Study in mice uncovers new protective benefit of breast milk

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An immune component of breast milk known as the complement system shapes the gut environment of infant mice in ways that make them less susceptible to certain disease-causing bacteria, according to a study led by researchers at the Johns Hopkins Bloomberg School of Public Health.

The researchers found that mouse pups that nursed from lactating mice whose breast milk lacked a key complement protein had different gut microbe populations than pups that nursed on standard mouse breast milk, making them highly vulnerable to Citrobacter rodentium, a bacterium that infects the guts of mice. Citrobacter rodentium is similar to certain types of diarrhea-causing E. coli that can infect humans but not mice.

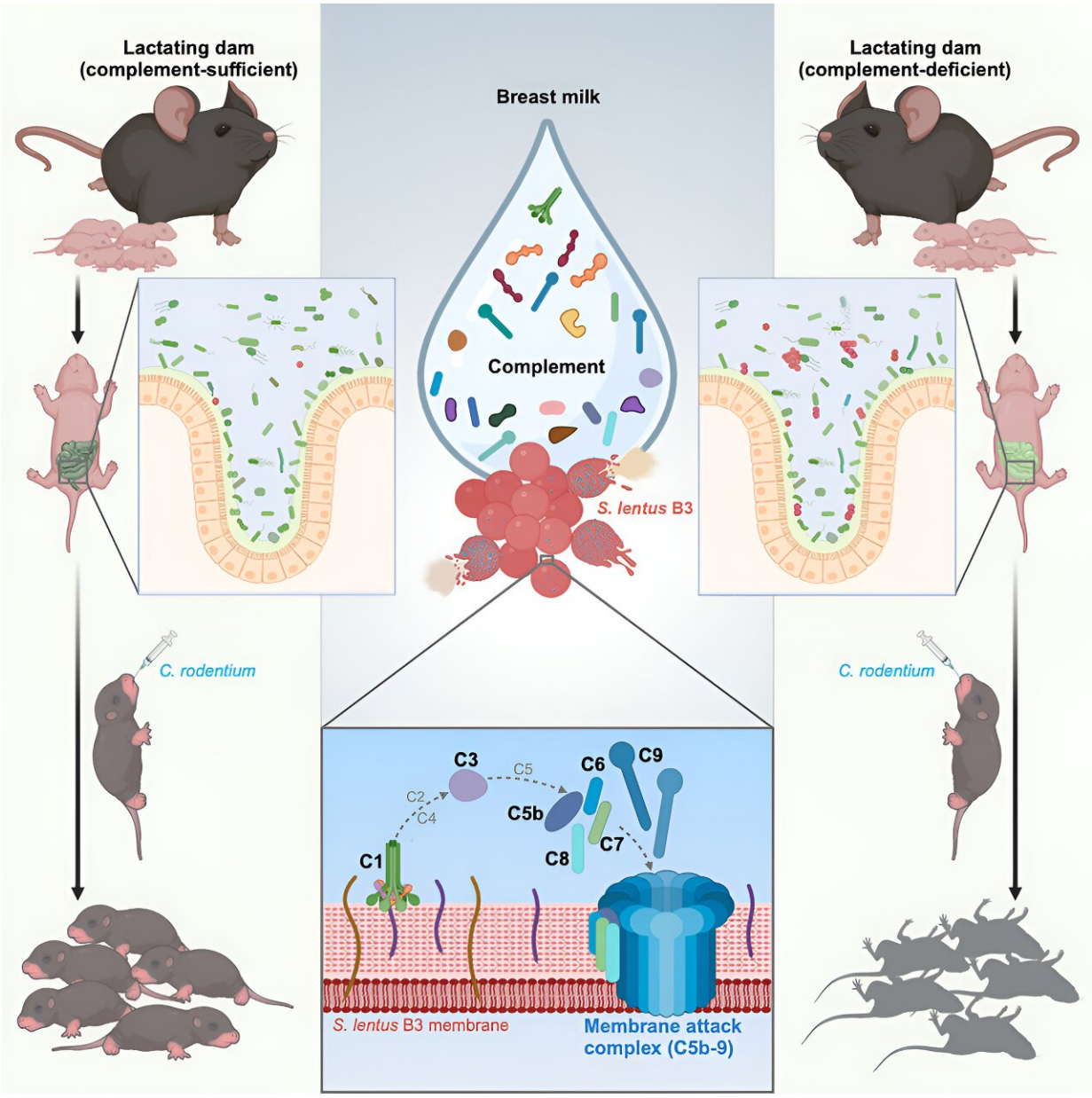
The researchers' experiments suggest that mouse breast milk's complement components boost mouse infant health by directly eliminating some types of gut-dwelling bacteria. This reshaping of the gut microbiota leaves the infant mice far less susceptible to Citrobacter rodentium infection, thus protecting the young from certain infectious threats. The reshaping activity is not dependent on antibodies, in contrast to the way complement components are thought to typically work.

The researchers also confirmed in separate in vitro analyses that human breast milk contains these complement components, which demonstrated similar activity in targeting specific bacteria.

Taken together, these findings shed light on the mechanisms of how breast milk functions to provide protection from certain bacterial infections.

The study was published online January 18 in the journal *Cell*.

"These findings reveal a critical role for breast milk complement proteins in shaping offspring's gut microbe compositions and protecting against bacterial infection in the gut in early life," says study senior author Fengyi Wan, Ph.D., a professor in the Bloomberg School's Department of Biochemistry and Molecular Biology. "This represents an important expansion of our understanding of breast milk's protective mechanisms."



Graphical abstract. Credit: *Cell* (2024). DOI: 10.1016/j.cell.2023.12.019

The study's first author is Dongqing Xu, Ph.D., an assistant scientist in Wan's research group.

Breastfeeding has many known and suspected benefits. It provides excellent nutrition to infants and appears to protect against some short-term or long-term illnesses. Breast milk is also known to help protect against common infections by sharing antibodies and white blood cells from the mother.

Breast milk also contains complement proteins that can work with or "complement" antibodies in attacking bacteria. While complement proteins that circulate in the blood have been the focus of much research, complement proteins in breast milk have been far less studied, and until now their role has been unclear.

In the new study, Wan and his team used engineered mice that lacked critical complement genes. They found that milk from female mice of this type left several-weeks-old mouse pups—even those with normal complement genes—highly susceptible to colitis, often lethal, from Citrobacter rodentium infections. By contrast, pups feeding on normal, complement-containing milk showed only minor and transient signs of gut infection.

The team discovered that this protective effect of breast milk complement proteins depends on their capacity in shaping infant gut microbiota. The complement proteins kill certain gut bacterial species, and this culling of microbes creates an overall gut environment in which harmful inflammation is much less likely in the presence of Citrobacter rodentium.

"Gut microbiota is of great importance to health," says Wan. "Breast milk complement proteins contribute crucially to the establishment of a 'protective' gut microbiota during the early stages of development, promoting infant health and defending against pathogens."

The study also appears to mark an advance in basic immunology.

Complement proteins in blood, although known to be capable of causing direct damage to bacterial cells, have been thought to typically work in partnership with antibodies in a specific immune response. However, Wan and his team showed that this breast milk complement activity against bacteria does not require antibodies and is a nonspecific immune response.

"This opens the door to a lot of new investigations, for example, elucidating the specific complement biology in breast milk and comparing that to complement biology in the blood, and assessing the role of complement beyond the antibody-dependent specific immune system," Wan says.

More information: Dongqing Xu et al, Complement in breast milk modifies offspring gut microbiota to promote infant health, *Cell* (2024). DOI: 10.1016/j.cell.2023.12.019

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