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INFLAMMATION

A gutsy repair job

Thymic stromal lymphopoietin (TSLP) has multiple effects on T cell responses, including promoting T helper 2 (T_H2) cell responses and inducing regulatory T cells. It is produced by intestinal epithelial cells (IECs) in response to bacterial stimulation and has been suggested to have a role in regulating the colonic inflammation induced by dextran sulphate sodium (DSS-induced colitis); mice deficient for the TSLP receptor (*Crlf2*$^{-/-}$ mice) had increased production of T_H1-type cytokines in the gut, and this increased the severity of DSS-induced colitis. However, work by Tak Mak and colleagues now shows that TSLP regulates a T cell-independent pathway that controls the recovery from inflammation rather than the inflammatory process itself.

The authors showed that the severity of DSS-induced colitis was equivalent in *Tslp*$^{-/-}$ and *Tslp*$^{+/+}$ mice at 8 days after DSS administration; however, when the *Tslp*$^{+/+}$ mice began to recover 9–10 days after DSS administration, the *Tslp*$^{-/-}$ mice were unable to do so. Similar results in terms of equivalent morbidity but increased mortality were obtained for *Crlf2*$^{-/-}$ mice. The data indicate that lack of TSLP-mediated signalling inhibits the ability to recover from colonic inflammation without affecting the strength of the inflammatory response.

Consistent with the lack of an effect of TSLP on disease severity, no differences were observed between *Crlf2*$^{-/-}$ and *Crlf2*$^{+/+}$ mice in terms of serum and colonic levels of key T_H1, T_H2 and T_H17 cell cytokines, at baseline or during inflammation. Therefore, the lack of TSLP-mediated signalling alone did not alter T cell-mediated inflammation in this study. Also, macrophage and neutrophil recruitment to the colon was normal in *Tslp*$^{-/-}$ mice. Further experiments showed that *Tslp*$^{-/-}$ mice did not have an intestinal barrier defect or any deficiencies of secretory IgA production or goblet cell number, and the colonic microbiota was not altered. Therefore, the increased mortality of *Tslp*$^{-/-}$ mice in response to DSS cannot be explained by impaired host defences or a weakness of the epithelial barrier.

An analysis of genes that are involved in the resolution of inflammation showed that the expression of secretory leukocyte peptidase inhibitor (*Slpi*) was increased after DSS-induced colitis in *Tslp*$^{+/+}$ but not *Tslp*$^{-/-}$ mice. The lower level of expression of *Slpi* in *Tslp*$^{-/-}$ mice compared with *Tslp*$^{+/+}$ mice resulted in increased colonic activity of neutrophil elastase (which is degraded by SLPI) in *Tslp*$^{-/-}$ mice 8 days after DSS administration. Neutrophil elastase is known to degrade the wound-healing protein progranulin (PGRN); consistent with this, decreased protein expression of PGRN was observed during inflammation in *Tslp*$^{-/-}$ mice. The conclusion is that TSLP is required to induce the expression of SLPI, which in turn inhibits neutrophil elastase activity, allowing PGRN to carry out its wound-healing functions; these were shown to include the stimulation of IEC proliferation.

Finally, the authors used bone-marrow chimaeras to show that the role of TSLP in the resolution of colonic inflammation is mediated by non-haematopoietic cells. TSLP and SLPI are expressed by IECs, as is the TSLP receptor. This study therefore shows that TSLP in the gut can signal through an autocrine pathway in IECs to promote healing of the epithelial barrier after transient inflammation.

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ORIGINAL RESEARCH PAPER Reardon, C. *et al.* Thymic stromal lymphopoetin-induced expression of the endogenous inhibitory enzyme SLPI mediates recovery from colonic inflammation. *Immunity* 4 Aug 2011 (doi:10.1016/j.immuni.2011.05.015)