Medical Xpress

Vitamin B2 derivatives can alleviate chronic kidney inflammation, research suggests

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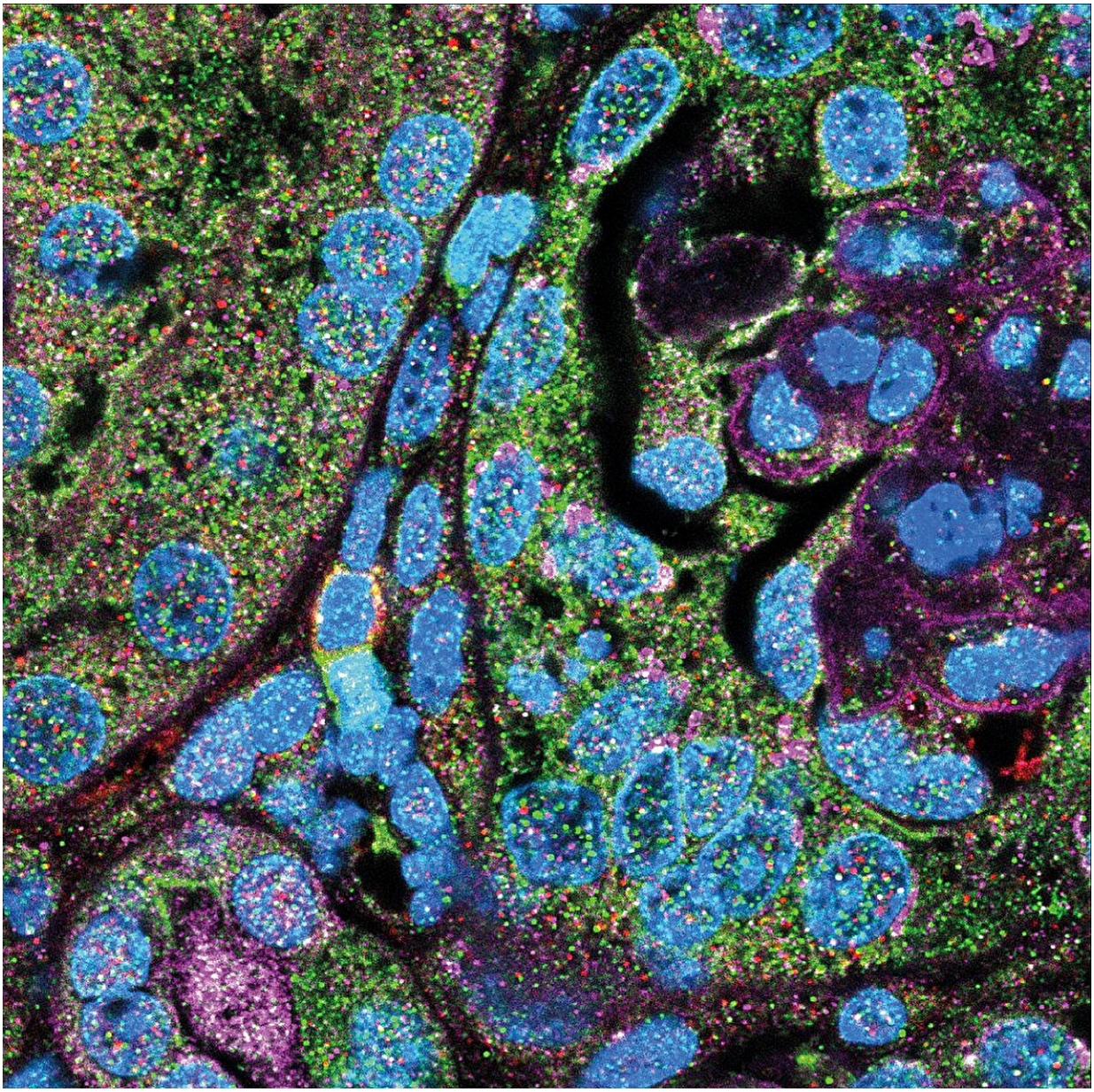


Immunofluorescence - staining of MAIT cells (green) next to mononuclear phagocytes (red) in kidney sections of mice with experimental glomerulonephritis. Cell nuclei in blue. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-43269-0

Researchers from the University Medical Center Hamburg-Eppendorf and the University Hospital Bonn have demonstrated that certain derivatives of vitamin B2 can alleviate chronic kidney inflammation in mice. Their findings have been published in the journal *Nature Communications*.

The term glomerulonephritis denotes several types of chronic kidney inflammation that can lead to the loss of renal function. Most of these conditions are due to autoaggressive immune responses that damage the kidney tissue. Although glomerulonephritis can be treated with immunosuppressive drugs such as corticosteroids, sometimes there is no way of stopping the self-destructive immune response. This may lead to a complete loss of renal function, necessitating continuous dialysis or a kidney transplant.

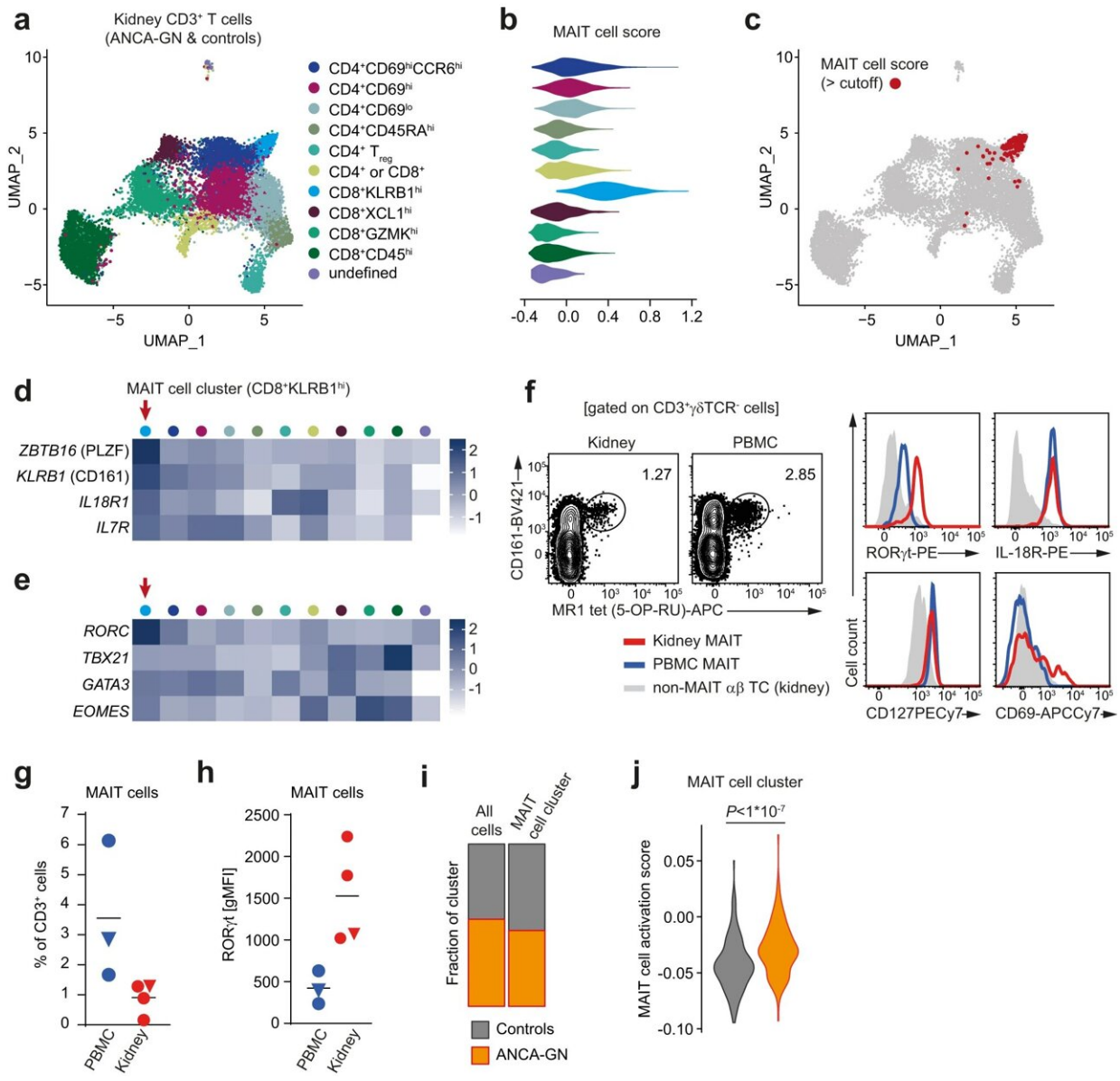
Researchers led by Professor Jan-Eric Turner from the Center for Internal Medicine at the University Medical Center Hamburg-Eppendorf and by Professor Christian Kurts from the Institute of Molecular Medicine and Experimental Immunology at the University Hospital Bonn, who is a member of the ImmunoSensation2 Cluster of Excellence and the Life & Health Transdisciplinary Research Area at the University of Bonn, have now found that certain vitamin metabolites can support the treatment of these conditions.

The researchers were the first to observe so-called mucosal-associated invariant T cells (MAIT cells) in both healthy and inflamed human

kidneys. These rare immune cells are normally found in mucosal tissue, such as in the intestine or lungs, where they perform sentinel functions against infections. "They are activated by metabolites of vitamins B2 and B9, which many infectious bacteria produce, and trigger defense responses as a result," Professor Kurts says.

MAIT cells protecting the kidney

"In kidneys of glomerulonephritis patients and of mice with models of such diseases, these rare immune cells were activated by the resident kidneys immune cells —known as mononuclear phagocytes— that produce molecules that attracted the MAIT cells," Professor Turner explains. Mice that lacked MAIT cells or in which mononuclear phagocytes could not attract MAIT cells experienced a more severe progression of their glomerulonephritis. Conversely, some of the mice that possessed more MAIT cells were protected.



Mucosal-associated invariant T (MAIT) 17 cells reside in the human kidney and are activated in anti-neutrophil cytoplasmatic antibody (ANCA)-associated glomerulonephritis (GN). **a** Unsupervised Uniform Manifold Approximation and Projection (UMAP) clustering (resolution 0.6) of a published data set[31] of pooled single-cell RNA sequencing (scRNAseq) data from $CD3^+$ T cells isolated from kidney biopsy specimens of ANCA-GN patients ($n = 6$) and unaffected kidney tissue of tumor nephrectomy patients (controls, $n = 3$). Eleven clusters were identified and named according to cluster defining genes. **b** Expression of an uncurated MAIT cell-defining gene signature generated from a MAIT cell

cluster identified in the bronchoalveolar lavage fluid of Coronavirus Disease 2019 patients[32] (MAIT cell score, see Supplementary Fig. 1) in the indicated clusters. Color coding as in (**a**). **c** Cells that show high expression of the MAIT cell score were marked in red and plotted on the original UMAP plot. Gene expression heat map of MAIT cell-defining genes (**d**) and T cell lineage-defining transcription factors (**e**) in the indicated clusters. Color coding as in (**a**). **f** Representative flow cytometric identification and characterization of MAIT cells in paired kidney and blood samples of a tumor nephrectomy patient. Gating strategy is specified in brackets and numbers indicate the percentage of cells in the gate. MAIT cell frequencies in the $CD3^+$ T cell fraction (**g**) and RORγt expression in MAIT cells (**h**) from unaffected kidney tissue and blood of tumor nephrectomy patients, as well as from the blood of healthy human donors. Samples from the same patient are marked with a triangle symbol. Each symbol in (**g**) and (**h**) represents one biologically independent sample (n = 3 for PBMC, n = 4 for kidney) and horizontal lines represent the mean. **i** Contribution of cells from controls and ANCA-GN patients to the MAIT cell cluster ($CD8^+KLRB1^{hi}$) identified in scRNAseq analyses. **j** Expression of an uncurated gene signature defining in vitro activated human peripheral blood MAIT cells (MAIT cell activation score (Hinks et al.[22])) in the MAIT cell cluster of controls and ANCA-GN patients. The two-sided Student's t test was used for comparison between the two groups. (UMAP uniform manifold approximation and projection for dimension reduction, ANCA-GN anti-neutrophil cytoplasmic antibody-associated glomerulonephritis, PBMC peripheral blood mononuclear cells, gMFI geometric mean fluorescent intensity). Source data are provided as a Source Data file. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-43269-0

These findings suggested that MAIT cells play a protective role in the kidney. In a therapeutic trial, the researchers treated mice suffering from glomerulonephritis with an artificial vitamin B2 metabolite that matched their natural ligand, and this alleviated the disease progression.

"The protective effect was not strong enough to prevent the experimental glomerulonephritis entirely," Professor Kurts concedes. However, the

researchers believe that it could be used to supplement existing therapies and make them more effective or to reduce the dose of glucocorticoids required in treatment. "More research and clinical trials will be needed before this becomes a viable option in therapy," Professor Turner points out.

More information: Ann-Christin Gnirck et al, Mucosal-associated invariant T cells contribute to suppression of inflammatory myeloid cells in immune-mediated kidney disease, *Nature Communications* (2023). DOI: 10.1038/s41467-023-43269-0

Provided by University of Bonn