

# A 'Memory' For Tolerance to Self-Antigens

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To avoid autoimmunity, the immune system has a series of mechanisms to render self-antigen-specific T-cells tolerant of protein antigens expressed in normal healthy tissue. These mechanisms include deletion of the most strongly self-reactive T-cells during their development, and alteration or functional silencing of the remaining self-reactive T-cells. Understanding if, and how, these persisting tolerant T-cells regain function is necessary to comprehending and addressing autoimmunity. In addition, T-cell based immunotherapy for cancer requires overcoming this tolerance to deliver potent anti-tumor effector functions. Recent studies by Drs. Andrea Schietinger and Philip Greenberg and their colleagues in the Clinical Research Division have shown that self-reactive T-cells can be transiently forced to break tolerance, but will revert back to a tolerant phenotype even in the absence of the tolerizing antigen, thus suggesting that a more permanent program regulating 'memory' of their previously tolerant self has been established.

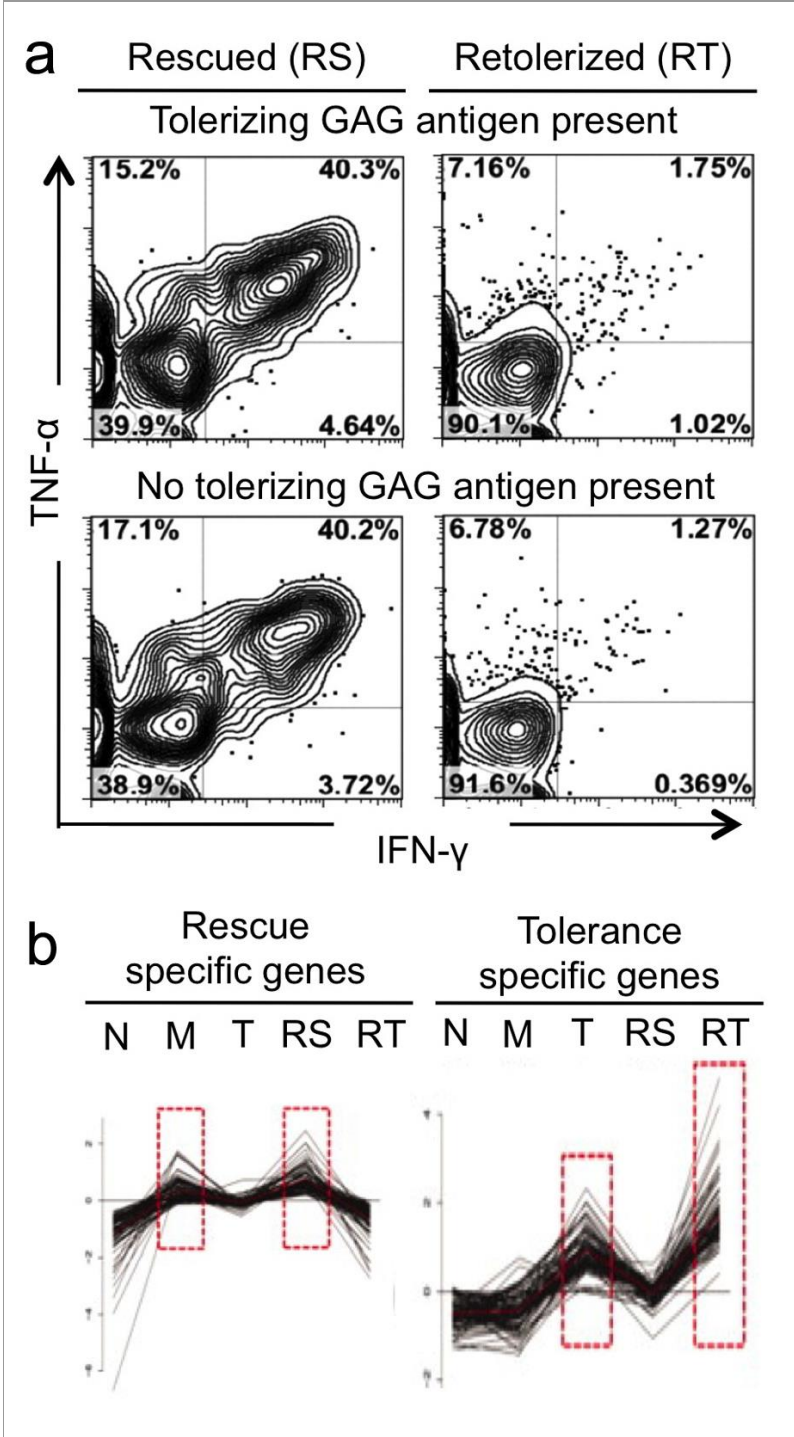
To examine how tolerance can be modulated, Schietinger *et al.* used a mouse model system in which CD8 T-cells express a T-cell receptor specific for the viral antigen GAG. Selective expression of GAG protein in the liver of mice results in the generation of functionally incompetent self-reactive T-cells, whereas GAG-specific T-cells that develop in the absence of GAG remain fully functional. Removing GAG-specific T-cells from the tolerizing antigen was not sufficient to break tolerance, suggesting that at some point the cells became no longer dependent on TCR signals, and that additional pathways were now operative.

Lymphodepletion has successfully been used in adoptive T-cell therapies to enhance proliferation and responses of T-cells following transfer into patients. Similarly, the authors found that tolerant T-cells transferred to lymphopenic hosts proliferated and became functionally rescued. Surprisingly, proliferation of GAG-specific T-cells was improved by the presence of tolerizing self-antigen. However, self-reactive T-cells regained tolerance once the immune system was repopulated, as shown by reacquisition of defects in cytokine production and expansion upon GAG antigen exposure. Furthermore, retolerization of self-reactive T-cells occurred regardless of whether the tolerizing self-antigen was present or not. Thus, self-reactive T-cells demonstrate an intriguing 'memory' of their initial tolerant state, which can be transiently disrupted with enforced proliferation, but is reinstated without any additional tolerogenic stimulation. In addition, Schietinger *et al.* found

that the phenotypic changes from tolerant to functionally rescued and back to retolerant were associated with reprogramming of gene expression. The expression of the microRNA miR-181a was found to be highest among tolerant and retolerized T-cells, and inversely correlated with the expression profiles of predicted target genes. However, the exact role of miR-181a in the context of tolerance remains unclear, as it has been previously shown to increase receptor sensitivity in developing CD4 T-cells.

These results point to a cell-intrinsic programming of tolerance during initial encounter with tolerizing antigens, and suggest a new control mechanism operating to prevent persistent autoimmunity in settings in which tolerant T-cells may get inappropriate or inadvertent activation signals. Understanding what epigenetic mechanisms or signaling feedback loops contribute to the establishment of tolerance will provide insight to design better methods for T-cell based immunotherapies. Finally, it will be necessary to understand and distinguish which of these tolerance mechanisms are defective in patients with autoimmunity.

[Schietinger A, Delrow JJ, Bason RS, Blattman JN, Greenberg PD](#). 2012. Rescued tolerant CD8 T cells are preprogrammed to reestablish the tolerant state. *Science* 335:723-7.



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Rescued T-cells reacquire tolerance even in the absence of tolerizing antigen. (a) Tolerized T-cells are functionally rescued after homeostatic proliferation in lymphodepleted hosts (left side), as shown by production of effector cytokines TNF-alpha and IFN-gamma. Upon repopulation of the immune system (right side) T-cells reacquired tolerance and lost effector function. (b) Gene signature changes in naive (N), memory (M), tolerant (T), rescued (RS) and retolerized (RT) cell populations.