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REGULATORY T CELLS

# WASP helps $T_{Reg}$ cells sting their prey

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**URLs**
WAS
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=301000

WASP
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7454

Wiskott–Aldrich syndrome (WAS) is a primary immunodeficiency resulting from defective expression of the WAS protein (WASP). Up to 70% of patients with WAS also develop some form of autoimmune disease. Given the role of naturally occurring $CD4^+CD25^+$ regulatory T ($T_{Reg}$) cells in preventing autoimmunity, three new studies have examined the role of WASP in the development and function of $T_{Reg}$ cells. The three groups agree that WASP has an important role in $T_{Reg}$ cells, but they propose slightly different explanations for its effects.

Both Humblet-Baron *et al.* and Marangoni *et al.* showed that WASP is not required for the normal thymic development of $T_{Reg}$ cells, whereas Maillard *et al.* found decreased numbers of $T_{Reg}$ cells in the thymus of *Wasp*$^{-/-}$ mice, as well as in the spleen and lymph nodes. Marangoni *et al.* next showed that *Wasp*$^{-/-}$ $T_{Reg}$ cells had a decreased capacity to suppress the proliferation of both wild-type and *Wasp*$^{-/-}$ effector T cells *in vitro*. Maillard *et al.* obtained similar *in vitro* results and further showed that, in contrast to wild-type $T_{Reg}$ cells, *Wasp*$^{-/-}$ $T_{Reg}$ cells could not prevent the induction of colitis by the adoptive transfer of wild-type effector T cells *in vivo*.

Therefore, Marangoni *et al.* and Maillard *et al.* both conclude that WASP deficiency abrogates the suppressive activity of $T_{Reg}$ cells, and Maillard *et al.* also propose that the decreased production of $T_{Reg}$ cells has a role. The defect in the suppressive activity observed for *Wasp*$^{-/-}$ $T_{Reg}$ cells was shown to result partly from a defect in the production of transforming growth factor-β (Marangoni *et al.*) or interleukin-10 (IL-10) (Maillard *et al.*).

However, Humblet-Baron *et al.* showed that wild-type and *Wasp*$^{-/-}$ $T_{Reg}$ cells mediated equivalent suppression of *Wasp*$^{-/-}$ effector T cells *in vitro*, but that the number of *Wasp*$^{-/-}$ $T_{Reg}$ cells in peripheral lymphoid compartments was decreased. On the basis of three independent *in vivo* mouse models, they propose that WASP deficiency decreases the competitive fitness of $T_{Reg}$ cells, rather than their function. For example, when chimeric bone marrow containing a mixture of wild-type and *Wasp*$^{-/-}$ cells was transplanted into lethally irradiated *Wasp*$^{-/-}$ mice, there was a preferential expansion of wild-type compared with *Wasp*$^{-/-}$ $T_{Reg}$-cell populations. The failure of adoptively transferred *Wasp*$^{-/-}$ $T_{Reg}$ cells to engraft in wild-type hosts (Marangoni *et al.*) and their defective homing to peripheral lymphoid organs (Maillard *et al.*) also lend support to the idea that *Wasp*$^{-/-}$ $T_{Reg}$ cells have decreased fitness.

Finally, all three groups considered the potential contribution of changes in effector T cells to the decreased activity of $T_{Reg}$ cells in *Wasp*$^{-/-}$ mice. *Wasp*$^{-/-}$ effector T cells were not as effectively suppressed as wild-type effector T cells by wild-type $T_{Reg}$ cells (Marangoni *et al.*), and both Marangoni *et al.* and Maillard *et al.* showed that the addition of exogenous IL-2 could partially rescue the suppression defect of *Wasp*$^{-/-}$ $T_{Reg}$ cells. Humblet-Baron *et al.* agree that the decreased competitive fitness of *Wasp*$^{-/-}$ $T_{Reg}$ cells could be exacerbated by decreased production of IL-2 by effector T cells in *Wasp*$^{-/-}$ mice, although this does not explain the decreased fitness of *Wasp*$^{-/-}$ $T_{Reg}$ cells in *Wasp*$^{+/-}$ female mice.

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**ORIGINAL RESEARCH PAPERS** Humblet-Baron, S. *et al.* Wiskott–Aldrich syndrome protein is required for regulatory T cell homeostasis. *J. Clin. Invest.* **117**, 407–418 (2007) | Marangoni, F. *et al.* WASP regulates suppressor activity of human and murine $CD4^+CD25^+FOXP3^+$ natural regulatory T cells. *J. Exp. Med.* **204**, 369–380 (2007) | Maillard, M. H. *et al.* The Wiskott–Aldrich syndrome protein is required for the function of $CD4^+CD25^+FOXP3^+$ regulatory T cells. *J. Exp. Med.* **204**, 381–391 (2007)