UKE Paper of the Month März 2023

CD4+ T cells produce GM-CSF and drive immune-mediated glomerular disease by licensing monocyte-derived cells to produce MMP12

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ABSTRACT:

Glomerulonephritis is a group of immune-mediated diseases that cause inflammation within the glomerulus and adjacent compartments of the kidney and is a major cause of end-stage renal disease. T cells are among the main drivers of glomerulonephritis. However, the T cell subsets, cytokine networks, and downstream effec-tor mechanisms that lead to renal tissue injury are largely unknown, which has hindered the development of targeted therapies. Here we identify a population of granulocyte-macrophage colony-stimulating factor (GM-CSF)-producing T cells that accumulates in the kidneys of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis, infiltrates the renal tissue in a mouse model of glomerulonephritis, and promotes tissue destruction and loss of renal function. Mechanistically, we show that GM-CSF-producing T cells license monocyte-derived cells to produce matrix metalloproteinase 12 (MMP12), which cleaves components of the glomerular basement membrane and exacerbates renal pathology. Moreover, targeting GM-CSF or MMP12 reduced disease severity in mice with glomerulonephritis. Together, these findings provide a mecha-nistic rationale for the immunopathology of T cell-mediated diseases and identify this GM-CSF–monocyte-derived cells–MMP12 axis as a promising therapeutic target for the treatment of glomerulonephritis.

STATEMENT:

Our study provides for the first time a mechanistic rationale for the immunopathology of T cell–mediated disease and identify this GM-CSF monocyte–derived cells–MMP12 axis as a promising therapeutic target or the treatment of glomerulonephritis.

BACKGROUND:

This work was a joint and interdisciplinary effort involving numerous groups of the UKE and partners in Zürich. The majority of the work was performed in the research group lead by Prof. Ulf Panzer (III. Department of Medicine and Hamburg Center for Translational Immunology). The first authorship is shared between Dr. Hans-Joachim Paust, Dr. Ning Song and Dr. Donatella De Feo. The authors share a common research focus on auto-immune (kidney) diseases and T cell biology. The project was funded by the DFG the Collaborative Research Center 1192 “Immune-mediated kidney diseases”.