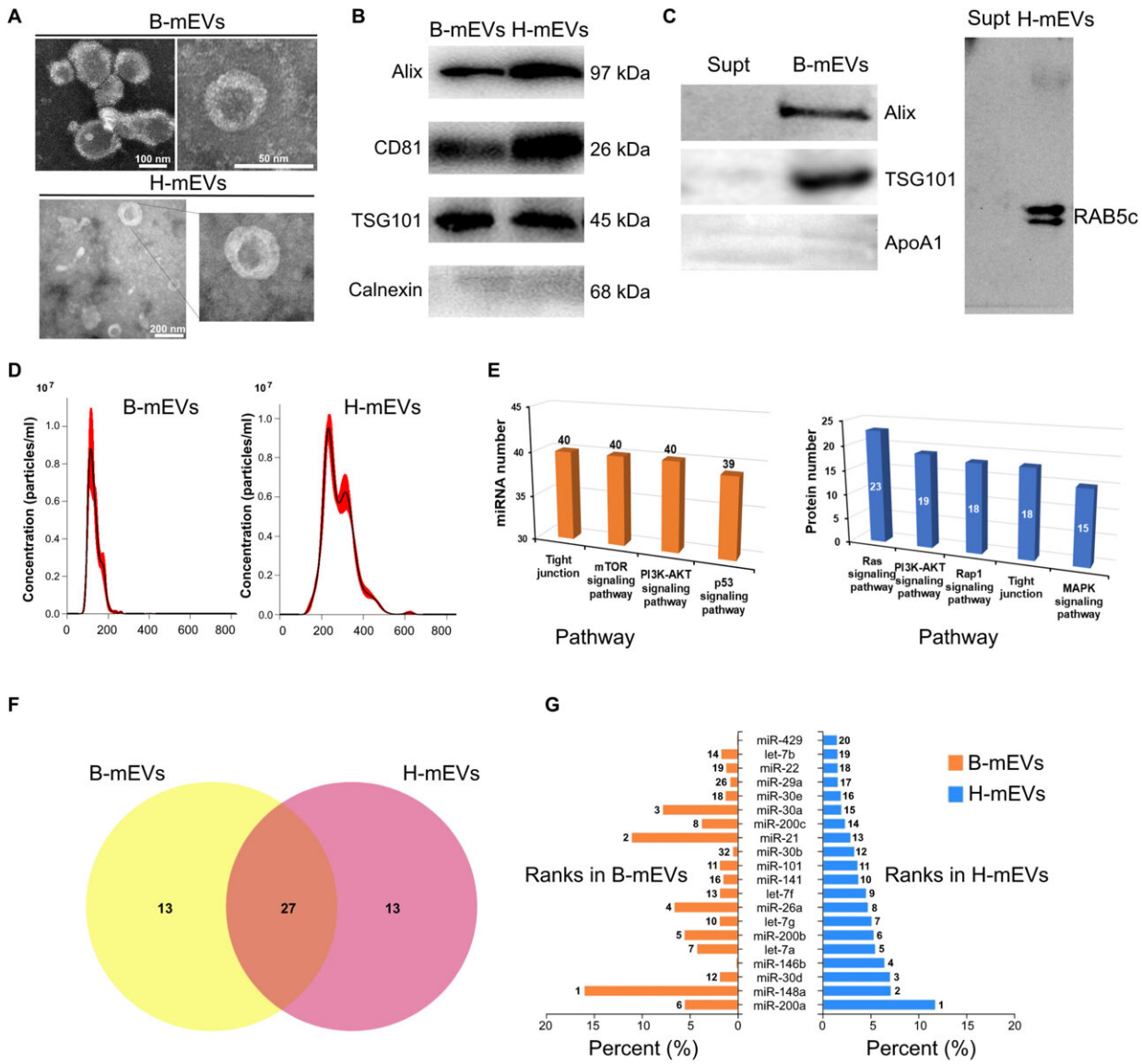
Researchers report potential new treatment for leaky gut using milk-derived extracellular vesicles

April 13 2023



Characterization of bovine and human milk-derived extracellular vesicles (mEVs).(**A**) Representative transmission electron microscope (TEM) images of mEVs derived from bovine (B-mEVs) and human (H-mEVs) milk. (**B** and **C**) Western blot analysis of extracellular vesicles (EVs) markers and non-EV proteins. (**D**) Size distribution of mEVs analyzed via nanoparticle tracking analysis (NTA). (**E**) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of B-mEV proteins and microRNAs associated with intestinal barrier function. (**F**) Venn diagrams of top 40 microRNAs in bovine and human mEVs. (**G**) Ranking of microRNAs in bovine mEVs corresponding to the top 20 microRNAs in human mEVs. Supt, supernatant. Credit: *Science Advances* (2023). DOI: 10.1126/sciadv.ade5041

The intestinal or gut barrier is crucial for nutrient absorption and preventing harmful substances from leaking into the blood stream. Under diseased conditions, the disruption of the gut barrier may increase its permeability and result in a "leaky gut."

The "leaky gut" syndrome often comes with symptoms like chronic diarrhea, constipation, or bloating. It has been associated with many diseases, including inflammatory bowel disease and non-alcoholic fatty liver disease.

Both diseases are highly prevalent in the general population, with the latter affecting around 40% of the Singaporean population, while inflammatory bowel disease affects 1-3 in 10,000 Singaporeans. However, treatment options for these two highly common diseases are limited. Repairing the leaky gut is thus a potential strategy for the treatment of these diseases.

At the same time, milk, as nature's first functional food, plays essential roles in the development of the intestinal barrier and gut immune system. Both human and bovine milk are rich in extracellular vesicles (mEVs),

which are nanosized particles containing beneficial components that can improve gut immunity and quality of gut bacteria.

However, it is unclear whether mEVs protect the gut barrier and treat the leaky gut.

To this end, Assistant Professor Jiong-Wei Wang from the Nanomedicine Translational Research Programme and Centre for NanoMedicine at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), in collaboration with Professor Huaxi Yi from Ocean University of China, led a research team to investigate the potential treatment effects of mEVs on the leaky gut. This study is published in *Science Advances*.

The mEVs are obtained by removing milk fat, proteins and lactose with an in-house approach developed by Asst Prof Wang and his team. They discovered that large amounts of proteins and small nucleic acids carried in mEVs are associated with gut barrier function. The mEVs extracted from both human breast milk and cow milk carry similar therapeutic contents. The treatment efficacy of mEVs was demonstrated in laboratory models.

After orally administering mEVs to the models, the researchers observed that their intestinal inflammation was suppressed, and the damaged gut barrier was repaired. More importantly, the mEVs prevented the leakage of gut bacterial toxins into the blood stream, effectively averting toxin-induced liver damage.

This illustrates that oral administration of mEVs can potentially heal the leaky gut, and effectively slow down the progression of inflammatory bowel disease and nonalcoholic fatty liver disease.

"A leaky gut is a common effect of many diseases. However, whether

the leaky gut is a symptom, or a cause of those diseases, remains debatable. Our research shows that treating the leaky gut with mEVs can ameliorate both inflammatory bowel disease and nonalcoholic fatty liver disease, two types of diseases that are seemingly unrelated," said Asst Prof Wang, the lead author of this study.

"Another interesting finding is that mEVs extracted from milk produced at different stages after pregnancy¾colostrum, transient or mature milk, all exert similar gut barrier protection," Asst Prof Wang added.

Colostrum milk refers to the milk initially produced by the breast during pregnancy, while transitional milk refers to milk produced 2 to 3 days postpartum. The milk then gradually changes from colostrum to mature milk.

According to the research team, a human adult may need to drink 1 liter of milk a day to achieve therapeutic effects on the aforementioned disease conditions. The mEVs are thus more beneficial for individuals with lactose intolerance.

Currently, the researchers are exploring the mechanisms underlying the treatment effects. The team is also working with doctors to explore clinical trials with patients in the near future.

More information: Lingjun Tong et al, Milk-derived extracellular vesicles protect intestinal barrier integrity in the gut-liver axis, *Science Advances* (2023). DOI: 10.1126/sciadv.ade5041

Provided by National University of Singapore

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