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MUCOSAL IMMUNOLOGY

Inflammasome shapes the microbiota

The microbiota has been shown to contribute to immune homeostasis in mucosal tissues. Different intestinal microbial profiles are associated with higher or lower susceptibilities to inflammatory diseases. But what determines which microorganisms will colonize the gut? Flavell and colleagues report in *Cell* that NOD-, LRR- and pyrin domain-containing 6 (NLRP6) inflammasome signalling in intestinal epithelial cells shapes the gut microbial profile.

The NLRP6 inflammasome complex (which contains the adaptor protein ASC and caspase 1 in addition to NLRP6) is highly expressed in intestinal epithelial cells and is required for the processing of interleukin-1β (IL-1β) and IL-18. Here, the authors observed that ASC-deficient mice developed more severe dextran sulphate sodium (DSS)-induced colitis than wild-type mice. However, this was not the case for ASC-deficient mice that had been fostered by wild-type mothers. Moreover, fostering or co-housing of wild-type mice with ASC-, caspase 1- or NLRP6-deficient mice (but not with mice deficient for other NLRP proteins) resulted in exacerbated DSS-induced colitis in wild-type animals, and this was prevented by antibiotic treatment.

Taken together, these findings suggest that defective NLRP6 inflammasome signalling results in gut colonization by a colitogenic microbiota, which is transmissible and can displace the commensal microorganisms of wild-type mice. Indeed, mice with defective NLRP6 inflammasome signalling and wild-type mice co-housed with these knockout mice shared a microbial profile that was distinct from that of single-housed wild-type animals. Further analysis showed that members of the Prevotellaceae family and the candidate division TM7 were the most prominent bacteria in the intestinal crypts of both the knockout and co-housed wild-type animals, but were absent from the intestine of control mice.

So, how do these bacteria contribute to the exacerbation of DSS-induced colitis? The authors found that CC-chemokine ligand 5 (CCL5)-deficient mice co-housed with *Nlrp6*$^{-/-}$ mice developed less severe DSS-induced colitis than wild-type animals co-housed with *Nlrp6*$^{-/-}$ mice, despite the transmission of the colitogenic microbiota. This suggests that CCL5 is involved in the microbiota-dependent mechanism that exacerbates DSS-induced colitis.

Finally, Flavell and colleagues propose that IL-18 is involved in the regulation of gut colonization by the NLRP6 inflammasome. By using mice deficient in IL-18 and bone marrow chimaeras they showed that activation of the NLRP6 inflammasome induced IL-18 secretion by colonic epithelial cells, and this prevented gut colonization by the colitogenic microbiota.

Thus, this study sheds light on a role for epithelial NLRP6 inflammasome signalling in the gut and describes how colonic epithelial cells can influence susceptibility to inflammatory disease by shaping the intestinal microbiota.

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