genetic mutations and variations in the complement regulators, highlighting the need for the full repertoire of these proteins to prevent pathologic complement activation and autologous injury. Interestingly, systemic defects in complement regulation often manifest with disease that is limited to specific organs, and the kidneys are particularly susceptible to injury in this setting.[3]

A key example of this is C3 glomerulopathy (C3G), a recently described form of glomerulonephritis in which complement proteins are deposited in the glomeruli in the relative absence of immunoglobulin.[4] C3G is associated with numerous different molecular defects that cause systemic alternative pathway (AP) dysregulation, including mutations in the genes for complement regulatory proteins and autoantibodies that block AP regulation.[5–9] Although these defects affect complement regulation throughout the body, patients typically present with isolated glomerulonephritis. Most patients with C3G have C3nef, an autoantibody that prevents degradation of the alternative pathway C3 convertase by factor H.[10] Furthermore, the genetic mutations that have been identified in patients with C3G have most frequently involved the gene for factor H.[5,6,11,12] Mice with a targeted deletion of the gene for factor H ($fH^{-/-}$ mice) develop spontaneous glomerulonephritis with the histologic characteristics of C3G, including abundant C3 deposits along the glomerular basement membrane (GBM).[13]

It is not known why the kidney is so frequently and so uniquely affected in patients with systemic defects in regulation of the AP. Factor H controls AP activation both in the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