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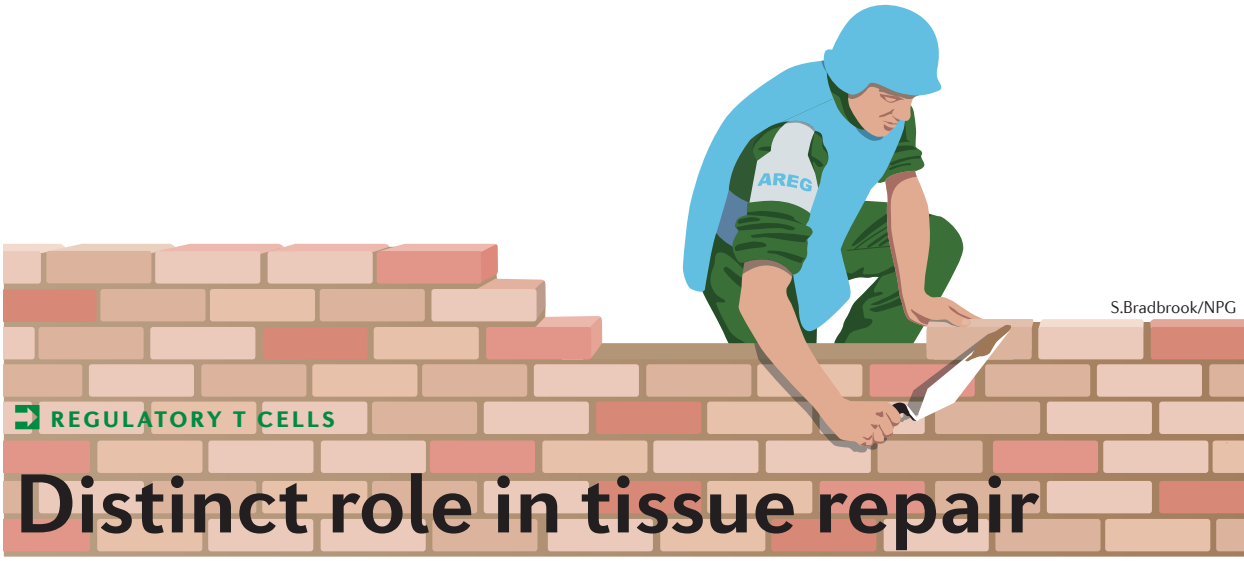

S.Bradbrook/NPG

REGULATORY T CELLS

Distinct role in tissue repair

Regulatory T (T_{Reg}) cells have a central role in maintaining immune tolerance through multiple mechanisms. They have also been shown to indirectly limit inflammation-induced tissue damage. But do T_{Reg} cells have a direct role in tissue protection? Reporting in *Cell*, Rudensky and colleagues show that, through the production of amphiregulin, T_{Reg} cells have a direct and non-redundant role in tissue repair and maintenance during infection that is independent of their suppressive activity and is induced by different cues.

Previous studies have shown that tissue-resident T_{Reg} cells can produce amphiregulin (which is encoded by *AREG*): a molecule produced by several cell types — including some activated immune cell populations — that has a role in organ development and promotes tissue repair under inflammatory conditions. To determine the exact role of T_{Reg} cell-derived amphiregulin, Arpaia *et al.* generated knockout mice in which *Areg* expression was specifically ablated in FOXP3$^+$ T_{Reg} cells (*Areg*$^{fl/fl}$*Foxp3*$^{YFP\text{-}Cre}$ mice). These mice developed normally, showed normal lymphocyte differentiation and did not develop autoimmune disease. Further *in vitro* and adoptive transfer studies confirmed that loss of amphiregulin expression by T_{Reg} cells does not affect their suppressive functions.

To determine the role of T_{Reg} cell-derived amphiregulin in the context of infection and tissue damage, the authors moved to a model of influenza virus infection. Lung-resident T_{Reg} cells were shown to be the main source of amphiregulin early during the infection. Antiviral CD4$^+$ and CD8$^+$ T cell responses, as well as viral loads, were similar in infected *Areg*$^{fl/fl}$*Foxp3*$^{YFP\text{-}Cre}$ mice and control mice. However, compared with control mice, *Areg*$^{fl/fl}$*Foxp3*$^{YFP\text{-}Cre}$ mice showed a rapid decline in lung function and an increase in the severity and extent of lung tissue damage, with loss of barrier integrity and diffusion of viral proteins into the lung parenchyma. These data indicate that amphiregulin produced specifically by tissue-resident T_{Reg} cells has a key role in protecting against tissue damage and maintaining barrier integrity during virus-induced inflammatory responses in the lungs.

Next, the authors assessed whether the signals that promote the tissue-protective functions of T_{Reg} cells are the same as or distinct from the T cell receptor (TCR)-dependent signals that induce their suppressive functions. The pro-inflammatory cytokine interleukin-18 (IL-18) and the alarmin IL-33, expression of which is associated with inflammation and tissue damage, both induced amphiregulin production by T_{Reg} cells *in vitro* independently of TCR stimulation. Following influenza virus infection, ~80% of amphiregulin-expressing T_{Reg} cells expressed the IL-18 receptor (IL-18R) and ~30% of T_{Reg} cells expressed both amphiregulin and the IL-33 receptor ST2, with the majority of these co-expressing IL-18R. Furthermore, TCR-deficient T_{Reg} cells isolated from mice following influenza virus infection produced amphiregulin *ex vivo*. These data indicate that the tissue-repair functions of T_{Reg} cells are evoked in an 'innate' manner by IL-18 and IL-33 and are independent of TCR signalling.

Other studies have shown that T_{Reg} cells isolated from injured skeletal muscle, adipose tissue and inflamed gut tissue can express ST2, IL-18R and amphiregulin, suggesting that 'repair' T_{Reg} cells may exist at multiple tissue sites.

> "the tissue-repair functions of T_{Reg} cells are evoked in an 'innate' manner by IL-18 and IL-33"

Olive Leavy

ORIGINAL RESEARCH PAPER Arpaia, N. *et al.* A distinct function of regulatory T cells in tissue protection. *Cell* **162**, 1078–1089 (2015)