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In Context

IN CONTEXT

Inhibition of clonal expansion of parietal epithelial cells and crescent–podocyte transition in severe glomerulonephritis: on the way to targeted therapy?

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The human kidney possesses progenitor cells in the glomerular and tubular compartments of the nephron, capable of self-renewal, proliferation and differentiation. They maintain daily homeostasis and are involved in endogenous regenerative processes following injury [1]. However, defective or abnormal regenerative responses of these cells can result in pathological conditions [2].

The study by Melica *et al.* [3] found that parietal epithelial cells (PECs) are renal progenitor cells with similarities to the bone marrow stem cell niche. In keeping with hematopoietic stem cells in a quiescent state, podocytes also produce high amounts of CXCL12 to keep renal progenitor cells quiescent and undifferentiated [4]. In addition, the local presence of high amounts of vascular endothelial growth factor and transforming growth factor β contributes to both renal progenitor and hematopoietic stem cell survival [5, 6]. As this study demonstrates [3], crescents develop from clonal proliferation of an immature PEC subset similar to hematopoietic stem cell disorders such as myelodysplastic syndrome, leukemia or myelofibrosis.

With the aim of mitigating clonal expansion of PECs into crescents, three therapeutic agents used in the management of hematologic malignancies were tested. Panobinostat and givinostat are histone deacetylase inhibitors (HDACi), while ruxolitinab is a Janus kinase 1/2 inhibitor. HDACi regulate the expression of genes that are involved in diverse cellular pathways, by inducing acetylation of histones and nonhistone proteins [7]. Panobinostat is a non-selective HDACi with its anti-tumor effects primarily demonstrated in patients with multiple myeloma (MM) [8, 9]. Therapy with panobinostat prolonged median progression-free survival when added to intravenous bortezomib and oral dexamethasone in relapsed or relapsed and refractory MM patients [10], and received transient Food and Drug Administration approval in 2015.

In this study, only panobinostat was shown to reduce crescent dimensions and induce immature PECs' differentiation into new mature podocytes which restore injured glomerular filtration barrier (Fig. 1). Panobinostat strongly decreased proteinuria, and improved excretory kidney function in mice who were injected with anti–glomerular basement membrane serum, which was used to induce crescentic glomerulonephritis. Its renoprotective capacity was also shown after treatment delay of 4 days. Mice treated with panobinostat achieved complete remission at 90 days of follow-up.

Furthermore, the authors aimed to identify underlying mechanistic steps leading to efficacy of panobinostat. The crescent-forming PEC subset in humans was found to be characterized by expression of CD133, a marker of renal progenitor cells, and stratifin, a cell cycle checkpoint protein involved in stem cell proliferation/differentiation. Their expressions were significantly higher in the glomeruli of patients with ANCA-associated vasculitis and lupus nephritis compared with healthy controls, and lower expression of $CD133^{+}$stratifin^{+} cells in their crescents correlated with favorable long-term outcomes. In addition, patients with good renal outcomes showed a higher percentage of $CD133^{-}$stratifin^{-} cells in their crescents. Panobinostat was shown to down-regulate stratifin in stratifin-expressing

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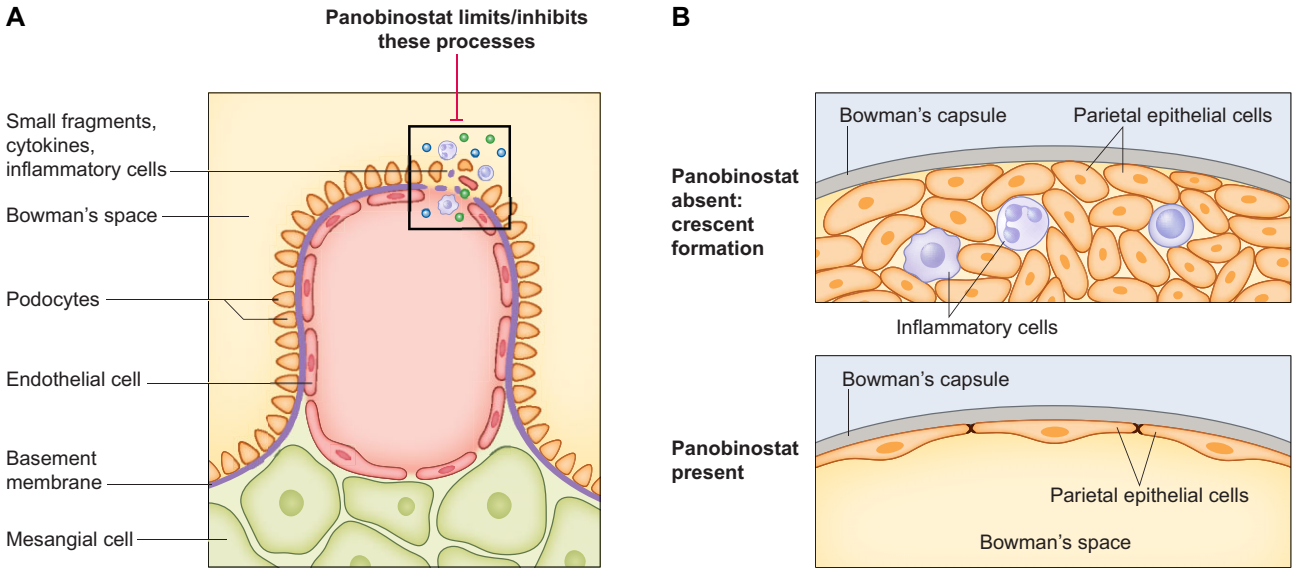

Figure 1: Disruption of the glomerular basement membrane and release of cytokines into Bowman's space, leading to an inflammatory response and eventually crescent formation (A). This process can be mitigated by panobinostat. Crescent formation is a consequence of an inflammatory influx of interstitial immune cells secreting cytokines and circulating immune cells. PECs are activated and form crescents in combination with inflammatory cells deposited in crescents.

human PECs, and in contrast, up-regulation of podocyte-specific markers including *NPHS1* or *NPHS2*.

Efficient differentiation of renal progenitor cells into podocytes might determine the outcome of glomerular disorders presenting with crescentic lesions, showing that remodeling of glomerular architecture is possible and does not necessarily follow a transition from acute lesions to chronic damage. Thus, panobinostat could be a promising treatment option in patients with crescentic glomerulonephritis and eventually podocytopathies. Serious hematological and other systemic adverse events as reported in previous studies might limit its use in glomerular diseases, and further research is warranted to confirm its efficacy and safety (Fig. 1).

CONFLICT OF INTEREST STATEMENT

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