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Maturation and senescence of the Foxp3$^+$ regulatory T cell response during autoimmunity

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To better define the fate of Foxp3$^+$ regulatory T cells (Treg) responding during autoimmunity, we used genetic and immunophenotypic analyses to monitor the Treg response during experimental allergic encephalomyelitis (EAE), a model of Multiple Sclerosis. We observe a marked elevation in the number of CNS-infiltrating Treg that express KLRG1, a cadherin receptor associated with senescence in Foxp3$^-$ T cells. KLRG1$^+$ Treg show an activated phenotype and elevated Foxp3 and CD25 levels. They proliferate more rapidly than KLRG1$^-$ cells, potentially explaining their increased prevalence. However, KLRG1$^-$ Treg also show substantial conversion into KLRG1$^+$ cells, providing an additional source for the expanded KLRG1$^+$ population. Conversion is unidirectional; KLRG1 is not down regulated on positive cells. KLRG1$^+$ but not KLRG1$^-$ Treg survives poorly in vivo, indicative of terminal differentiation. Most Treg in EAE are nTreg and not iTreg. However, KLRG1 is upregulated on iTreg developing spontaneously during EAE, though not on those generated in vitro. KLRG1$^+$ Treg produce more IL10, and show altered effector cytokine production compared with KLRG1$^-$ cells. Despite their differences, both KLRG1$^+$ and KLRG1$^-$ Treg show similar potency in suppressing EAE. Phenotyping of Treg during EAE for multiple activation-associated markers indicates a progressive diversification of Treg in association with autoimmunity, with the extent and pattern of marker expression dependent both on cellular location and inflammation. Our results support an extensive diversification of Treg during autoimmunity, and associate KLRG1 with altered Treg function and senescence.

Biography

Geiger received his M.D. and Ph.D. from Yale University in 1993. He joined St. Jude Children's Research Hospital in 1999 after completing clinical and research fellowship training at Yale-New Haven Hospital and Yale University. He is currently a Member and Medical Director of Clinical Pathology in the Department of Pathology at St. Jude and an Adjunct Professor of Pathology at the University of Tennessee. Geiger's research focuses on the regulation of T cell responses during autoimmune and auto inflammatory diseases.

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