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ANTIBODIES

Septic shock absorbers

IgA antibodies are typically associated with non-inflammatory immune responses at mucosal surfaces, but IgA is also present in the serum although its functions here are poorly understood. Wilmore *et al.* now report that commensal bacteria in the gut induce the production of serum IgA that protects against polymicrobial sepsis.

The authors noticed that B6 mice reared under specific-pathogen free (SPF) conditions in their animal facility (PENN-SPF) had higher serum IgA levels than SPF B6 mice from Jackson Laboratories (JAX-SPF), despite both sets of animals having similar frequencies of IgA^+ plasma cells in the small intestine. Co-housing of the two groups increased serum IgA levels in the JAX-SPF mice, and large numbers of IgA^+ plasma cells were detected in the bone marrow of PENN-SPF mice and co-housed JAX-SPF mice, whereas few IgA^+ plasma cells were present in isolated JAX-SPF mice. This suggested that bacteria from the PENN-SPF mice can enhance serum IgA levels; in agreement with this, serum IgA levels did not increase in JAX-SPF mice co-housed with antibiotic-treated PENN-SPF mice.

Using 16S ribosomal gene sequencing of stool samples, the authors showed that gut microbiota of PENN-SPF mice and co-housed JAX-SPF mice were enriched in members of the Proteobacteria phylum and specific *Helicobacter* species. Oral delivery of the commensal *Helicobacter muridarum* to isolated JAX-SPF mice induced *H. muridarum*-specific IgA in the serum, as well as *H. muridarum*-specific IgA^+ plasma cells in the bone marrow and small intestine. In further experiments, the authors characterized the bacteria from stool samples or small intestinal faeces that bound to serum IgA. They found that serum IgA from PENN-SPF mice bound to a range of small intestinal bacteria, including members of the *Burkholderia* and *Sphingomonas* genera, which belong to the Proteobacteria phylum. Although recent work suggested that the IgA that coats intestinal bacteria is T cell-independent, the authors found that serum IgA from T cell-deficient PENN-SPF mice did not coat faecal bacteria. Furthermore, they could not detect IgA^+ plasma cells in the bone marrow of T cell-deficient PENN-SPF mice. Therefore, intestinal commensals appear to induce serum IgA in a T cell-dependent manner.

As a recent study suggested that people with IgA deficiencies are more susceptible to sepsis, the authors assessed whether serum IgA is protective in a mouse model of sepsis. In these experiments PENN-SPF and JAX-SPF mice were co-housed briefly (1.5 weeks, to allow transfer of the microbiota but not induction of systemic IgA) or for longer periods (4 or 10 weeks, to allow microbiota transfer and systemic IgA induction). Strikingly, whereas less than 20% of PENN-SPF mice developed lethal sepsis, more than 85% of the 1.5-week co-housed JAX-SPF mice succumbed. Notably, 4-week co-housed JAX-SPF mice were partially protected and 10-week co-housed JAX-SPF mice showed similar survival to PENN-SPF mice. Finally, transfer of serum from PENN-SPF mice to JAX-SPF mice protected the latter against lethal sepsis, whereas IgA-deficient PENN-SPF mice showed increased mortality. Therefore, commensal bacteria in the intestine induce the production of serum IgA that can protect against sepsis in mice — the authors suggest that this may provide protection against systemic invasion by enteric bacteria in a non-inflammatory manner.

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> “commensal bacteria in the intestine induce the production of serum IgA that can protect against sepsis”

ORIGINAL ARTICLE Wilmore, J. R. *et al.* Commensal microbes induce serum IgA responses that protect against polymicrobial sepsis. *Cell Host & Microbe* https://doi.org/10.1016/j.chom.2018.01.005 (2018)