MAIT Cells as Drivers of Renal Fibrosis and CKD

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The incidence of CKD has risen significantly in the last years not only because of higher prevalences of diabetes and hypertension but also, because of other nontraditional causes.[1,2] It is thus becoming a global health problem.

Although it is widely accepted that CKD is caused by a steady inflammatory process, we still do not fully understand how renal fibrosis, a central and final component of CKD regardless of its origin, develops and can be therapeutically targeted.

The development of novel technologies, such as single-cell RNA sequencing or multiparameter flow cytometry and immune histology profiling, has contributed to descriptions of cellular alterations in different chronic inflammatory diseases.[3–6] However, we still need a better understanding of regulatory circuits driving chronic inflammation, in particular of the overall contribution of altered immune cells or expression to the disease process.[7]

In this issue of JASN, Law *et al.*[8] address this issue by not only studying alterations of mucosal-associated invariant T (MAIT) cells in specimens from healthy and fibrotic kidney but also, developing an *in vitro* coculture system to analyze their mode of action under hypoxic/inflammatory conditions similar to those in diseased kidneys.

MAIT cells belong to a family of innate-like T cells, which function at the interface between the innate and adaptive immune system.[9] They express a semi-invariant T cell receptor (TCR) recognizing nonpeptide ligands presented by MHC-like molecules, such as MR1.

Recently, the relevance of innate or innate-like lymphocyte populations for the development or progression of chronic inflammatory diseases has become more and more appreciated. Indeed, recent evidence shows that MAIT cells do not only function as antimicrobial effector cells at mucosal barriers but might have a pathogenic role in various autoimmune diseases, such as multiple sclerosis, type 1 diabetes, or inflammatory bowel disease.[10] For CKD, no reports have been published so far.

Within their manuscript, Law *et al.*[8] first perform a phenotypic analysis of MAIT cells in healthy kidneys, which were collected in conjunction with tumor resections. Indeed, MAIT cells can be found in healthy kidneys, express their signature cytokine receptors, and display a tissue-resident phenotype. Importantly, MAIT cell numbers are increased in CKD specimens and correlate with reduced kidney function and interstitial fibrosis. This is independent of the underlying kidney disease and thus, more a reflection of the disease severity.

Furthermore, although their overall phenotype as defined by TCRα7.2, CD161, IL-18Rα, IL-7Rα, CCR5, and CXCR3 expression was comparable between healthy and diseased kidney specimens, MAIT cell expression of CD69 was elevated in fibrotic kidney specimens. Because CD69 is not only a marker of tissue residency but also defines the activation state of a cell, MAIT cells seem to respond to the inflammatory environment. Indeed, with fibrotic kidneys containing more IL-18 in addition to TNF and IL-1β and MAIT cells expressing the corresponding receptor, a local activation is possible.

Next, applying immune histology, the authors could not only validate the increased number of MAIT cells in fibrotic kidneys but also, show that MAIT cells localize within the tubulointerstitial compartment in close proximity to peritubular proximal tubular epithelial cells (PTECs). This points to an active interaction between MAIT cells and PTECs during tubulointerstitial injury and fibrosis development.

Next, the authors set up cocultures between PTECs collected from healthy kidney samples and MAIT cells purified from buffy coats. To mimic the tubulointerstitial injury environment, PTECs were precultured under hypoxic conditions. In addition, a cytokine cocktail consisting of IL-12, IL-15, and IL-18 was added during PTEC-MAIT cell cocultures. This resulted in MAIT cell upregulation of CD69 and production of typical effector molecules, such as perforin and granzyme B, characteristics of fibrotic kidney specimens.

Finally, the authors studied whether MAIT cells of hypoxic/inflammatory cocultures induce PTEC necrosis. Indeed, under these conditions, nearly 50% of the cocultured PTECs become Annexin V+ PI+ double positive.

On the basis of these results, the authors hypothesize that, during fibrosis development, hypoxic PTECs together with inflammatory cytokines activate cytotoxic MAIT cells, which cause PTEC damage.

As mentioned earlier, with these investigations and findings, the article not only reports on altered immune cell composition (in this case, MAIT cells) in fibrotic kidneys but also, provides evidence of a pathogenic circuit between PTEC and MAIT cells.

Clearly, with this first investigation on the role of MAIT cells during kidney fibrosis, several questions remain unanswered. The authors point to macrophages and dendritic cells as the cellular source for the inflammatory cytokines, such as the MAIT cell activating IL-18. However, this should be investigated in more detail along with the spatial distribution of cytokine producers. Also unclear is what drives the cytokine production. Furthermore, analysis did not reveal whether the MAIT cell numbers increase

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by extravasation and accumulation of new cells or proliferation of resident cells and whether only TCR-independent signals drive their activation.

The authors showed that MAIT cells can induce PTEC necrosis, but whether and how they contribute to other features of kidney fibrosis, such as matrix remodeling, remains unclear.

Nevertheless, this work presents an important step in deciphering the role of unconventional innate-like lymphocytes, such as MAIT cells, during chronic inflammatory diseases. In addition to the above-mentioned open questions, future studies should also aim at understanding the cellular crosstalk between MAIT and conventional T cells.

DISCLOSURES

None.

REFERENCES

1. Coresh J: Update on the burden of CKD. *J Am Soc Nephrol* 28: 1020–1022, 2017
2. Friedman D, Luyckx VA: Genetic and developmental factors in chronic kidney disease hotspots. *Semin Nephrol* 39: 244–255, 2019
3. Saez-Rodriguez J, Rinschen MM, Floege J, Kramann R: Big science and big data in nephrology [published online ahead of print March 5, 2019]. *Kidney Int* doi: 10.1016/j.kint.2018.11.048
4. Zhang F, Wei K, Slowikowski K, Fonseka CY, Rao DA, Kelly S, et al.; Accelerating Medicines Partnership Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP RA/SLE) Consortium: Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry [published online ahead of print May 6, 2019]. *Nat Immunol* doi: 10.1038/s41590-019-0378-1
5. Der E, Ranabothu S, Suryawanshi H, Akat KM, Clancy R, Morozov P, et al.: Single cell RNA sequencing to dissect the molecular heterogeneity in lupus nephritis. *JCI Insight* 2: pii:93009, 2017
6. Wu H, Humphreys BD: The promise of single-cell RNA sequencing for kidney disease investigation. *Kidney Int* 92: 1334–1342, 2017
7. Stanko K, Iwert C, Appelt C, Vogt K, Schumann J, Strunk FJ, et al.: CD96 expression determines the inflammatory potential of IL-9-producing Th9 Cells. *Proc Natl Acad Sci U S A* 115: E2940–E2949, 2018
8. Law BMP, Wilkinson R, Wang X, Kildey K, Giuliani K, Beagley KW, et al.: Human tissue-resident mucosal-associated invariant T (MAIT) cells contribute to renal fibrosis and chronic kidney disease (CKD). *J Am Soc Nephrol* 30: 1322–1335, 2019
9. Garner LC, Klenerman P, Provine NM: Insights into mucosal-associated invariant T cell biology from studies of invariant natural killer T cells. *Front Immunol* 9: 1478, 2018
10. Chiba A, Murayama G, Miyake S: Mucosal-associated invariant T cells in autoimmune diseases. *Front Immunol* 9: 1333, 2018

See related article, "Human Tissue-Resident Mucosal-Associated Invariant T (MAIT) Cells in Renal Fibrosis and CKD," on pages 1322–1335.