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IL-17F PROMOTES TISSUE INJURY IN AUTOIMMUNE KIDNEY DISEASES

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Introduction: The TH17 immune response plays a central role in the pathogenesis of autoimmune diseases, implicating the TH17 “master cytokine” IL-17A as the critical mediator of diseases such as human and experimental crescentic glomerulonephritis (GN). However, the relative importance of additional TH17 effector cytokines, including IL-17F, in immune-mediated tissue injury remains to be fully elucidated.

Methods: Here, we used a mouse model of acute crescentic GN (nephrotoxic Nephritis) including interventional studies using IL-17F-gene-deficient mice, IL-17F-neutralizing antibodies, as well as adoptive cell transfer experiments into Rag1-/- mice. Moreover, also in the chronic model of pristane induced systemic lupus, IL-17F-deficient mice were analyzed.

Results: In a mouse model of acute crescentic GN, we identified CD4+ T cells and T cells as the major cellular source of IL-17F in the inflamed kidney. In our studies using IL-17F-gene-deficient mice as well as IL-17F-neutralizing antibodies, and adoptive cell transfer experiments into Rag1-/- mice we demonstrated that CD4+ T cell-derived IL-17F drives renal tissue injury in acute crescentic GN. Moreover, also in the chronic model of pristane induced systemic lupus, IL-17F-deficient mice developed less severe disease with respect to survival and renal injury. Finally, we show that IL-17F induced expression of the chemokines CXCL1 and CXCL5 in kidney cells, which recruited destructive neutrophils.

Conclusions: In conclusion, using gene-deficient mice, neutralizing antibodies and adoptive cell transfer experiments, we demonstrate for the first time that IL-17F promotes kidney injury in acute and chronic experimental glomerulonephritis. Our data, which challenge the paradigm of IL-17A as being the unique TH17 master cytokine, might be of direct importance for future anti-TH17/IL-17 treatment strategies in human autoimmune diseases.

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IL-33-MEDIATED EXPANSION OF TYPE 2 INNATE LYMPHOID CELLS AMELIORATES PROGRESSIVE GLOMERULOSCLEROSIS

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Introduction: Chronic kidney disease (CKD) affects around 10% of the western population and is a major risk factor for cardiovascular mortality. Regardless of the type of primary injury, glomerular damage regularly results in progressive glomerulosclerosis with proteinuria and deteriorating kidney function. Over the last years, innate lymphoid cells (ILC) have been shown to play an important role in the immune system’s response to different forms of infectious and non-infectious pathologies. Especially, IL-5- and IL-13-producing type 2 ILC (ILC2) have been implicated in repair mechanisms with the aim of restoring tissue integrity after injury.

Methods: ILC populations in the human and murine kidney were analysed by flow cytometry. ILC2 were expanded in mice by treatment with IL-33. The effect of IL-33-mediated ILC2 expansion was tested in a mouse model of progressive glomerulosclerosis that is induced in BALB/c mice by injection of Adriamycin.

Results: In the present study, we show that ILC populations are present in the chronically inflamed human kidney. A detailed characterization of kidney-residing ILC populations in mice revealed that ILC2 are the most abundant ILC subtype in the mouse kidney. Short-term IL-33 treatment lead to a sustained expansion of IL-33R+ kidney ILC2 and ameliorated progressive glomerulosclerosis and attenuated the loss of kidney function induced by Adriamycin-injection in BALB/c mice. The IL-33 effect was independent of T and B cells and depletion of ILC in IL-33 treated mice abrogated the IL-33-mediated protection from progressive CKD. The tissue-protective mechanisms employed by IL-5- and IL-13-producing ILC2 included enhanced activation of alternatively activated macrophages, recruitment of eosinophils and limitation of neutrophil influx by downregulation of neutrophil-attracting chemokines.

Conclusions: In summary, we show that kidney-residing ILC2 can be effectively expanded by IL-33 in the mouse kidney and are central regulators of renal repair mechanisms. The presence of ILC in the human kidney tissue identifies ILC as attractive therapeutic targets for chronic kidney disease in humans.

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URINARY CELL SIGNATURE OF PATIENTS WITH ACUTE KIDNEY INJURY

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Introduction: Acute kidney injury (AKI) is among the most frequent causes for renal damage and associated with significant increase of morbidity and mortality. In rodent models for AKI it was demonstrated that immune cells time dependently contribute to tissue damage and repair, however there is a lack of data for human AKI.

Methods: Urine of patients with AKI was processed and prepared for flow cytometry within 6 hours after acquisition. Cell counts of immune and renoparenchymal cells were measured using flow cytometry. Kinetics of diverse cell subsets were investigated over two weeks past renal failure.

Results: Renal epithelial cell numbers are increased shortly after renal insult and decrease with recovery of the patients. They correlate with creatinine and AKI stadium. Neutrophils (CD66b+), Macrophages (CD36+, CD14+) and T cells (CD3+CD4+ and CD3+CD8+) were detected in the urine of patients with AKI. While urinary numbers of renal epithelial cells and neutrophils decreased