UKE Paper of the Month April 2016

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RORγt+Foxp3+ Cells are an Independent Bifunctional Regulatory T Cell Lineage and Mediate Crescentic GN

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ABSTRACT: Cells expressing both the regulatory T cell (Treg)-inducing transcription factor Foxp3 and the Th17 transcription factor RORγt have been identified (biTregs). It is unclear whether RORγt+Foxp3+ biTregs belong to the Th17-specific Treg17 cells, represent intermediates during Treg/Th17 transdifferentiation, or constitute a distinct cell lineage. Because the role of biTregs in inflammatory renal disease is also unknown, we studied these cells in the nephrotoxic nephritis (NTN) model of acute crescentic GN. Induction of NTN resulted in rapid renal and systemic expansion of biTregs. Notably, analyses of the biTreg expression profile revealed production of both anti-inflammatory (IL-10, IL-35) and pro-inflammatory (IL-17) cytokines. Additionally, biTregs expressed a signature of surface molecules and tran-scription factors distinct from those of Th17 cells and conventional Tregs (cTregs), and biTregs were identified in Treg17-deficient mice. Finally, fate reporter and cell transfer studies confirmed that bi-Tregs are not Treg/Th17 transdifferentiating cells. Therapeutic transfer of biTregs suppressed the development of nephritis to an extent similar to that observed with transferred cTregs, but in vitro studies indicated different mechanisms of immunosuppression for biTregs and cTregs. Intriguingly, as predicted from their cytokine profile, endogenous biTregs displayed additional pro-inflammatory functions in NTN that were abrogated by cell-specific deletion of RORγt. In summary, we provide evidence that RORγt+Foxp3+ biTregs are a novel and independent bifunctional regulatory T cell lineage distinct from cTregs, Treg17 cells, and Th17 cells. Furthermore, biTregs appear to contribute to crescentic GN and hence may be novel therapeutic targets.

STATEMENT: *Recently, cells expressing the unusual combination of the regulatory T cell defining transcription factor Foxp3 in combination with the Th17 master transcription factor RORγt have been described in various inflammatory settings. Their origin, stability, fate and function had remained completely elusive up until now. Our study, featured as "this month's highlight" in the current issue of the Journal of the American Society of Nephrology (JASN), now provides evidence that RORγt+Foxp3+ T cells constitute a hitherto unrecognized independent cell lineage, different from RORγt+ Th17 cells and conventional Foxp3+ Tregs by many aspects. Interestingly, in vivo studies in models of acute glomerulonephritis revealed that RORγt+Foxp3+ T cells possess both, potent pro- and anti-inflammatory features. This bifunctional nature prompted us to term these cells biTregs. Interestingly, the anti-inflammatory mechanisms used by bi-Tregs seem to differ from those used by conventional Tregs which underlines their independent nature. Importantly, the pro-inflammatory properties of biTregs were mediated by activation of RORγt. This aspect is of special importance in the light of multiple RORγt-blocking agents that are currently under development for the treatment of human autoimmune diseases.*
Taken together, we were able to identify a novel, previously unknown bifunctional T cell subset which represents a promising target for the treatment of autoimmune diseases. The interdisciplinary cooperation of several institutions within our "Klinische Forschergruppe KFO228" has substantially contributed to the scientific quality of this work.

BACKGROUND: This work was performed in the group of Priv.-Doz. Dr. Oliver M. Steinmetz

at the III. Medical Clinic/Department of Nephrology in close cooperation with the Institute of Experimental Hepatology and Immunology within the DFG-funded “Klinische Forschergruppe 228 - Immunopathogenesis and Therapy of Glomerulonephritis”. The authors have strong research interests in the counter-regulation of pathogenic T cell responses, which cause renal tissue damage in immune-mediated diseases, by specialized Treg subpopulations. The first author MAK is funded by the clinician scientist program, the shared first co-author MCM is part of the mentoring program for outstanding students of the medical faculty.