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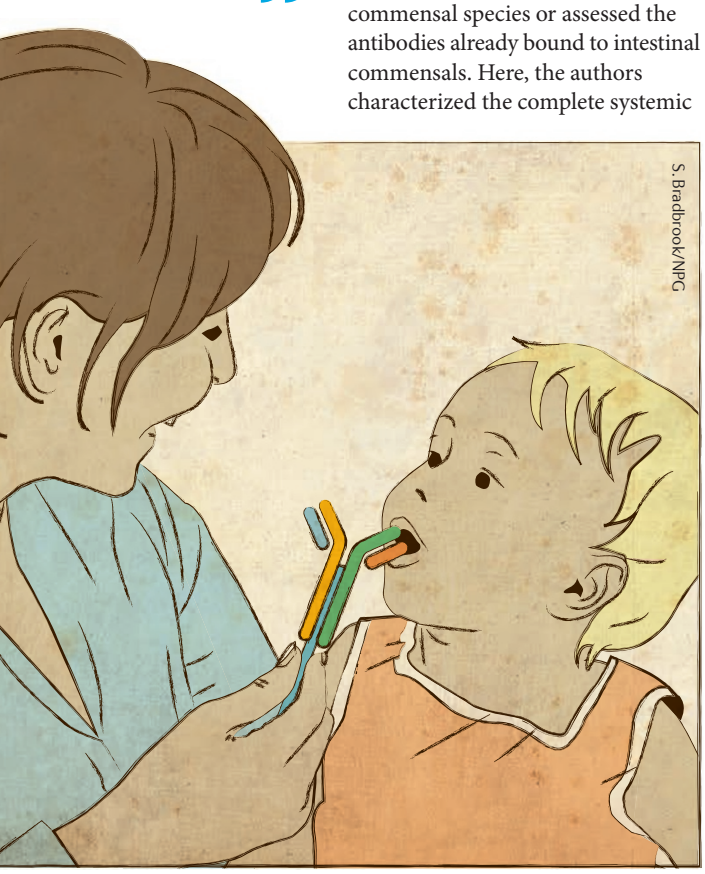
NEONATAL IMMUNITY

Maternal IgG promotes intestinal homeostasis

> maternally derived IgA and IgG cooperate to limit mucosal CD4$^+$ T cell responses to commensal antigens early after birth



S. Bradbrook/NPG

The commensal-specific antibody response has been proposed to be restricted to IgA. Reporting in *Cell*, Barton and colleagues now show that healthy mice generate a T cell-independent IgG response to a broad range of commensal bacteria. In early life, commensal-specific IgG antibodies are maternally acquired through breast milk and coordinate with IgA to limit CD4$^+$ T cell responses to newly acquired microorganisms.

Previous studies have analysed the antibody response to a subset of commensal species or assessed the antibodies already bound to intestinal commensals. Here, the authors characterized the complete systemic antibody response to the microbiota and found, as expected, that a fraction of the microbiota from adult mice was bound by IgA and IgM. However, a substantial proportion of the microbiota was also bound by IgG, specifically the IgG2b and IgG3 isotypes.

IgG2b$^+$ and IgG3$^+$ B cells were most prominent in the mesenteric lymph nodes (MLNs) and gut Peyer's patches, and the level of commensal-specific IgG antibodies was similar in wild-type mice and mice lacking T cells. However, mice deficient for both Toll-like receptor 2 (TLR2) and TLR4 had significantly reduced levels of commensal-specific IgG2b and IgG3. These data suggest that commensal-derived products promote a T cell-independent, TLR-dependent IgG2b and IgG3 antibody response against the gut microbiota.

Commensal-specific IgG2b and IgG3 responses were detected in mice as young as 2 weeks of age, so the authors generated mice lacking maternally derived antibodies by breeding B cell-deficient dams (known as μMT dams) with wild-type sires. Commensal-specific IgG2b and IgG3 responses were greatly reduced in pups born to μMT dams compared with those from wild-type dams. Furthermore, at day 25 post-birth, there was an increase in the frequency and number of effector (CD4$^+$FOXP3$^-$CD44^{hi}) T cells and activated (CD4$^+$FOXP3$^-$CD69$^+$) T cells in the MLNs and Peyer's patches of mice lacking maternal antibodies compared with controls. Bacteria were also routinely present in the MLNs of pups of μMT dams but not of wild-type dams. By cross-fostering offspring of μMT and wild-type dams, the authors excluded a role for differences in microbiota composition and confirmed that the acquisition of maternal antibodies post-birth was necessary to limit mucosal T cell activation in young mice.

Next, the authors compared the progeny of μMT, IgA-deficient and wild-type dams at day 25 post-birth. In contrast to pups lacking all maternal antibodies, the pups of IgA-deficient dams showed no increase in effector and activated T cell numbers in the MLNs and Peyer's patches compared with pups of wild-type dams. Similarly, the offspring of dams lacking neonatal Fc receptor (FcRn), which has a role in transporting IgG into breast milk, had no increase in T cell frequency. By contrast, the pups of dams lacking both FcRn and IgA had an increased frequency and number of effector and activated T cells compared with controls. These data suggest that maternally derived IgA and IgG cooperate to limit mucosal CD4$^+$ T cell responses to commensal antigens early after birth.

Finally, in the absence of maternal antibodies, there was a marked increase in the number of T follicular helper (T_{FH} cells) cells, but not other T helper cell populations, at day 25 post-birth. This increase in T_{FH} cell numbers preceded an increase in the number of germinal centre B cell, suggesting that in the absence of maternal antibodies, a compensatory T_{FH} cell-dependent immune response against commensals is initiated.

Together, this study shows that maternal IgG coordinates with IgA to limit mucosal T_{FH} cell and subsequent germinal centre responses in neonatal mice.

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ORIGINAL ARTICLE Koch, M. A. *et al.* Maternal IgG and IgA antibodies dampen mucosal T helper cell responses in early life. *Cell* http://dx.doi.org/10.1016/j.cell.2016.04.055 (2016)