Mouse model supports importance of fatty acid balance in chronic disease

July 26 2019

Using novel transgenic mouse models they developed, Massachusetts General Hospital (MGH) investigators have provided new evidence that it is the ratio of omega-6 and omega-3 fatty acids, rather than the total amount of them, that influences risk of developing chronic disease. This work has important implications for wellness and dietary guidelines. Their paper is just out in *Nature*'s *Communications Biology*.

"Understanding of the differential effects of these two classes of polyunsaturated fatty acids on the development of chronic disease is important but challenging due to confounding dietary factors. We have developed a unique approach to address that." says the study's senior author Jing X. Kang, MD, Ph.D., director of the Laboratory for Lipid Medicine and Technology at MGH and associate professor of Medicine at Harvard Medical School. The team led by Kang has created several novel mouse models for studying health effects of omega-6 and omega-3 fatty acids.

The role of polyunsaturated fatty acids (PUFAs) in human health has long been debated but is of great interest. They are one of many factors thought to influence chronic disease, such as obesity, type 2 diabetes, cardiovascular disease, and cancer, but studies have shown inconsistent results regarding exactly how they impact risk. The MGH researchers' new paper lends important new evidence to this field by using mouse models that helps eliminate some of the myriad confounding dietary factors that affect studies in this field. The transgenic mice used are identical—except in the levels of n-6 and n-3 they naturally produce,

whatever their diet.

The researchers used four strains of mice for their study, a wild type or "normal" mouse, and then three related mouse strains engineered to produce varying levels of n-6 and n-3 PUFA, no matter what they were fed. These mice can synthesize sufficient levels of specific PUFAs to adjust for dietary factors that would normally disrupt PUFA levels.

The MGH team studied whether the four types of mice showed different rates of metabolic disorders, including metabolic endotoxemia, systemic inflammation, obesity, fatty liver, glucose intolerance, and cancer. The mice that over-produced n-6 PUFA had a higher risk of metabolic disease and cancer, while mice able to convert n-6 to n-3, thereby lowering the ratio, showed a healthier phenotype. The researchers were also able to uncover details about the molecular interactions between these fatty acids and biological networks. For example, the alteration of the PUFA n-6 to n-3 ratio led to changes in the gut microbiome and fecal and serum metabolites.

"The beauty of these mouse models is that they reduce confounding effects," says the study's lead author Kanakaraju Kaliannan, MD, MGH investigator of the study and instructor in Medicine at Harvard Medical School. "We will be able to use them to study many other things, including how PUFA levels specifically impact disease risk."

"Many lines of evidence now support the notion that the omega-6/omega-3 imbalance is a critical factor that contributes to the development of chronic disease," Kang added. "Balancing the PUFA ratio may be a safe and effective solution to some modern health problems." His team is currently working on translational research to explore the clinical utility of the balancing intervention and the feasibility of using the tissue omega-6/omega-3 ratio as a new health biomarker.

More information: Kanakaraju Kaliannan et al, Multi-omic analysis in transgenic mice implicates omega-6/omega-3 fatty acid imbalance as a risk factor for chronic disease, *Communications Biology* (2019). DOI: 10.1038/s42003-019-0521-4

Provided by Massachusetts General Hospital