Is there a role for proximal tubular cells in regulating dendritic cell maturation and function in renal disease?

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Dendritic cells (DCs) are professional antigen-presenting cells that play a unique role in the priming and activation of effector T cells, but under certain circumstances, they might also protect against a detrimental inflammatory response by mechanisms, which are not yet well characterized. Landmark studies by the Kurts group demonstrated that under homeostatic conditions the mouse kidney contains an extensive network of DCs that are almost exclusively localized in the tubulointerstitium, which ensures complete surveillance of the kidney, to protect it against infections ascending through the tubular system [1]. Under inflammatory conditions such as human and experimental glomerulonephritis (GN), bone marrow-derived monocytes enter the inflamed tissue and give rise to monocyte-derived DCs [2, 3] that form perilumeral rings around inflamed glomeruli [4, 5] and are capable of producing inflammatory cytokine-like tumour necrosis factor α (TNF α) [6].

Functional studies in murine models of renal diseases provide strong evidence that DCs are capable of directly instructing immune effector cells, thus orchestrating the immunological response within the kidney. Interestingly, in the early stage of nephrotoxic nephritis, a murine model of crescentic GN, DCs attenuate renal inflammation [7], whereas at later stages they mature and efficiently present antigens to CD4+ T cells, thereby inducing a harmful nephritogenic Th1 immune response [8]. The potential pro- and anti-inflammatory role of DCs seems to be highly dependent on the surrounding environment and the activation status of DCs; for example, murine and human hepatic stellate cells (but not hepatocytes) prevented the activation of naïve T cells by DCs in the liver [9]. However, not much is known about the influence of resident renal cells on the phenotype and functional development of renal DCs under steady-state or inflammatory conditions, in particular in humans. A better understanding could lead to new therapeutic approaches.

In this issue, Kassianos et al. describe a previously underestimated cross-talk between human proximal tubular epithelial cells (PTECs) and autologous DCs. The authors isolated human PTECs from donors who underwent tumour nephrectomy, and showed that blood-derived CD14+ monocytes (from autologous blood samples) cultured in vitro and matured into DCs retain an immature monocyte-like phenotype when co-cultured with human PTECs (Figure 1). Furthermore, functional characterization of these cells revealed an anti-inflammatory phenotype in terms of a decrease in inflammatory cytokine production upon TLR3 stimulation and a reduced ability to stimulate T-cell proliferation and polarization [into a potentially nephritogenic interferon (IFN)-γ producing Th1 type]. These findings and a previous study published in NDT by the same group show that PTECs are capable of directly inhibiting autologous T- and B-lymphocyte immune responses [10], indicating that PTECs interacting with infiltrating immune cells could attenuate renal inflammation.

In a recent publication, Lee et al. further emphasized the potential function of tubular cells in the regulation of the inflammatory response in renal disease. The authors analysed the functional role of macrophages in the course of acute kidney injury and demonstrated that murine pro-inflammatory M1 macrophages can be directly modulated by murine tubular cells to express markers of the anti-inflammatory M2-type macrophages, which have been shown to provide protection against an overwhelming immune response [11].

In addition, it is known that kidney tubular cells express granulocyte-macrophage colony-stimulating factor (GM-CSF), thus contributing to the maturation of resident GM-CSF receptor-expressing DCs, which are subsequently able to activate T cells and cause them to exert their pathogenic effects [12–14]. Furthermore, it has recently been shown that co-cultured, bone marrow-derived DCs can acquire and process albumin that was reabsorbed by tubular cells from the ultrafiltrate. In this way, antigenic epitopes for cross-presentation to nephritogenic CD8+ T cells might be generated [15].

This indicates that the interaction of tubular cells and DCs might be a two-edge sword contributing to both pro- and anti-inflammatory effects in kidney disease. It is therefore of central importance to better identify and characterize the underlying mechanisms that drive the functionally relevant interaction between mononuclear phagocytes (macrophages/DCs) and PTECs. Kassianos et al. hypothesized that direct cell-to-cell contact might critically drive the interplay between DCs and PTECs.
The authors discussed preliminary results suggesting that monocytes that matured in contact-independent PTEC co-cultures did not have a substantial effect on monocytes/DC activation and maturation (data not shown). In this context another recently published study by Kronsteiner et al. [16] is also of great interest. Using a very similar approach, the authors were able to demonstrate that fully differentiated human renal tubular cells are capable of inhibiting the maturation and differentiation of monocyte-derived DCs and of stimulating monocyte-derived cells to produce interleukin-10 in vitro. Unlike Kassianos et al., however, they used a Transwell® system and indirect co-cultures to avoid direct cell-to-cell contact. The authors noticed that soluble human leukocyte antigen-G (sHLA-G) was exclusively detectable in co-cultures consisting of renal tubular cells and monocytes, but not in control co-cultures. sHLA-G has been implicated to be beneficial in autoimmunity [17]. Thus, a soluble factor like sHLA-G might play a pivotal role in controlling immune responses, which needs to be verified in further studies.

In addition, it would be of great interest to know whether the effects observed in monocytes/DCs are PTEC specific or whether other resident kidney cells such as mesangial cells and endothelial cells may exert similar effects. It has, indeed, been reported that mesenchymal stem cells do have similar effects [16, 18]. Furthermore, it is well recognized that the surrounding environment also has a strong influence on the polarization and functional phenotype of resident kidney cells [19]. Tubular cells derived from inflammatory conditions might have an influence on DC function different from that of PTECs derived from unaffected parts of a tumour nephrectomy. In this context, it is of interest that human renal carcinoma cells induce a DC subset that is capable of reducing local cytotoxic T cell response [20]. If PTECs play a unique role in the regulation of renal DC function by direct cell-to-cell contact, it might be possible that DCs, which form the periglomerular rings under inflammatory conditions, might be beyond the control of tubular cells and therefore contribute to an uncontrolled, overwhelming inflammatory response in renal disease.
Taken together, these data provide evidence for a functional interplay between resident kidney cells (e.g. tubular cells) and DCs in the human system. The study by Kassianos et al. nicely demonstrates that tubular cells could play a regulative role during an immunological response. However, it remains less clear what exactly defines the role of renal DCs during human kidney disease and homeostasis in the human system.

Conflict of interest statement. None declared.


References


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