TOLERANCE

The dual mucus defence

GETTY

Mucus prevents inflammation in the large intestine by forming a barrier that is impervious to bacteria and food antigens. Now, Shan *et al.* report that in the small intestine some luminal antigens can access the epithelial surface and the underlying dendritic cells (DCs) but that the mucus component mucin 2 (MUC2) confers a tolerogenic phenotype on the DCs.

Intestinal homeostasis relies on various immune cell populations, including CD103⁺CD11b⁺CX₃CR1 (CX₃C-chemokine receptor 1)⁺ macrophage-like DCs, CD103⁺CD11b⁺CX₃CR1⁺ myeloid DCs and CD103⁺CD11b⁺CX₃CR1⁺ lymphoid DCs, which all have immune and regulatory properties. Confocal microscopy of mouse and human CX₃CR1⁺ or CD103⁺ intestinal DCs revealed that they can bind and internalize MUC2-coated bacteria. Strikingly, in the presence of MUC2, the production of the pro-inflammatory cytokines interleukin-12 (IL-12), IL-6, IL-8 and tumour necrosis factor (TNF) by lipopolysaccharide-stimulated

human DCs was markedly reduced. By contrast, DC exposure to MUC2 increased the production of IL-10, transforming growth factor- β 1 (TGF β 1) and retinaldehyde dehydrogenase (RALDH; also known as ALDH), which have all been implicated in the generation of regulatory T (T_{Reg}) cells. Thus, MUC2 seems to promote an immunoregulatory DC phenotype.

Studies with *Muc2*^{-/-} mice showed that, in the absence of MUC2, DCs in the lamina propria of the small intestine have impaired tolerogenic properties. This correlated with a decreased number of T_{Reg} cells, and an increased number of pro-inflammatory T helper 1 (T_H1) and T_H17 cells. Administration of exogenous MUC2 to *Muc2*^{-/-} mice enhanced the tolerogenic properties of DCs and decreased the levels of pro-inflammatory T_H1 and T_H17 cells, and this increased the resistance of *Muc2*^{-/-} mice to chemically induced colitis. Moreover, oral administration of ovalbumin (OVA) resulted in OVA-specific intestinal and systemic

tolerance in wild-type mice but not in *Muc2*^{-/-} mice.

But how does MUC2 promote the anti-inflammatory activity of intestinal DCs? The authors observed that deglycosylated MUC2 fails to bind to DCs. Galectins are soluble carbohydrate-binding proteins with tolerogenic function, which suggests that they could be MUC2 binding partners. Indeed, galectin 3 co-localized with MUC2 in intestinal DCs, and intestinal epithelial cell-derived galectin 3 increased the binding of MUC2 to DC surfaces. Further analyses showed that the C-type lectin receptor dectin 1 forms a complex with the inhibitory Fc receptor for IgG Fc γ RIIB in the presence of MUC2–galectin 3. Importantly, dectin 1, Fc γ RIIB and galectin 3 were all required for the induction of anti-inflammatory gene expression in MUC2-treated DCs. In fact, MUC2 promoted anti-inflammatory gene expression by inducing β -catenin and cAMP-responsive element-binding protein (CREB) activation downstream of dectin 1. In addition, the recruitment of SH2 domain-containing inositol-5-phosphatase 1 (SHIP1) via Fc γ RIIB constrained dectin 1-dependent nuclear factor- κ B signalling and pro-inflammatory gene expression.

Thus, MUC2 enhances gut homeostasis and oral tolerance by delivering immunoregulatory signals. These signals may be particularly important in the small intestine, where mucus is less organized, which allows the antigen-sampling activity of DCs.

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“MUC2 seems to promote an immunoregulatory DC phenotype”