CONFLICT OF INTEREST STATEMENT

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Novel target in the treatment of RPGN: the activated parietal cell

Marcus J. Moeller and Bart Smeets

Correspondence and offprint requests to: Marcus J. Moeller; E-mail: mmoeller@ukaachen.de

Division of Nephrology and Immunology, University Hospital of the Aachen University of Technology (RWTH), Aachen, Germany

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Iyoda et al. have provided strong experimental evidence for beneficial effects of PDGF signalling inhibition in two seemingly unrelated glomerular diseases: rapidly progressive glomerulonephritis (RPGN) in the present study and focal and segmental glomerulosclerosis (FSGS) in a previous study. Novel insights into the pathogenesis of these two diseases have unravelled a common cellular mechanism: activation of parietal epithelial cells (PECs). In addition, recent studies have shown that PDGF signalling is sufficient to mediate the PEC activation and formation of cellular crescents, the hallmark of RPGN. In this comment, we make an attempt to assemble the pieces of the puzzle arguing that the activated PECs might play a significant role and could represent a target for novel treatment strategies for RPGN and FSGS.

Rapidly progressive glomerulonephritis (RPGN) is characterized by proliferating cells within Bowman’s space, which typically form crescentic accumulations. RPGN is associated...
with a rapid and often irreversible loss of renal function. For this reason, it is regarded as a medical emergency requiring immediate diagnosis and treatment. The relatively non-specific treatment with a combination of high-dose steroids and cyclophosphamide is effective but also bears a significant risk of potential side effects such as myeloid toxicity, immunosuppression and subsequent infectious complications or long-term toxicity such as neoplasms. In the past decades there has been relatively little progress to improve the treatment for the disease entity of RPGN.

In this issue, Iyoda et al. [1] present experimental evidence for a beneficial therapeutic effect of imatinib in a rat anti-glomerular basement membrane glomerulonephritis model. Imatinib (Gleevec®) is an inhibitor of tyrosine kinase phosphorylation with some specificity for c-Abl, c-Kit and PDGF receptors. It was introduced to treat specific forms of leukaemia or gastrointestinal stromal tumours.

The present study builds on a previous study published in 2009, where the authors showed that the administration of imatinib ameliorates anti-GBM nephritis [2]. Importantly, the authors found that imatinib was still beneficial when it was administered beginning from Day 7 after the induction of the disease. The first 7 days of anti-GBM nephritis are characterized by endocapillary necrosis with thrombotic occlusions of individual capillary loops due to endothelial injury. Extracapillary proliferations and formation of cellular crescents start to form around Day 7 when imatinib exerted its effect during this proliferative phase.

The present study in this issue by Iyoda et al. [1] is a follow-up study where the authors have now investigated the long-term outcome (i.e. the degree of interstitial fibrosis) of their experimental animals up to 50 days after disease induction. As outlined in more detail below, the extent of interstitial fibrosis is a good parameter to evaluate the sum of glomerular disease activity, which happened throughout the entire course of the disease. Iyoda et al. confirmed that imatinib indeed ameliorated interstitial fibrosis in the anti-GBM model consistent with their previous findings.

In addition, they show that imatinib only needs to be administered over a relatively short time frame, i.e. from Days 7 to 13, which is the proliferative phase of the anti-GBM model.

This leads us to two interesting questions: by which molecular mechanism might imatinib exert its beneficial effect on RPGN, and are immune cells truly the primary targets for imatinib or might there be other candidates?

Recently, novel insights into our understanding of the pathogenesis of RPGN have been achieved: the inflammatory stimuli (i.e. antibody deposition, release of inflammatory mediators and endocapillary necrosis) result in rapid cellular activation of glomerular parietal epithelial cells (PECs) and podocytes. In lineage tracing experiments, it could be shown conclusively that activated PECs start to proliferate beginning from Day 7 and form early cellular crescents (i.e. extracapillary proliferations) [3]. Activated podocytes also contribute to early cellular crescents [4, 5]. They reach the inner aspect of Bowman’s capsule via adhesions [6]. Cellular crescents have been shown to cause irreversible and acute loss of renal function by blocking the flow of the primary filtrate into the proximal tubule [7]. Once the flow of urine is blocked the connected tubule degenerates rapidly [7]. This sequence of events is relevant for the significance of the present study by Iyoda et al. [1]. In their study, imatinib treatment ameliorated interstitial fibrosis, which directly correlates with the amount of individual tubuli that have been obstructed by cellular crescents and subsequently degenerated. For this reason, it can be concluded that imatinib reduced cellular crescent formation.

In mice, infiltration of cellular crescents by a fibrocellular infiltrate consisting primarily of macrophages/monocytes and fibroblasts occurs subsequently from the periglomerular area through breaches of Bowman’s capsule [8] but it can also occur directly from the glomerular capillaries [9]. In summary, activated proliferating glomerular epithelial cells (most importantly PECs) play an important role in the formation of cellular crescents and determine renal survival (Figure 1, RPGN).

So far, basically all therapeutic strategies for RPGN have aimed at suppressing the immune system. There are studies indicating a direct effect of imatinib on the lymphatic system, primarily monocytes/macrophages and T cells [10–19]. In mice (and rabbits), a significant contribution of monocytes/macrophages to early cellular crescents (i.e. during the first 14 days of induction) has been ruled out [3, 4, 7, 20]. In rats, the contribution of macrophages to cellular crescents is still unclear, since lineage tracing experiments are not possible so far and the use of immunohistological markers has proved to be unreliable due to ‘metaplastic events’ [21, 22]. In humans, formation of cellular crescents usually occurs over a longer period of time and is ‘asynchronous’, so that the role of infiltrating monocytes/macrophages in initiating crescent formation is difficult to investigate.

Long-term treatment with imatinib causes myelosuppression [23]. However, overall the experimental evidence for a

**FIGURE 1:** Activation of parietal epithelial cells (PECs) represents a common pathophysiological phenomenon in two very different glomerular diseases: rapidly progressive glomerulonephritis (RPGN) and focal and segmental glomerulosclerosis (FSGS). As outlined in this article, imatinib might exert its beneficial effect on both diseases by inhibition of the PEC activation.
pronounced immunosuppressive effect of imatinib is not very strong and the clinical experience with patients receiving short-term imatinib treatment does not indicate a significant immunosuppressive effect, either [24].

There are experimental indications suggesting that imatinib acts directly on intrinsically glomerular cells, specifically on activated PECs forming the crescental cell. The primary target for imatinib is the PDGFβ receptor. Van Roeyen et al. [25] over-expressed a selective activator of the PDGFβ receptor specifically in podocytes. This activator was coupled to GFP, preventing its backfiltration across the glomerular filtration barrier. Thus, it exerted its effect primarily on PECs and podocytes. Van Roeyen et al. observed the formation of cellular crescents in this transgenic mouse model in a gene-dosage-dependent fashion. This study shows that a functional PDGFβ receptor is expressed on PECs and that it is sufficient to mediate the activation and proliferation of these cells.

A direct effect of imatinib on activated PECs is also consistent with the finding that it was sufficient to inhibit PDGF signalling for only 7 days during the proliferative phase of PEC activation (i.e. from Days 7 to 13 of the anti-GBM nephritis model) [1, 2].

One more interesting study by the group of Iyoda suggested a direct effect of imatinib on activated PECs, which might appear unrelated at a first sight. In a rat renal ablation model for focal and segmental glomerulosclerosis (FSGS), they have shown that the inhibition of PDGF signalling by a related small molecule inhibitor nilotinib can prevent progression of sclerosis [26]. In this model, there is a general consensus that glomerular sclerosis is primarily mediated by haemodynamic effects and that the immune or lymphatic system plays no major role. In particular, there are no monocye/macrophages involved in glomerulosclerosis. Recently, it was shown that in FSGS, PECs are also focally activated to then participate in the scarring process [27, 28]. Activated PECs can be observed within the sclerotic lesions of essentially all forms of FSGS, primary or secondary (own unpublished observations). Therefore, an unexpected parallel links RPGN and FSGS: the activated PEC. It can be speculated that PDGFβ inhibition likely also inhibited the PEC activation in this FSGS model (Figure 1).

Other therapies that aim at directly inhibiting the activation and proliferation of glomerular epithelial cells have also recently emerged, most significantly, the inhibition of the epidermal growth factor (EGF) [29]. Here, the direct effect of EGF signalling on glomerular epithelial cells was already shown by cell-specific knock-out models.

In summary, pieces of the puzzle can be assembled to open up potentially exciting possibilities for novel treatment strategies for RPGN and FSGS. Iyoda et al. have provided strong experimental evidence for beneficial effects of PDGF signalling inhibition in two seemingly unrelated glomerular diseases (RPGN and FSGS). Novel insights into the pathogenesis of these two diseases have unravelled a common cellular mechanism: activation of PECs. In addition, recent studies have shown that PDGF signalling is sufficient to mediate the PEC activation and induction of RPGN. We believe that it is time to move ‘from bench to bedside’ to test whether this novel therapeutic concept is also useful for patients.

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