REGULATORY T CELLS

Mother knows best (about gut T_{reg} cells)

> bacterial IgA coating established after birth by strain-specific IgA levels in mother's milk inversely correlates with the proportion of colonic RORγt$^+$ T_{reg} cells

Regulatory T (T_{reg}) cells in the gut have a crucial role in maintaining homeostasis at the mucosal barrier. In particular, colonic RORγt$^+$ T_{reg} cells differentiate locally in response to specific bacterial species and reduce colitis susceptibility. However, the total number of RORγt$^+$ T_{reg} cells seems to be restricted by a pre-established maximum even in the presence of 'high-inducer' bacteria. In investigating the mechanisms that regulate colonic T_{reg} cell numbers, Ramanan et al., reporting in *Cell*, describe a maternally transmitted setpoint that is stable over many generations and is not mediated by genetics or the microbiota.

The authors observed that RORγt$^+$ T_{reg} cells constitute 40–60% of colonic T_{reg} cells in C57BL/6 mice compared with ~20% in BALB/c mice, which have a compensatory increase in the proportion of Helios$^+$ T_{reg} cells. This inter-strain difference remained after the mice were mono-colonized with bacteria such as *Clostridium ramosum* that induce high levels of RORγt$^+$ T_{reg} cells. Interestingly, when C57BL/6 and BALB/c mice were intercrossed, the frequency of colonic RORγt$^+$ T_{reg} cells in F1 offspring matched that of the mother's genotype even when fathers were left in the breeding cages.

Credit: ImagineGolf/Getty

The progeny of F1 crosses also matched the RORγt$^+$ T_{reg} cell phenotype of their mothers, and this was repeated through several generations.

When F1 pups were cross-fostered at birth, they had RORγt$^+$ T_{reg} cell proportions that were more similar to their foster mothers than their birth mothers and these proportions could be transmitted by female pups to their own progeny. However, the time window for transmission of the RORγt$^+$ T_{reg} cell trait was very narrow, with cross-fostering needing to occur before 3 days of age for C57BL/6 pups and before 7 days for BALB/c pups. This time window occurs before the appearance of RORγt$^+$ T_{reg} cells at 15–20 days of age, which coincides with weaning and changes in microbiota composition. Together, the results suggest that the RORγt$^+$ T_{reg} cell trait is maternally transmitted by a non-genetic, non-epigenetic, non-microbial factor.

Further investigation of the mechanism of transmission showed that the maternally inherited RORγt$^+$ T_{reg} cell trait survived transient T_{reg} cell ablation and transient clearance of the intestinal microbiota in adult mice, which indicates that it is imprinted in the neonatal period, is not self-regulated by the mature T_{reg} cell pool and is resistant to changes in the microbiota. Furthermore, the RORγt$^+$ T_{reg} cell phenotype could not be transmitted by faecal or milk gavage, and using metagenomic profiling the authors could not identify any bacterial species that correlated with maternal genotype and RORγt$^+$ T_{reg} cell phenotype.

The authors did observe that adult F1 mice born to BALB/c mothers had higher frequencies of IgA$^+$ plasma cells in the colon than those born to C57BL/6 mothers, which was associated with higher levels of IgA in stool and greater coating of stool bacteria with IgA. Similar differences in bacterial coating by IgA were noted in 3-day-old pups, in which all gut IgA is derived from mother's milk. This IgA coating phenotype could then be transmitted by female pups to their own offspring, with intestinal plasma cells being shown to migrate to the mammary glands during late pregnancy.

On the basis of these combined results, and previous studies showing that RORγt$^+$ T_{reg} cells and IgA inhibit each other in adult mice, Ramanan et al. suggest a double-negative-feedback loop in which the level of bacterial IgA coating established after birth by strain-specific IgA levels in mother's milk inversely correlates with the proportion of colonic RORγt$^+$ T_{reg} cells that are induced. In turn, the number of RORγt$^+$ T_{reg} cells inversely determines the level of intestinal IgA in adults and hence the IgA level in milk, which is then transmitted to the next generation. Mice born to IgA-deficient BALB/c mothers had increased levels of RORγt$^+$ T_{reg} cells comparable to those born to wild-type C57BL/6 mothers, and mice deficient for RORγt$^+$ T_{reg} cells had increased IgA coating of bacteria.

The authors caution that IgA is not the only factor that regulates the RORγt$^+$ T_{reg} cell phenotype but rather sets a range within which other factors such as short-chain fatty acids can take effect. It is also unclear how the IgA signal from mother's milk during the neonatal window can affect the development of T_{reg} cells more than a week later.

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ORIGINAL ARTICLE Ramanan, D. et al. An immunologic mode of multigenerational transmission governs a gut Treg setpoint. *Cell* https://doi.org/10.1016/j.cell.2020.04.030 (2020)