Scientists reveal a new mechanism mediating environment-microbe-host interactions

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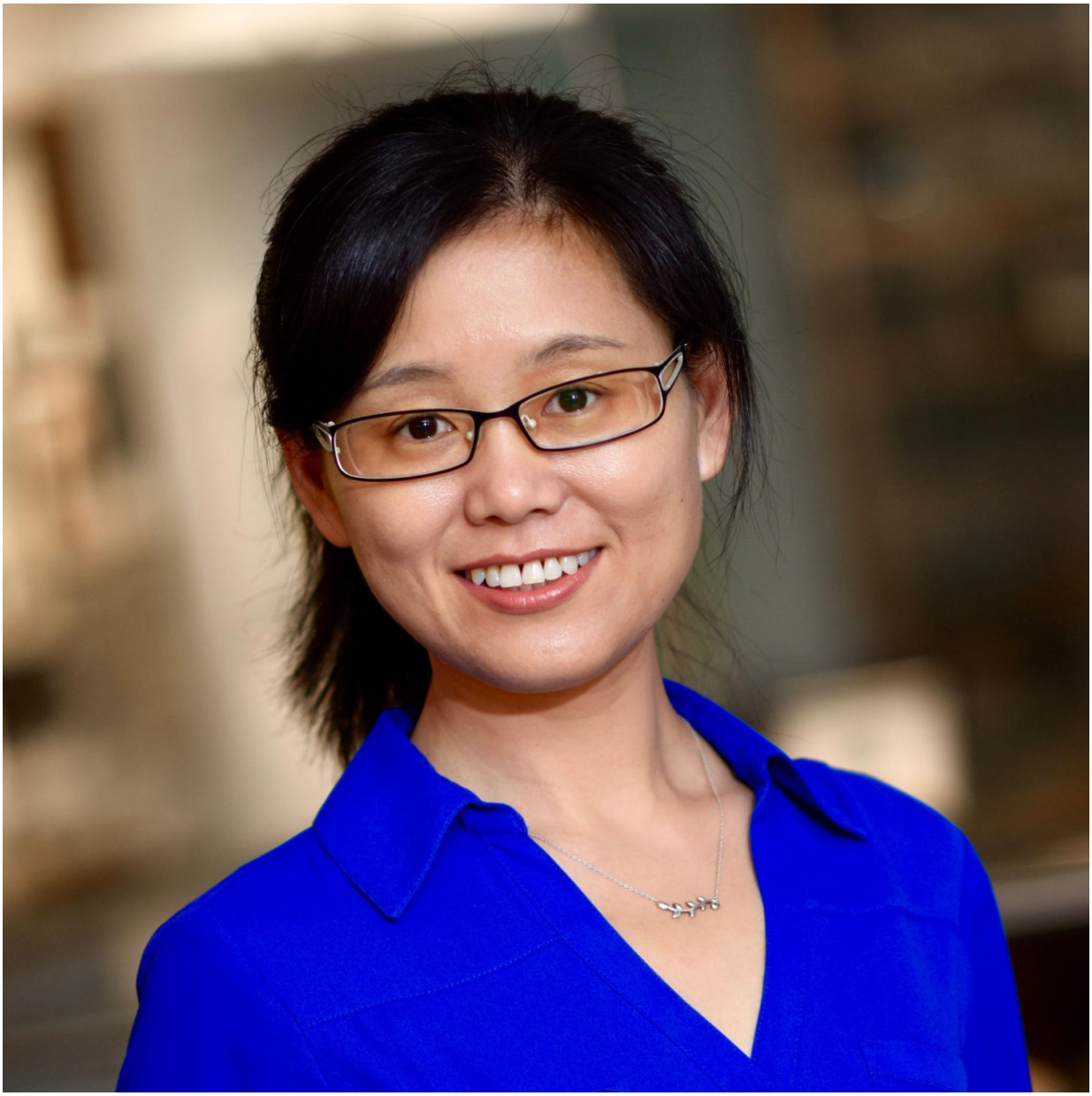

Dr. Meng Wang is an associate professor of the Huffington Center On Aging at Baylor College of Medicine. Credit: Baylor College of Medicine

Researchers at Baylor College of Medicine have uncovered a new mechanism showing how microbes can alter the physiology of the organisms in which they live. In a paper published in *Nature Cell Biology*, the researchers reveal how microbes living inside the laboratory worm *C. elegans* respond to environmental changes and generate signals to the worm that alter the way it stores lipids.

"Microbe-host interactions have been known for a long time, but the actual molecular mechanisms that mediate the interactions were largely unknown," said senior author Dr. Meng Wang, associate professor of molecular and human genetics at Baylor and the Huffington Center On Aging. "Microbes living inside another organism, the host, can respond to changes in the environment, change the molecules they produce and consequently influence the normal workings of the host's body, including disease susceptibility."

In this study, Wang and first author Dr. Chih-Chun Lin working in the Wang Lab have dissected for the first time a molecular mechanism by which *E. coli* bacteria can regulate *C. elegans*' lipid storage.

How *E. coli* changes lipid storage in *C. elegans*

C. elegans is a laboratory worm model scientists use to study basic biological mechanisms in health and disease.

"This worm naturally consumes and lives with bacteria in its gut and interacts with them in ways that are similar to those between humans and microbes. In the laboratory, we can study basic biological mechanisms

by controlling the type of bacteria living inside this worm as well as other variables and then determining the effect on the worm's physiology," Wang said.

In this study, Wang and Lin compared two groups of worms. One group received bacteria that had been grown in a nutritionally rich environment. The other group of worms received the same type of bacteria, but it had grown in nutritionally poor conditions. Both groups of worms received the same amount and type of nutrients, the only difference was the type of environment in which the bacteria had grown before they were administered to the worms.

Interestingly, the worms carrying bacteria that came from a nutritionally poor environment had in their bodies twice the amount of fat present in the worms living with the bacteria coming from the nutritionally rich environment.

The researchers then carried out more experiments and determined that it was the lack of the amino acid methionine in the nutritionally poor environment that had triggered the bacteria to adapt by producing different compounds that then initiated a cascade of events in the worm that led to extra fat accumulation. In addition, the researchers observed that the tissues showing extra fat accumulation also had their mitochondria fragmented. The activities of the mitochondria, the balance between their fusion and breaking apart, are known to be tightly coupled with metabolic activities.

A mechanism that reveals unsuspected connections

The researchers found that the bacteria were able to trigger mitochondrial fragmentation and then extra lipid accumulation because the molecular intermediates the bacteria had triggered allowed them to 'establish communication' with the mitochondria.

"We have found evidence for the first time that bacteria and mitochondria can 'talk to each other' at the metabolic level," Wang said.

Bacteria and mitochondria are like distant relatives. Evolutionary evidence strongly suggests that mitochondria descend from bacteria that entered other cell types and became incorporated into their structure. Mitochondria play essential roles in many aspects of the cell's metabolism, but also maintain genes very similar to those of their bacterial ancestors.

"It's interesting that the molecules bacteria generate can chime in the communication between mitochondria and regulate their fusion-fission balance," Wang said. "Our findings reveal this kind of common language between bacteria and mitochondria, despite them being evolutionary distant from each other."

Some components of this common language involve proteins such as NR5A, Patched and Sonic Hedgehog. The latter is of particular interest to the researchers because it has not been involved in regulating lipid metabolism and mitochondrial dynamics before.

"Microbes in the microbiome can affect many aspects of their host's functions, and here we present a new molecular mechanism mediating microbe-host communication," Wang said. "Having discovered one mechanism encourages us to investigate others that may be related to other physiological aspects, such as the stress response and aging, among others."

More information: Microbial metabolites regulate host lipid metabolism through NR5A–Hedgehog signalling, *Nature Cell Biology* (2017). nature.com/articles/doi:10.1038/ncb3515

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