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Christoph T. Berger, Christoph Hess

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*Treg Commentary*

Tregs are critical for control of self-reactive T cells that escape thymic selection and end up in the periphery. Treg subsets suppress effector T cell populations through the secretion of immunosuppressive molecules and inhibitory cytokines as well as cell contact–dependent mechanisms. In this issue of the *JCI*, Wen and colleagues describe another mechanism by which Tregs suppress effector T cell populations. Specifically, the authors reveal that CD8+ T cells in close contact with target T cells release NADPH oxidase 2–containing microvesicles that inhibit TCR activation by elevating ROS and thereby reducing phosphorylation of the TCR-associated kinase ZAP70. Together, the results of this study provide important insight into CD8+ Treg function and into the development of autoimmunity in older individuals.

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Neglected for too long? – CD8⁺ Tregs release NOX2-loaded vesicles to inhibit CD4⁺ T cells

Christoph T. Berger¹² and Christoph Hess²³

¹Translational Immunology, Department of Biomedicine, ²Medical Outpatient Clinic and Clinical Immunology, and ³Immunobiology, Departments of Biomedicine and Medicine, University Hospital Basel, Basel, Switzerland.

Tregs are critical for control of self-reactive T cells that escape thymic selection and end up in the periphery. Treg subsets suppress effector T cell populations through the secretion of immunosuppressive molecules and inhibitory cytokines as well as cell contact–dependent mechanisms. In this issue of the JCI, Wen and colleagues describe another mechanism by which Tregs suppress effector T cell populations. Specifically, the authors reveal that CD8⁺ T cells in close contact with target T cells release NADPH oxidase 2–containing microvesicles that inhibit TCR activation by elevating ROS and thereby reducing phosphorylation of the TCR-associated kinase ZAP70. Together, the results of this study provide important insight into CD8⁺ Treg function and into the development of autoimmunity in older individuals.

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Conflict of interest: The authors have declared that no conflict of interest exists.
Having unraveled the cellular mechanisms, Wen and colleagues went on to demonstrate that the function of CD8+ Tregs inversely correlates with age (3). In aged, healthy individuals, T cells have an augmented activation threshold (8); therefore, the reduction of CD8+ Treg function may reflect a physiologic balancing response to maintain protective immunity. However, if this balancing act fails, dysfunctional CD8+ Tregs may allow self-reactive T cell clones to expand. Wen et al. explored this possibility in a clinical context by studying giant cell arteritis (GCA). GCA is a paradigm of autoimmune disease in the elderly that is characterized by inflammation of large arteries. In support of the notion that loss of CD8+ Treg function may be linked to development of autoimmune disease, NOX2 coexpressing CD8+ Tregs were almost completely lacking in patients with GCA. T cells are thought to be important for establishing and/or maintaining vascular inflammation in GCA, and immunophenotypic, histopathologic, and genetic studies all point to Th1 and Th17 CD4+ T cell-mediated damage of the vessel wall (9). A model in which age-related loss of peripheral tolerance due to a decline of CD8+ Treg function that allows expansion of autoreactive T cells is therefore an intriguing possibility. Additionally, recent translational studies found normal or only slightly reduced CD4+ Treg numbers (10–12) but normal CD4+ Treg function (11) in patients with GCA.

**Clinical implications and future directions**

With the spotlight on NOX2, studying CD8+ Tregs in the pathology of chronic granulomatous disease (CGD) may be highly informative. Patients with CGD harbor mutations in genes encoding for NOX (most commonly gp91-PHOX on the X chromosome) (13) and suffer from recurrent infections and bowel inflammation reminiscent of Crohn’s disease. Other autoimmune manifestations — typically lupus-like autoinflammatory syndromes — occur in roughly 1 of 10 patients with CGD (14). Further, case reports of children with CGD have described the presence of Kawasaki disease, a vasculitis of the coronary arteries (14). Immunologically, while patients with CGD have lower numbers of CD4+ and CD8+ T cells compared with age-matched controls (15, 16), these individuals have an expanded population of Th17 cells (17) — an observation that would be compatible with insufficient CD8+ Treg function due to absence of NOX2. Large-vessel vasculitis, such as Takayasu’s arteritis or GCA, however, has not been described in patients with CGD to date. It will be important to define the role of CD8+ Tregs in additional age-associated autoimmune conditions, such as late-onset rheumatoid arthritis (LORA), in chronic infections, and in vaccine responses? How is CD8+ Treg function affected in individuals with genetic NOX2 deficiency, such as those with CGD? Finally, what impact does the loss of CD8+ Treg function have on CD4+ Treg and/or Th subset compartments?
or hepatitis C virus — induce CD8+ Tregs and thus exploit these cells to their benefit? How does suppression of naïve CD4+ T cells by CD8+ Tregs affect CD4+ Treg numbers or other CD4+ T cell subsets? Why do elderly individuals have reduced vaccine responses, despite the proposed reduction of CD8+ Treg function proposed by Wen et al.? Addressing these questions will be challenging in humans, especially as it is becoming clearer that T cell subsets can have substantial plasticity and may change phenotype and function (19). Eventually, sophisticated comprehensive network analyses that incorporate dynamic changes of cellular functions over time may be required to firmly dissect the appropriate targets, possibly including CD8+ Tregs, for high-precision immunoregulatory therapies.

Irrespective of how these intriguing issues are approached, it should be remembered that is has taken three decades to appreciate the importance of CD4+ Tregs — we should be more open-minded this time around.

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Address correspondence to: Christoph Hess, Immunobiology, Department of Biomedicine, 20 Hebelstrasse, CH-4031 Basel, Switzerland. Phone: 41.0.61.265.44.75; E-mail: chess@uhbs.ch.


