IMMUNE TOLERANCE

Mind the gap

Oral tolerance is an essential homeostatic mechanism to ensure that we do not mount an immune response to the foods that we eat; it is so efficient that we are normally unaware of its function, but its failure can be life-threatening. This study describes a crucial role in this process for gap junctions that transfer processed antigens between different types of antigen-presenting cell (APC).

Oral tolerance involves $CD11c^+CD11b^+CD103^+$ dendritic cells (DCs), which are found in the intestinal lamina propria in the steady state, and can migrate to mesenteric lymph nodes (MLNs) where they induce regulatory T (T_{Reg}) cells. However, it is unclear how $CD103^+$ DCs acquire soluble antigens for the induction of tolerance. $CD11c^+CX_3CR1^+$ macrophages are highly efficient at extending protrusions into the intestinal lumen, whereas $CD103^+$ DCs do not readily do so in the steady state.

> “$CD103^+$ DCs might receive antigen from CX_3CR1^+ macrophages for the induction of oral tolerance”

Using *Cx3cr1*$^{GFP/+}$ mice to track CX_3CR1^+ cells, the authors showed that ovalbumin (OVA) injected into the intestinal lumen localized to the cytosol of CX_3CR1^+ cells, but not to that of other $CD11c^+$ APCs, in the lamina propria. The extension of macrophage protrusions into the intestinal lumen for antigen sampling depends on expression of CX_3CR1. Hence, there was a marked decrease in the uptake of OVA by CX_3CR1^+ cells in *Cx3cr1*$^{GFP/GFP}$ mice (in which both copies of *Cx3cr1* have been substituted), compared with *Cx3cr1*$^{GFP/+}$ mice.

Despite the preferential uptake of antigen by CX_3CR1^+ cells, $CD103^+$ DCs from OVA-fed wild-type mice had a superior ability to induce the proliferation of naive OVA-specific T cells, compared with all other $CD11c^+$ APC populations. The priming ability of $CD103^+$ DCs was completely abolished in *Cx3cr1*$^{GFP/GFP}$ mice, and these mice were unable to establish oral tolerance to OVA in a delayed-type hypersensitivity (DTH) model. Together, the results indicate that $CD103^+$ DCs might receive antigen from CX_3CR1^+ macrophages for the induction of oral tolerance.

CX_3CR1^+ macrophages and $CD103^+$ DCs were observed in close contact *in vivo* with juxtaposing membranes, so the authors hypothesized that they might communicate through gap junctions. Of the connexin proteins that constitute gap junctions, CX43 (encoded by *Gja1*) was mainly expressed by CX_3CR1^+ macrophages and $CD103^+$ DCs. $CD103^+$ DCs isolated from *Gja1*$^{fl/fl}$*Itgax-Cre* mice (in which *Gja1* is deleted in all $CD11c^+$ cells) had lost the ability to present orally administered OVA to T cells, which indicates a physiological role for gap junctions in transferring antigen between $CD11c^+$ APCs. Furthermore, *Gja1*$^{fl/fl}$*Itgax-Cre* mice fed with OVA had a decreased frequency of T_{Reg} cells in the MLNs compared with wild-type mice, and showed impaired induction of oral tolerance to OVA as assessed in the DTH model.

Specialized APC populations in the intestines can cooperate through CX43-containing gap junctions to maintain homeostasis in response to oral antigens. The mechanism controlling the direction of transport from CX_3CR1^+ macrophages to $CD103^+$ DCs requires further investigation, but intriguingly the authors showed that MHC molecules can be transferred from donor to acceptor cells through cell contact-dependent membrane transfer by directional trogocytosis.

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