Necrotizing crescentic glomerulonephritis—a conditional knockout model discloses new therapeutic challenges*

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Keywords: chemokine (C-X-C motif) receptor 4; rapidly progressive glomerulonephritis; von Hippel–Lindau tumour suppressor protein

Necrotizing extracapillary glomerulonephritis is considered the histological hallmark of pauci-immune renal vasculitis, a potentially life-threatening condition, in which glomerular involvement is mostly rapidly progressive [1]. A timely therapeutic intervention is mandatory to avoid the establishment of end-stage renal disease in a short period of time. First-line treatment consists of steroids and immunosuppressive drugs at high dosages that have radically improved the disease’s prognosis, but that remain charged by frequent relapses, the appearance of side-effects, and do not obtain remission in 10% of the cases, with dramatic consequences for the patient [2].

Circulating anti-neutrophil cytoplasmic autoantibodies (ANCAs), present in about 90% of the cases, have been implicated in the pathogenesis of the disease most convincingly by Xiao et al. [3], whereas a compelling pathogenetic hypothesis is still missing for either ANCA-negative cases or for situations in which remission is accompanied by the persistence of high ANCA titres [1,4].

In the September 2006 issue of *Nature Medicine* [5], the group of Susan Quaggin proposes an alternative, completely unexpected mechanism, whereby podocytes become the main players of the disease because the glomerular lesion is triggered by an intrinsic podocyte defect.

The study shows that specific podocyte deletion of VHL, the gene encoding for von Hippel–Lindau tumour suppressor protein, leads to the appearance of a rapidly progressive glomerulonephritis (RPGN), clinically characterized by acute renal failure, and histologically marked by features of crescentic glomerulonephritis that, importantly, is also necrotizing, as demonstrated by glomerular fibrin deposition. Mice are ANCA-negative, nephritis occurs by the age of 4 weeks, and inevitably leads to death of all animals by 7 weeks.

VHL is a crucial gene involved in the pathogenesis of renal cell carcinoma, a fact that incidentally might also explain the frequent association of this neoplastic disease with crescentic glomerulonephritis [6]. VHL is a recognition subunit of an E3 ubiquitin protein ligase complex that targets proteins for proteasome degradation [7]. Of relevance, VHL protein product interacts with hypoxia-inducible factor 1 (HIF-1), a master governor of oxygen homeostasis, whose oxygen-regulated z-subunit is proteasome-degraded in normal conditions, right through its VHL interaction [8]. Among HIF-1-z target molecules, several have been already shown to participate in glomerular damage in renal vasculitis, such as tumour necrosis factor-z (TNF-z) (Figure 1), vascular endothelial growth factor-A (VEGF-A), and especially considered in the present manuscript, the chemokine (C-X-C motif) receptor 4 (CXC-R4) and its ligand stromal cell-derived factor-1 (Sdf-1) [8–11].

Here the authors are able to elegantly demonstrate that loss of VHL leads to the increased expression of HIF-1-z, and consequently of CXC-R4 and Sdf-1.

Furthermore, they take the opportunity to reveal that, at least in this model, glomerular crescents are composed by podocytes. This is a very important side result, not easily reachable with other, not genetic manipulating approaches, because podocytes that leave the glomerular basement membrane and start proliferating to form the crescent probably de-differentiate, and are no longer identifiable by classical specific markers, whereas they acquire a different, probably more epithelial phenotype [12].

In the past years, many authors have dealt with the cellular origin of extracapillary proliferation, and
crescents have been often proposed to be formed by the parietal cells of the Bowman’s capsule. Our group, among others, has mainly focused on the participation of numerous monocyte-macrophages in necrotizing extracapillary lesions that represent a distinctive feature of necrotizing lesions from idiopathic, non-necrotizing, extracapillary glomerulonephritis [13]. Instead, from recent work and again by using a genetic approach, it has been demonstrated that podocytes can contribute to crescent formation [14].

As for the chemokine receptor CXC-R4, the authors of the manuscript have constructed transgenic mice that selectively express this chemokine receptor within their podocytes. Although not affected by a true extracapillary nephritis, these mice prove that de novo expression of CXC-R4 alone is sufficient to cause glomerular disease. On the other hand, CXC-R4 role in RPGN seems to be central, because treatment of VHL-conditional knockout mice with anti-CXC-R4 antibodies is effective in preserving renal function and avoiding mice death. Furthermore, the authors extend their observation to humans, where a diffuse and intense upregulation of CXC-R4, not limited to the glomerular extracapillary lesions, is evident by immunohistochemistry in RPGN human biopsies, which is paralleled by the increase of its mRNA, obtained from human RPGN glomeruli and studied by both cDNA microarrays and real-time RT-PCR.

That this mechanism could be relevant to human RPGN seems also to be confirmed by previous observations, demonstrating that signalling through the CXC-R4–Sdf-1 pathway is enhanced also by other molecules [15], which are well known to be directly involved in human necrotizing extracapillary lesions, namely the adhesion molecules ICAM-1, and especially, at least in the experience of our group, VCAM-1 [16]. So, we can infer that independently of the specific initiation factor demonstrated by this model, which is based on the selective deletion of VHL from podocytes, we are facing a more generalized mechanism that could be targeted by specific therapies.

In summary, the work presented here not only gives confirmatory data on the role of podocytes in crescent formation, but also and more importantly, provides at least two potential new paradigms for human RPGN pathogenesis and treatment.

First, a necrotizing crescentic glomerular lesion can be due not only to a primary endothelial damage, followed by an ‘inside–outside’ involvement of the other glomerular cell components, but also to a primary podocyte defect and a consequent ‘outside–inside’ glomerular damaging mechanism, that could represent the first reasonable explanation for ANCA-negative cases.

Second, independent of the initial triggering factor, activation of the CXC-R4–Sdf-1 system, either induced by HIF-1-α, or by adhesion molecules such as ICAM1 and VCAM1, appears to be a possible common pathway in human necrotizing extracapillary glomerulonephritis, that could be specifically targeted by new therapies, making it possible to envisage immediate benefits at least for cases resistant to traditional immune suppression.
Conflict of interest statement. None declared.

References


Received for publication: 30.10.06
Accepted in revised form: 29.11.06