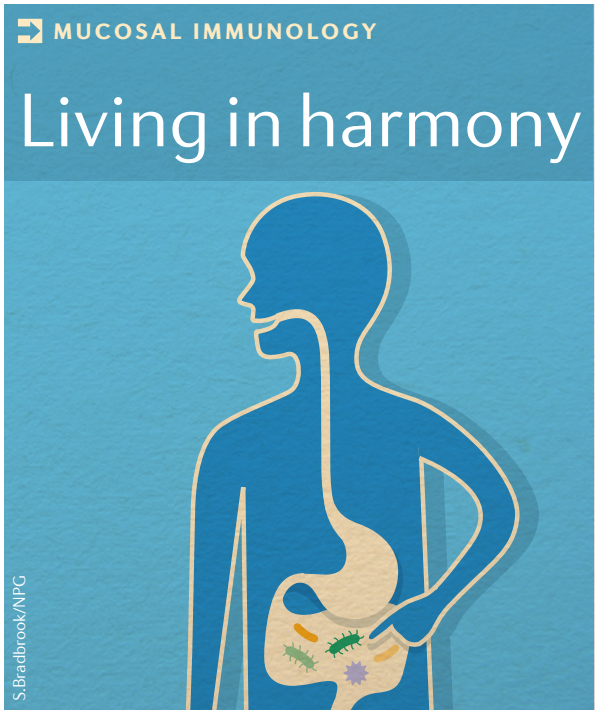

Living in harmony with our gut bacteria requires a range of tolerogenic processes that prevent the immune system from mounting unwanted inflammatory responses. Three recent studies describe new ways of achieving this mucosal tolerance and establishing commensalism.

Zhang *et al.* focused on Paneth cells, which are located at the bottom of intestinal crypts and maintain epithelial barrier function by secreting antimicrobial peptides (AMPs). The authors noted that mice lacking the gene *Lrrk2* (which encodes leucine-rich repeat serine/threonine protein kinase 2 and is a major susceptibility gene for intestinal bowel disease) failed to control intestinal infection with *Listeria monocytogenes*, which depends on the bactericidal activity of Paneth cells for clearance. Protein expression analysis revealed that *Lrrk2* deficiency led to a specific reduction in Paneth cell production of the AMP lysozyme but not of other AMPs. Indeed, in the absence of LRRK2, lysozyme was being degraded in lysosomes rather than being sorted into specialized secretory granules, known as dense core vesicles (DCVs), and released into the gut lumen. This sorting defect resulted from a failure to recruit the small GTPase RAB2A to DCVs by LRRK2. Notably, LRRK2–RAB2A-mediated DCV localization of lysozyme was also defective in germ-free mice, suggesting that commensal bacteria are required for proper lysozyme sorting and release. Finally, the intracellular sensor NOD2 was shown to link commensal bacteria to lysozyme sorting. NOD2 was recruited to the surface of DCVs in Paneth cells of wild-type but not those of germ-free mice, and treatment of germ-free mice with the NOD2 ligand muramyl dipeptide restored lysozyme localization in DCVs in Paneth cells. The finding that commensal bacteria could direct Paneth cell AMP sorting to promote host defence demonstrates the reciprocal relationship between the host and commensals.

> “the intracellular sensor NOD2 was shown to link commensal bacteria to lysozyme sorting”

Elsewhere in the intestine, Wang *et al.* describe how the sensing of commensal bacteria by Toll-like receptors (TLRs) on regulatory T (T_{Reg}) cells in Peyer's patches establishes a tolerogenic IgA-focused immune response that enables maintenance of a healthy microbial flora. Mice with a T_{Reg} cell-specific deletion of the TLR signalling adaptor MYD88 had reduced numbers of T_{Reg} cells and a reciprocal increase in T helper 17 (T_H17) cell populations in the gut mucosa, which contributed to more severe colitis. T_{Reg} cell-specific MYD88 deficiency also led to a reduction in the number of T follicular regulatory (T_{FR}) cells and T follicular helper (T_{FH}) cells. As a consequence, intestinal production of IgA was impaired and commensal bacteria were poorly controlled; there was an overgrowth of segmented filamentous bacteria and increased microbial loads in deep tissues. The authors conclude that defective MYD88- and STAT3-dependent T_{FR} and T_{FH} cell differentiation from T_{Reg} cells in Peyer's patches impairs the generation of IgA responses to control bacterial invasiveness and establish commensalism.

The third paper, by Sefik *et al.*, describes a distinct population of T_{Reg} cells that are crucial for constraining intestinal inflammation and supporting symbiosis. The authors show that a subset of T_{Reg} cells that expresses the transcription factor nuclear receptor RORγ is induced by various, and even individual, symbiotic members of the gut microbiota and contributes substantially to regulating colonic inflammation. This role for RORγ in commensalism contrasts with the accepted notion that RORγ antagonizes FOXP3 function to promote T_H17 cell differentiation. However, the transcriptional footprint of RORγ differed between RORγ$^+$ T_{Reg} cells and T_H17 cells, suggesting that its function and outcome are highly context-specific. A microbiota-induced RORγ$^+$ T_{Reg} cell population, that suppresses type 2 immunity, has also been recently reported by another group (see Further reading).

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ORIGINAL RESEARCH PAPERS Zhang, Q. *et al.* Commensal bacteria direct selective cargo sorting to promote symbiosis. *Nat. Immunol.* http://dx.doi.org/10.1038/ni3233 (2015) | Wang, S. *et al.* MyD88 adaptor-dependent microbial sensing by regulatory T cells promotes mucosal tolerance and enforces commensalism. *Immunity* http://dx.doi.org/10.1016/j.immuni.2015.06.014 (2015) | Sefik, E. *et al.* Individual intestinal symbionts induce a distinct population of RORγ$^+$ regulatory T cells. *Science* http://dx.doi.org/10.1126/science.aaa9420 (2015)

FURTHER READING Bordon, Y. Microbiota-induced T cells block allergic inflammation. *Nat. Rev. Immunol.* 15, 468 (2015)