INFECTIOUS DISEASE

New mouse model reveals the role of the gut microbiome in EBV and HIV infection

Wahl, A., Yao, W., Liao, B. et al. *Nat. Biotechnol*. (2023) https://doi.org/10.1038/s41587-023-01906-5

Accumulating evidence indicates that the gut microbiota participates in immune system maturation and has a central role in host defense against a variety of pathogens. However, according to new research published in *Nature Biotechnology*, the microbiome may not always be protective against human-specific pathogens. Quite the opposite, in fact.

Using a new germ-free humanized mouse model, Wahl and colleagues at UNC-Chapel hill demonstrated that the gut microbiota promotes the acquisition, replication and pathogenesis of two human-specific pathogens, the Epstein–Barr virus (EBV) and the human immunodeficiency virus (HIV).

Germ-free rodent models, which are animals completely free of microbiota, have been an important resource to understand host–microbiota relationships in vivo; however, to date, they have been of limited value to study the role of the microbiome in human infections. This is because many human pathogens, such as HIV and EBV, have a narrow host range and do not replicate in mice. To circumvent this limitation, the investigators created germ-free mice with a human immune system by surgically implanting human thymus and liver tissue in germ-free, immunodeficient NSG mice, and transplanting them with autologous human $CD34^+$ stem cells (germ-free, bone marrow–liver–thymus mice (GF-BLT mice)). Flow cytometric analysis showed that the peripheral blood and tissues of GF-BLT mice were reconstituted with human innate and adaptive immune cells, making the model suitable to study human infections.

Next, the researchers exposed GF-BLT mice to EBV and HIV and compared their response to that of conventional (CV) humanized mice (CV-BLT mice) that harbor gut microbiota. They found that CV-BLT mice infected with HIV showed increased acquisition of HIV and increased systemic HIV replication compared to GF-BLT mice. Similarly, EBV-infected CV-BLT mice showed greater acquisition of EBV and greater tumor burden compared to GF-BLT mice, demonstrating the critical role of the gut microbiota in promoting the acquisition of two human-specific pathogens and increasing disease.

"The results presented herein support the implementation of humanized mice to investigate approaches that target the effects of the microbiome, microbial products or downstream pathways on these and other human-specific pathogens," conclude the investigators in their report.

Alexandra Le Bras

Published online: 27 September 2023
https://doi.org/10.1038/s41684-023-01266-2