RESEARCH HIGHLIGHT

Complement(ing) the microbiome in infants through breastmilk

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Breastfeeding has a major impact on the health of infants. In a recent study published in *Cell*, Xu et al. identify and disentangle a novel molecular role of the maternal complement system in mediating resistance to enteric infection of infants via modulation of their microbiome.

The microbiome is considered a critical regulator of health and disease in a growing number of clinical contexts. In particular, the microbiome has been implicated to play a role in mediating development of the immune system in early life.[1] Disruption of microbial colonization after birth may predispose to inflammatory diseases in adulthood, including asthma[2] and inflammatory bowel disease.[3] Multiple factors, including the mode of delivery and breastfeeding, have been suggested to influence development of a healthy microbiome in infancy.[4] Indeed, breastmilk plays an important role in protecting the infant from infection by some pathogens such as *Helicobacter pylori* before the neonatal immune system is fully developed.[5] However, the mechanisms by which breastmilk protects the infant from neonatal infection, and whether some of these milk-associated activities involve the gut microbiome, have not been fully defined to date (Fig. 1).

In a recent study in *Cell*,[6] Wan and colleagues now identify maternal complement as a critical regulator of protection of infants from infection with an intestinal pathogen. They identify that maternal complement passed to the offspring through breastmilk modulates the neonate's microbiome composition, which in turn protects it from enteric infection.

First, the authors demonstrate that breastfed complement-deficient mouse pups are highly susceptible to infection with the intestinal pathogen *Citrobacter rodentium*. They then show that this susceptibility is driven by the absence of complement in the complement-deficient maternal breastmilk, which ultimately leads to infection-induced growth retardation and lethality in pups. Interestingly, the authors suggest that breastmilk complement deficiency leads to changes in the gut microbiome of the breastfed offspring. This change in the makeup of the intestinal microbe community of pups is sufficient to transmit the lack of resistance to infection to wild-type germ-free pups upon stool transfer from breastfed offspring of complement-deficient mothers. Analysis of the microbiome in breastfed complement-deficient pups reveals that an expansion of *Staphylococci*, including the species *Staphylococcus lentus*, may negatively influence resistance of breastfed infants to *C. rodentium*. As such, specific pathogen-free mice co-colonized by *S. lentus* and infected with *C. rodentium* feature enhanced disease symptoms (mainly reduced weight) as compared to infected, non-*S. lentus*-colonized mice. Mechanistically, complement directly binds to *S. lentus*, and induces bacterial membrane lysis in vitro. This suggests that the presence of complement may inhibit *S. lentus* gut expansion, thereby enabling better resistance to intestinal infection. While the precise mechanism by which *S. lentus* supports and enhances *C. rodentium* infection remains to be investigated in future studies, these results exemplify the importance of commensal bacteria modulation by breastmilk-dependent mechanisms, and their downstream effects on host resistance to pathogens.

Conceptually, the elegant findings by Wan and colleagues have several interesting implications. First, they enhance our understanding of the beneficial impacts that breastmilk consumption exerts on newborn mammals, by extending the scope of key immune factors passively transmitted by the mother to her offspring, beyond maternal antibodies. They identify complement as a novel innate immune effector pathway that impacts neonatal immune development through maternal breastmilk supplementation. Surprisingly, some of the complement effects are mediated through modulation of the early-life gut microbiome. Second, the authors exemplify one mechanism by which complement exposure may impact commensal expansion, namely restriction of expansion of several bacterial genera in the intestine of pups, including *Staphylococcus*, *Ruminococcus* and *Coprococcus*. While the authors mechanistically delve into *S. lentus* as one specific microbe that is changed by the absence of complement, it would be interesting to explore in future studies the many other changes in microbiome composition induced by breastmilk complement or the lack thereof, and their effects on breastmilk modulation of newborn physiology. Integrating anaerobic culturing and shotgun metagenomic analysis in further analyzing microbial changes in infants in this setting would likely identify even more bacterial candidates responding to breastmilk compounds, while possibly modulating host responses. One such downstream detrimental impact of breastmilk complement deficiency, suggested by the authors, is an impairment of intestinal barrier. Possible microbiome-dependent and -independent mechanisms driving this important effect, merit further studies. Furthermore, identification of specific microbial factors such as metabolites derived from *S. lentus* and other potentially affected microbes could provide fascinating insights into our understanding of microbiome-based modulation of newborn gut ecology, immune function, and resistance to infection.

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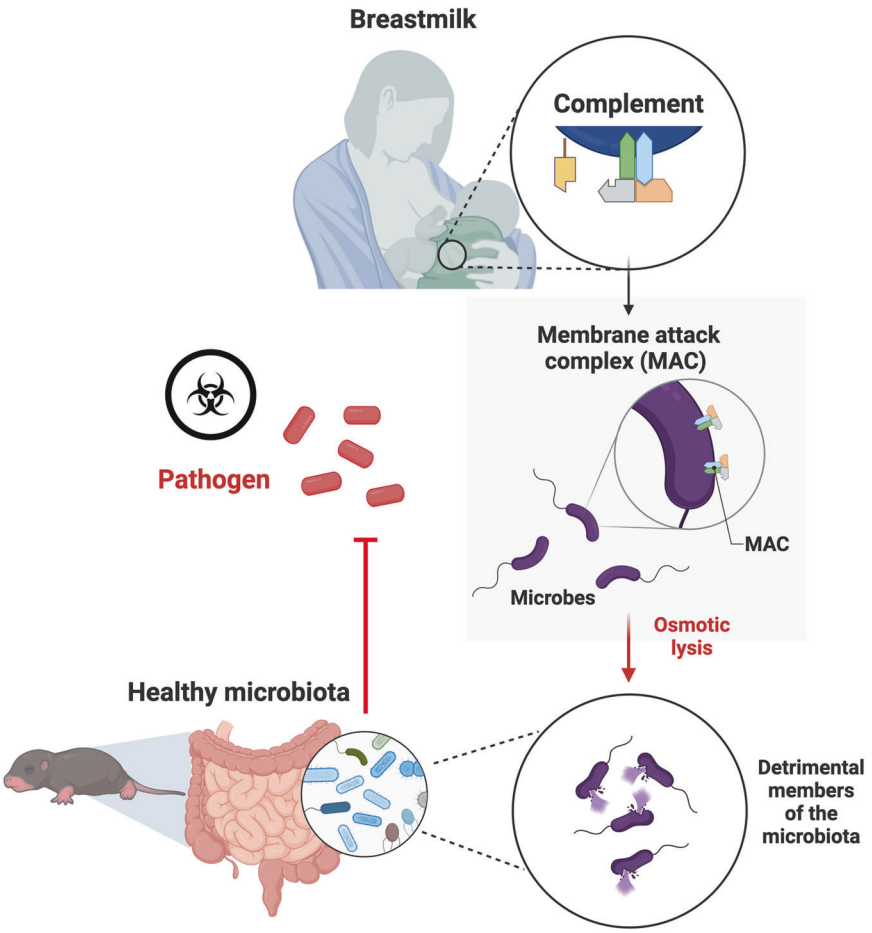

Fig. 1 Maternal complement in breastmilk protects infants from enteric infection. Complement in the breastmilk of mothers has a major impact on the resistance to intestinal infection of infants. It modulates the composition of the infant's intestinal microbiota, by inducing an elimination of detrimental microbial community members. This in turn makes infants more resistant to intestinal pathogen infection. Shown is a summary of the study findings. Figure generated with BioRender.com.

Collectively, the study by Wan and colleagues provides new conceptual insights into the important physiological roles conferred by breastmilk consumption and highlights novel immune and microbiome-based mechanisms driving such effects.

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COMPETING INTERESTS

E.E. is a scientific founder of Daytwo and BiomX, and a paid consultant to PurposeBio, Aposense and Zoe in topics unrelated to this piece.

ADDITIONAL INFORMATION

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