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UP FRONT MATTERS

Paradoxical Role of IL-17 in Progression of Diabetic Nephropathy

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Diabetic nephropathy (DN) is the most common cause of ESRD in the United States. Current standard of care for patients with DN can slow the progression of DN, but there are no effective therapies to halt progression of established DN. The lack of more effective therapies in established DN is in part because the underlying mechanisms involved in its progression are not fully understood. Therefore, there is an urgent need for novel, effective, and safe approaches for the prevention and reversal of diabetic kidney disease.

The IL-17 family is comprised of six structurally related ligands: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. The receptors for the IL-17 family members (IL-17RA–IL-17RE) form homo- and heterodimers leading to activation of downstream target gene expression. IL-17A, the most intensively studied family member, is produced by multiple cell types, such as CD4+$\alpha\beta$ T cells, $\gamma\delta$ T cells, natural killer cells, and neutrophils, and is principally implicated in neutrophil recruitment and migration. Increased IL-17A levels have been implicated in the pathogenesis of several diseases, including multiple sclerosis, rheumatoid arthritis, and cancer. Interestingly, loss of IL-17 has also been associated with disease susceptibility in part because it has been suggested that the absence of IL-17 results in enhanced production of other proinflammatory cytokines.[1] However, more recent studies have challenged the traditional pathogenic role of IL-17 as a purely proinflammatory cytokine. For instance, increased levels of IL-17 were shown to protect against autoimmune mediated type 1 diabetes in non-obese diabetic mice.[2] Furthermore, IL-17 knockout mice exhibited greater kidney damage in a deoxycorticosterone acetate and angiotensin II model of kidney injury.[3] Our interpretation on the seemingly paradoxical effects of IL-17 is that the modulatory effects of IL-17 on inflammation may be dependent on disease context, tissue, isoform, and receptor-ligand interactions.

Although inflammation is a key factor in the pathogenesis of diabetes and its major microvascular complications, including diabetic nephropathy (DN), less is known regarding the specific contributions of IL-17. On the basis of early work, IL-17 seemed to be implicated in type 1 diabetes progression; however, other studies have suggested opposite effects.[4] For instance, in mice with streptozotocin-induced type 1 diabetes, inhibition of intrarenal IL-17A+ CD4+ T cells, which secrete IL-17A, leads to improvements in many features of DN, implying that reduced levels of IL-17 levels may be protective in DN.[5,6] To address some of these discrepancies, Mohamed *et al.* set out to understand the role of IL-17 in DN pathogenesis and progression.[7] Their study stems from their initial observations, indicating that IL-17 levels were elevated in the urine from microalbuminuric diabetic patients and mice, but interestingly, these levels were significantly reduced with DN progression. On the basis of these initial findings, they reasoned that maintenance of IL-17 levels could exert renoprotection in DN. To test this hypothesis, the authors used an integrated pharmaceutic and genetic approach by taking advantage of global IL-17 knockout mice, epithelial cell-specific IL-17 transgenic mice, and recombinant IL-17 administration. Importantly, they demonstrate that increased levels of IL-17 are able to exert a robust protective role on podocytes and tubular cells as measured by reduced markers of inflammation and fibrosis in kidneys of mouse models with DN. The authors conclude that low dose IL-17 therapy has considerable promise in preventing the progression of DN. Mechanistically, the authors demonstrate that IL-17A suppressed phosphorylation of signal transducer and activator of transcription 3, upregulated an anti-inflammatory protein microglia/macrophage WAP domain protein (AMWAP), and improved oxidative stress in the kidney. The findings of their study suggest that both IL-17A and IL-17F have similar renoprotection. This is important because current evidence suggests that each of these ligands has a different affinity for the IL-17RA subunit of their shared IL-17RA/C heterodimeric receptor, which may result in unique signaling and specific downstream gene targets.[1,8] Therefore, it would be potentially interesting to consider investigating differentially expressed downstream target genes of IL-17A versus IL-17F in diabetic kidneys to identify unique signaling pathways, which could mediate the renoprotection of each specific

ligand. Similarly, further studies are required to investigate whether changes in IL-17 levels lead to alterations in the levels of other cytokines, which could also explain the effects observed on IL-17 restoration. This is of paramount importance because it has been previously shown, as discussed previously, that changes in IL-17 may give rise to modulatory and compensatory changes in other cytokines (*e.g.*, tumor necrosis factor alpha, interferon gamma)[9].

The study by Mohamed *et al.* does not establish which cell types in the kidney respond to IL-17 during diabetes; albeit, the authors provide evidence that IL-17 ultimately leads to increased survival in podocytes and tubular cells. One way to address the impact of IL-17 on specific cell types in the kidney would be to knockdown the IL-17A/F receptor specifically in podocytes and/or tubular cells *in vivo*. The expectation would be that IL-17A/F protective effects would be blunted in this mouse model. Future studies using conditional IL-17RA knockdown, in conjunction with current observations by Mohamed *et al.*, would help to delineate the cell-type specific response to low-dose IL-17 therapy in DN.

Among other important issues that remain unresolved in this study is the identification of regulatory mechanisms governing the temporal profile changes of IL-17 levels during DN progression. Early reports have suggested that high glucose can induce IL-17 expression in lymphocytes.[10] It remains unknown, however, whether the source of changes in IL-17 levels is from infiltrated or resident immune cells. Appreciation of the exact sources of IL-17 in the diabetic kidney would help to further understand its cellular targets and define how diabetes modulate the expression of endogenous IL-17 in the kidney.

Finally, although the findings of this study provide new evidence supporting the potential ability of IL-17A to protect against DN, the mechanisms underlying this protective impact are not completely understood. Mechanistically, reduced oxidative stress, phosphorylation of AMP-activated protein kinase, and inhibition of nuclear factor κB have been implicated as critical mediators of IL-17 protection. Importantly, the authors have identified AMWAP as a novel target of IL-17A. The AMWAP reduces proinflammatory responses, and in conjunction with AMP-activated protein kinase it acts to preserve cell survival. Similarly, AMWAP converts macrophages to a less inflammatory M2 phenotype. Although it may be expected to share similar signaling pathways between macrophage and epithelial cells, it would be interesting to assess whether macrophage specific knockdown of the AMWAP or transfer of macrophages lacking AMWAP could separate signaling in different cell types, expanding on our understanding on the protective role of IL-17 and its downstream target genes.

In conclusion, the study by Mohamed *et al.* provides novel insights allowing development of tailor-made anti-inflammatory–based therapies for treatment and reversal of DN. However, it still warrants further investigation to fully clarify the role of IL-17 in this disease process. Nonetheless, this work represents a novel therapy for DN, which could be potentially translated to clinical applications.

DISCLOSURES

None.

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