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CYTOKINES

An inflammatory situation

Interleukin-23 (IL-23) is an IL-12-related cytokine, consisting of IL-12 p40 and an IL-23-specific p19 chain. Expression of both IL-12 and IL-23 is determined by the availability of the p40 chain — which is tightly regulated and restricted to myeloid cells — and yet little is known about how the gene encoding p40 is controlled. Given that IL-23 preferentially activates memory T cells and stimulates T helper 1 (T_H1)-cell responses, such information has important implications for the pathogenesis of chronic inflammatory diseases.

To look at the regulation of p40 expression, Becker *et al.* created transgenic mice in which the firefly luciferase gene is under the control of the *p40* promoter. Various organs from healthy transgenic mice were then analysed for constitutive luciferase expression. High levels of luciferase were detected in Peyer's patch-free samples of the distal small intestine, but not the proximal part of this organ or the colon. The constitutive activity of the *p40* promoter in the distal small intestine was confirmed by showing that this region expresses high levels of p40 protein and also IL-23 (but not IL-12). The cell population producing IL-23 was then identified as CD8 α -CD11c⁺ CD11b⁻ lamina-propria dendritic cells (LPDCs).

There was no difference in the number of LPDCs between the proximal and distal regions of the small intestine, so the authors looked for an alternative explanation for the

differential p40 production. Previous studies have shown that the *p40* promoter can be activated by bacterial products through Toll-like receptor signalling involving nuclear factor- κ B, and mice bred under germ-free conditions did not have increased p40 expression in the distal small intestine, so the intestinal microflora might have some role. Using an oligonucleotide probe that binds to the ribosomal RNA of all eubacteria, p40 protein was shown to be co-localized with bacteria in LPDCs of the distal intestine. The same probe was used to show that there is a higher concentration of bacteria in the crypts of the distal intestine than the proximal intestine, and that these bacteria are taken up by LPDCs.

So, the local microenvironment might account for differential IL-23 production, giving the distal small

intestine a predisposition to chronic inflammation such as the T_H1-cell-mediated Crohn's disease, which occurs most often in this part of the gut in humans. However, in an accompanying commentary, Holm Uhlig and Fiona Powrie note that in most mouse models of intestinal inflammation, the main pathology occurs in the caecum and colon, and not in the distal small intestine, so the model might not be quite as simple as Becker *et al.* suggest.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Becker, C. *et al.* Constitutive *p40* promoter activation and IL-23 production in the terminal ileum mediated by dendritic cells. *J. Clin. Invest.* **112**, 693–706 (2003)

FURTHER READING Bouma, G. & Strober, W. The immunological and genetic basis of inflammatory bowel disease. *Nature Rev. Immunol.* **3**, 521–533 (2003) | Trinchieri, G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nature Rev. Immunol.* **3**, 133–146 (2003)