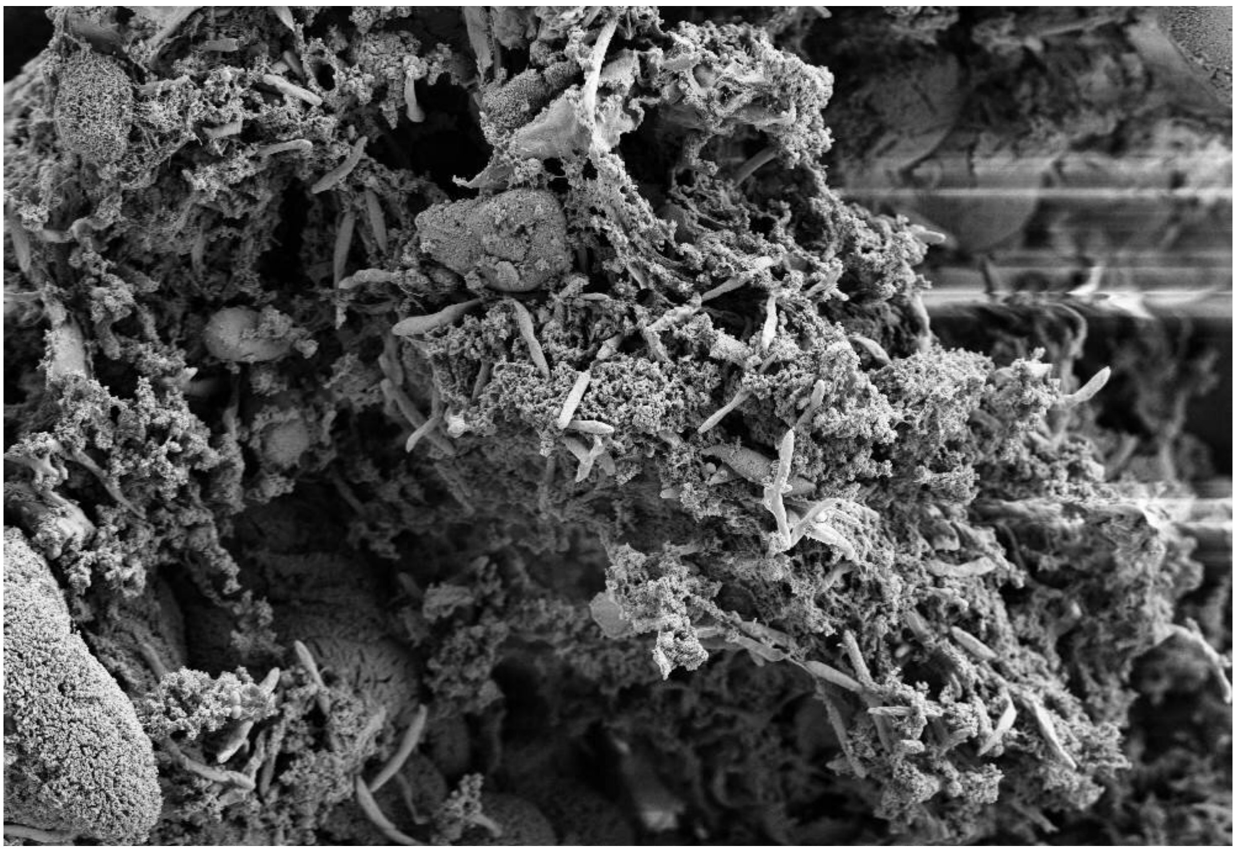
New evidence for the protective role of the microbiome in early life

April 7 2020



Microbes in the intestine. Credit: Quadram institute

A new study has provided insights into how microbes protect gut health from the moment of birth.

Researchers at the Quadram Institute and the University of East Anglia found that in very young mice, the cells lining the gut receive protection from inflammatory damage by their gut microbes and metabolites these produce. This protection appears to be lost with age as the microbiome composition changes. A better understanding of the interactions between microbes, the gut lining and the immune system will be vital in the search for therapies for chronic diseases linked to the gut.

The population of microbes, known as the microbiome, plays an important role in maintaining health from birth, when they first colonize, and then as we age. What happens in that very early colonizing period is crucial as it can affect lifelong health. One important protective role that the microbiome plays is in helping ensure the lining of the gut is an effective barrier. A 'leaky gut," where that barrier is compromised allowing microbes to cross, has been linked to many health conditions, including ulcerative colitis.

To keep the gut lining in tip-top condition, the body constantly replenishes the cells at the front line of the defense. Old cells are lost through a process called cell-shedding. This is usually highly controlled but in certain conditions there is an imbalance, leading to pathological cell-shedding and the development of related health conditions such as ulcerative colitis.

Previous work by Dr. Lindsay Hall and colleagues highlighted the important role that the early gut microbiome plays in regulating cell shedding. Funded by the Wellcome Trust and the Biotechnology and Biological Sciences Research Council, this new study aimed to link changes in the microbial profile during very early life with changes in cell shedding.

Published in the *FASEB Journal*, the study was carried out with mice, which are a well-established pre-clinical model for studies of the gut and the microbiome. They let researchers simulate conditions, for example pathological cell shedding. However, in newborn mice, the researchers were surprised to find that cell shedding couldn't be triggered in the normal way. Neonatal mice appeared to be resistant to induced cell shedding, which protected their gut barrier. But by adulthood, the cell-shedding response was as expected and the gut integrity of the gut barrier had broken down.

Further analysis showed that the cellular signaling pathways that trigger cell shedding were present as normal. What was different in neonates compared to adults was an abundance of chemical markers that indicated that the immune system was suppressing inflammation and other processes that were preventing pathological cell shedding and the development of leaky gut. Some of these immune system factors are known to be induced by specific members of the microbiome.

The researchers found that the profile of microbial species in the microbiome also changed dramatically with age, as did the metabolites those microbes produce. These shifts coincide with changes in the diet, moving into weaning and then on to adult food.

To answer the question of whether this signature was linked to the protection, the researchers disrupted the neonatal microbiome with antibiotics, and using fecal microbial 'poo' transplants from adults. This restored the pathological cell shedding in these young mice by effectively removing the protection that the neonatal microbiome was supplying.

More research is still needed to unpick which microbes, or which metabolites, provide the protective effects, and too see how these findings translate into humans. But this study does go some way to unraveling the complex interactions between microbes, cells in the gut, the immune system and diet. It shows how these dynamics shift rapidly with different life stages. As we learn more about how these interplay, we can start to develop targeted therapies to benefit newborn babies, as well as ensuring we all get the best start for lifelong health.

More information: Kevin R. Hughes et al. The early life microbiota protects neonatal mice from pathological small intestinal epithelial cell shedding, *The FASEB Journal* (2020). DOI: 10.1096/fj.202000042R

Provided by Quadram Institute