Crescentic nephritis—is it in your genes?

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Crescentic glomerulonephritis is frequently associated with a rapid clinical course and poor outcome, particularly if treatment is delayed. The severity of the renal injury and the suboptimal treatment modalities for this disease have provided considerable impetus to studies of the underlying immuno-pathogenic mechanisms. Well-documented variation in susceptibility to crescentic glomerulonephritis between inbred strains of rodents has strongly suggested the influence of genetic predisposing factors in animal models. In mice, susceptibility to crescentic disease in strains showing strong Th1 responses to nephritogenic antigens indicates that genetic factors may operate (in part) through regulation of adaptive T helper subset responses [1,2]. Recent elegant work by Professor Cook and others from Imperial College London has identified genetic factors controlling innate immune responses [3,4] and intrinsic renal cell biology [5] that contribute to the exquisite susceptibility of Wistar Kyoto (WKY) rats to development of crescentic glomerulonephritis.

The work of Behmoaras et al. published recently in Nature Genetics [4] demonstrates that a polymorphism in the promoter region of JunD, the gene for the AP-1 transcription factor JunD, accounts for a significant component of the susceptibility of WKY rats to crescentic glomerulonephritis. It expands previous work by this group that identified seven genetic susceptibility loci (named Crgn1–7) identified in WKY rats [3] may be associated with these augmented mesangial cell inflammatory responses.

Crescentic glomerulonephritis in humans is frequently associated with evidence of autoimmunity, e.g. circulating IgG and aggregated IgG-stimulated activity in rat macrophages. Furthermore, inhibition of JunD using siRNA inhibited LPS-stimulated IL-10, TNF-α and IL-6 production by human macrophages and iNOS expression and Fc stimulated oxidative burst activity in rat macrophages.

Although JunD expression was dysregulated in macrophages from WKY rats [4], dysregulation of JunD was not observed in mesangial cells. This is of interest as previous studies by the same group involving bone marrow and kidney transplantation between WKY and MHC haplotype compatible non-susceptible Lewis rats showed that part of the susceptibility to crescentic glomerulonephritis in WKY rats could be attributed to intrinsic renal cell factors [5]. Cultured mesangial cells from WKY kidneys showed increased basal and TNF-α and aggregated IgG-stimulated MCP-1 production. It is possible that one or more of the other six crescentic glomerulonephritis susceptibility loci (Crgn1, 3–7) identified in WKY rats [3] may be associated with these augmented mesangial cell inflammatory responses.

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anti-neutrophil cytoplasmic, anti-DNA or anti-GBM antibodies. Although these studies in WKY rats did not employ an autoimmune model of crescentic GN, other studies have started to define genetic susceptibility using autoimmune models. Susceptibility to autoimmune anti-GBM glomerulonephritis in WKY rats has been associated with inflammatory and renal factors independent of the MHC haplotype or the gene encoding the autoantigen (α3(IV)NC1) [11,12]. In SCG/Kj mice that develop spontaneous crescentic glomerulonephritis associated with myeloperoxidase-specific anti-neutrophil cytoplasmic antibodies, 14 quantitative trait loci independent of their Fas gene mutation have been mapped [13].

A significant achievement of the work by Behmoaras et al. [4] is their demonstration that an animal model can be used to define specific genetic defects in a complex inflammatory disease by working backwards from a clinically relevant phenotype to a mutated gene. The association of an increased incidence of human lupus nephritis with low copy number of FCGR3B (the human equivalent of copy number polymorphisms of Crgn-1 in WKY rats) [3] demonstrates the potential relevance of studies in inbred rats to human crescentic glomerulonephritis. The next step is to determine if genetic defects in Jund are associated with susceptibility to crescentic glomerulonephritis in humans and, if so, to explore how this knowledge may be used to aid prevention, diagnosis and treatment. It is possible that JunD may be a useful therapeutic target in crescentic glomerulonephritis or that Jund may be a relevant susceptibility gene in other more prevalent human inflammatory diseases (such as atherosclerosis) where macrophages are important mediators of injury.

Nephrologists are starting to appreciate that genetics may play an important role in determining susceptibility to crescentic glomerulonephritis in humans, particularly where autoimmunity is involved. Studies in animal models may provide significant novel insights into the specific genetic loci and the pathogenic mechanisms involved.

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References


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