Nature Reviews Rheumatology | Published online 27 Jul 2017; doi:10.1038/nrrheum.2017.120

INFLAMMATION

Resolving — rather than suppressing — inflammation in RA might be the answer

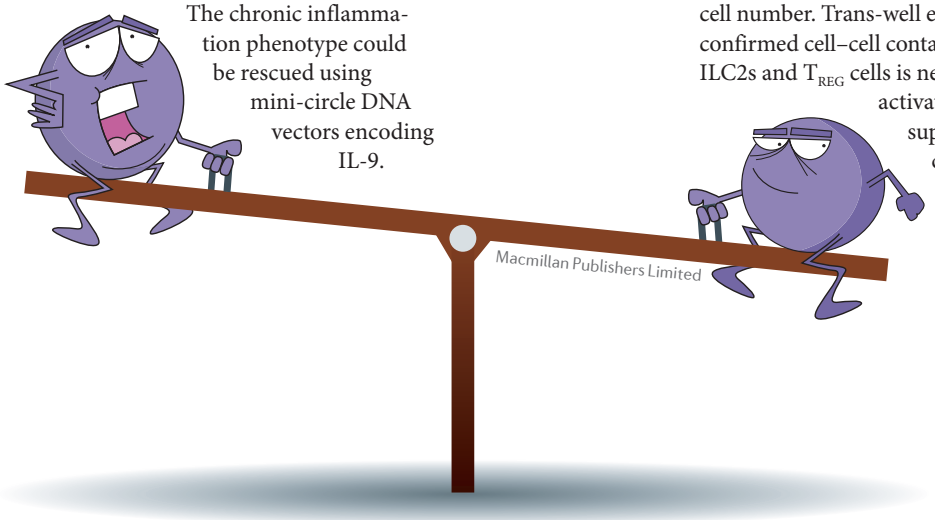
New research published in *Nature Medicine* has revealed that IL-9, produced by group 2 innate lymphoid cells (ILC2s), might be a regulatory factor that contributes to the resolution of damage in chronic inflammatory diseases such as rheumatoid arthritis (RA). These findings support the notion that 'rebalancing' of the inflammatory response in RA might be an effective treatment.

IL-9 has many documented pleiotropic functions in the immune system, and has previously been shown to promote acute inflammation. "However, the role of IL-9 in chronic inflammatory disease remained unknown," explains Andreas Ramming, lead author of the new paper, on the motivation behind this work. Using the antigen-induced arthritis (AIA) model of RA, in which wild-type mice typically display spontaneous resolution of inflammation, they showed that *Il9*$^{-/-}$ knockout mice had chronic inflammation, persistent synovitis and cartilage degradation. The chronic inflammation phenotype could be rescued using mini-circle DNA vectors encoding IL-9.

> "IL-9 ... acts as a natural breakpoint in limiting arthritis"

The researchers went on to interrogate the role of IL-9 and how it mediates these effects. Using *Il9*^{citrine} reporter mice, they deduced that the main source of IL-9 was ILC2s, which were drastically decreased in the AIA-challenged *Il9*$^{-/-}$ knockout mice. "We could decipher an autocrine loop of IL-9 production from ILC2s with subsequent ILC2-driven activation of regulatory T (T_{REG}) cells," says Ramming.

Immunofluorescence microscopy confirmed that ILC2s co-localize with T_{REG} cells in the inflamed tissues of arthritic mice, supporting the functional link between these cell types and RA. Co-culture experiments revealed that the suppressive capacity of T_{REG} cells from *Il9*$^{-/-}$ knockout mice was impaired compared with *Il9* wild-type mice — the functional defect of these T_{REG} cells was related to reduced expression of the effector molecules glucocorticoid-induced TNFR-related protein (GITR) and inducible T-cell co-stimulator (ICOS, also known as CD278) rather than cell number. Trans-well experiments confirmed cell–cell contact between ILC2s and T_{REG} cells is needed to activate the suppressive capacity of T_{REG} cells, which in turn reduced T helper 17 (T_H17) cell polarization and promoted the resolution of inflammation. Ramming proposes that "IL-9 thereby acts as a natural breakpoint in limiting arthritis."



Indeed, synovial tissue and blood samples from patients with RA corroborated the experimental data. For example, patients with persistent inflammatory activity (28-joint Disease Activity Score (DAS28) of ≥3.2) had lower serum ILC2 numbers than those who were in remission (DAS28 <2.6). "Longitudinal observations in patients also revealed a reciprocal link between tissue-resident and circulating ILC2s and disease activity," Ramming goes on.

Building on this report, one can envisage using circulating ILC2s as a tool to measure resolution of inflammation, which has not been possible to date. Furthermore, these data suggest that upregulating IL-9-driven regulatory processes to rebalance the inflammatory milieu might be a viable target for future RA therapies, as opposed to current treatments that suppress inflammation. "Since RA is one of the most chronic forms of inflammatory disease in humans, a new understanding of the reasons why inflammation fails to resolve is urgently needed," concludes Ramming.

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Chief editor, Nature Reviews Disease Primers

ORIGINAL ARTICLE Rauber, S. *et al.* Resolution of inflammation by Interleukin-9-producing type 2 innate lymphoid cells. *Nat. Med.* http://dx.doi.org/10.1038/nm.4373 (2017).
FURTHER READING Perretti, M. *et al.* Immune resolution mechanisms in inflammatory arthritis. *Nat. Rev. Rheumatol.* **13**, 87–99 (2017).