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MICROBIOME

Gut bacteria cross malaria

Glycosylation processes are under high natural selection pressure and it is thought that this is owing to their roles in shaping the immune response to infection. Yilmaz *et al.* now report that the loss of Galα1-3Galβ1-4GlcNAc-R (α-Gal) expression as a self-antigen allows the immune system to respond to α-Gal-expressing malaria parasites. Furthermore, they show that colonization of the intestine by α-Gal-expressing bacteria induces α-Gal-specific natural antibodies that can protect the host against subsequent malaria infection.

In vitro experiments have shown that antibodies targeting α-Gal are cytotoxic towards α-Gal-expressing pathogens; the authors set out to explore whether such antibodies can provide resistance to malaria *in vivo*. Initial experiments identified α-Gal expression on the surface of sporozoites of the human malaria parasite *Plasmodium falciparum* and that of the rodent malaria parasites *Plasmodium berghei* and *Plasmodium yoelii*. When the authors assessed the levels of α-Gal-specific antibodies in healthy uninfected children before and during the malaria season in Mali, they found that the children who remained uninfected during the malaria season had higher levels of pre-existing α-Gal-specific IgM antibodies compared with the children who became infected. No correlation was found between the levels of α-Gal-specific IgG and malaria incidence, suggesting that only IgM natural antibodies that recognize α-Gal are important for protection. Interestingly, the levels of α-Gal-specific antibodies increased with age and were lowest in children under 2–3 years old, an age group that is particularly vulnerable to malaria infection.

> “the gut microbiota can induce the production of natural antibodies that protect the host during subsequent exposure to parasitic infections”

To test the protective effects of α-Gal-specific antibodies *in vivo*, the authors turned to mouse models of malaria infection. As wild-type mice express α-Gal, they used mice deficient in *Ggta1* (also known as *α1,3Gt*), which encodes an enzyme that is necessary for α-Gal synthesis. This gene has become inactivated in the human genome and this prevents humans from expressing α-Gal as a self-antigen. Previous work showed that *Ggta1*-deficient mice produce α-Gal-specific antibodies under steady-state conditions and that the production of these antibodies is enhanced by the intestinal microbiota. In addition, the production of α-Gal-specific antibodies in *Ggta1*-deficient mice is increased if they are colonized with *Escherichia coli* O86:B7, a pathobiont that is found in the human gut. The authors confirmed that *E. coli* O86:B7, but not the laboratory strain *E. coli* K12, expresses high levels of α-Gal and found that colonization of *Ggta1*-deficient mice with *E. coli* O86:B7 boosted circulating levels of α-Gal-specific IgM. Furthermore, they showed that colonization of *Ggta1*-deficient mice with *E. coli* O86:B7, but not with *E. coli* K12, provided protection against parasite transmission when mice were exposed to *P. berghei*-infected mosquitoes. Immunization of *Ggta1*-deficient mice against α-Gal led to even greater resistance against *Plasmodium* transmission, with α-Gal-specific IgM, IgG2b and IgG3 antibodies mediating protection.

The authors found that α-Gal-specific IgM, IgG2b and IgG3 antibodies can bind sporozoites and activate the classical complement pathway. In support of a complement-mediated mechanism of protection, the passive transfer of α-Gal-specific antibodies to *Ggta1*-deficient mice that also lacked complement component C3 failed to confer protection against *P. berghei* transmission. Finally, experiments in which fluorescent sporozoites were cultured with mouse complement and α-Gal-specific antibodies showed that antibody-mediated complement activation has a cytotoxic effect on *Plasmodium* sporozoites.

These findings show that specific components of the gut microbiota can induce the production of natural antibodies that protect the host during subsequent exposure to parasitic infections. The authors also suggest that vaccination to boost circulating levels of α-Gal-specific antibodies could be effective in preventing the transmission of malaria parasites.

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