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REGULATORY T CELLS

A message of peace

Regulatory T (T_{Reg}) cells use a variety of strategies to suppress inflammation and protect the host from immune-mediated pathology. Okoye *et al.* now describe an additional skill in the T_{Reg} cell repertoire; they have found that T_{Reg} cells can suppress effector T cells by delivering microRNAs (miRNAs) via exosomes.

The authors measured exosome release by different populations of activated lymphocytes *in vitro* and found that T_{Reg} cells produce substantially more exosomes compared with B cells or other T cell populations. Detailed analysis of T_{Reg} cell-derived exosomes showed that they contained premature and mature miRNAs, and were particularly enriched in miRNAs with pro-apoptotic or anti-proliferative functions. To examine whether T_{Reg} cells can deliver miRNAs to effector T cells, the authors developed a flow cytometry-based system that enabled the tracking of T_{Reg} cell-derived double-stranded RNA. T_{Reg} cells were shown to transfer RNA to co-cultured T cells, B cells and dendritic cells, even when the cells were physically separated in transwell plates, suggesting that the RNA transfer was mediated by extracellular microvesicles. Experiments in which wild-type T_{Reg} cells were co-cultured with conventional T cells lacking the endoribonuclease Dicer (which processes miRNAs into their mature form) further supported the idea that T_{Reg} cells transfer suppressive miRNAs to neighbouring T cells; mature miRNAs could be isolated from the co-cultured *Dicer*$^{-/-}$ T cells and these cells showed downregulation of several pro-inflammatory genes.

The authors next examined whether this T_{Reg} cell-mediated suppressive mechanism operates *in vivo*. Using a T cell transfer model of colitis, they found that the transfer of *Dicer*$^{-/-}$ effector T cells into T cell-deficient mice caused a systemic wasting disease that could be prevented by the co-transfer of wild-type but not *Dicer*$^{-/-}$ T_{Reg} cells. Furthermore, when they compared *Dicer*$^{-/-}$ effector T cells that had been transferred alone (so-called 'pathogenic' T cells) with *Dicer*$^{-/-}$ effector T cells that were co-transferred with T_{Reg} cells ('regulated' T cells), they found that the regulated *Dicer*$^{-/-}$ T cells expressed lower levels of mRNAs encoding interferon-γ (IFNγ) and tumour necrosis factor, and that they contained the miRNAs miR-155, let-7b and let-7d. By contrast, these miRNAs were not present in the pathogenic *Dicer*$^{-/-}$ effector T cells that were transferred alone, indicating that their delivery is T_{Reg} cell dependent.

Finally, to definitively show that the miRNAs in T_{Reg} cell-derived exosomes are immunosuppressive, the authors purified exosomes from wild-type and *Dicer*$^{-/-}$ T_{Reg} cells. They found that exosomes from wild-type but not *Dicer*$^{-/-}$ T_{Reg} cells suppressed proliferation and IFNγ production in T helper 1 (T_H1) cell cultures. Comparison of the properties of individual miRNAs from T_{Reg} cell-derived exosomes suggested that let-7d inhibits *Ptgs2* (which encodes cyclooxygenase 2) and is particularly important for suppression of T_H1 cells. Indeed, T_{Reg} cell-derived exosomes lacking let-7d failed to suppress effector T cells in both *in vitro* and *in vivo* systems.

> "exosome-mediated delivery of miRNAs [is] … an additional suppressive mechanism used by T_{Reg} cells"

In summary, this study identifies exosome-mediated delivery of miRNAs as an additional suppressive mechanism used by T_{Reg} cells. By delivering miRNAs that can inhibit *Ptgs2*, this mechanism may be particularly important for limiting T_H1 cell-associated responses.

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ORIGINAL RESEARCH PAPER Okoye, I. S. *et al.* MicroRNA-containing T-regulatory-cell-derived exosomes suppress pathogenic T helper 1 cells. *Immunity* **41**, 89–103 (2014)
FURTHER READING Robbins P. D. & Morelli A. E. Regulation of immune responses by extracellular vesicles. *Nature Rev. Immunol.* **14**, 195–208 (2014)