Transgenic mice produce both omega-3 and omega-6 fatty acids on carbohydrate diet

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Massachusetts General Hospital (MGH) investigators have developed a transgenic mouse that synthesizes both the omega-3 and omega-6 essential fatty acids within its tissues on a diet of carbohydrates or saturated fats. Called "essential" because they are necessary to maintain important bodily functions, omega fatty acids cannot naturally be synthesized by mammals and therefore must be acquired by diet. Significant evidence suggest that the ratio of dietary omega-6 to omega-3 has important implications for human health, further increasing interest in the development of foods rich in omega-3s, which are found in certain species of fish as well as some nuts and green vegetables.

"Introducing into mammals the capacity to convert non-essential nutrients into essential fats could lead to new, sustainable and cost-

effective resources of beneficial omega-3 fatty acids," says Jing X. Kang, MD, PhD, of the Laboratory for Lipid Medicine and Technology in the MGH Department of Medicine, senior author of the report in the open-access journal *PLOS ONE*. "Our study also provides a mouse model for addressing research questions about the true health impacts of these essential fatty acids."

Numerous studies have shown that diets rich in omega-3 fatty acids reduce the risks and effects of cardiovascular disease and may have other health benefits. While omega-6 fatty acids – found in some vegetable oils as well as nuts and seeds – are also essential to health, they are quite common in the Western diet, and some evidence suggests that high omega-6 consumption can have harmful effects. While it is believed that humans evolved on a diet equally balanced between the two fatty acids, the typical Western diet – rich in omega-6s along with saturated fats – has led to a omega-6 to omega-3 ratio as high as 20 to 1.

It is known that molecules produced by omega-6 metabolism can promote inflammation, while omega-3 metabolites are anti-inflammatory; and since the same enzyme is required in both metabolic pathways, increased production in one causes a decrease in the other. This has led to the somewhat controversial hypothesis that the omega-6/omega-3 ratio is an important contributor to the risk of cardiovascular disease, cancer and inflammatory disorders. Part of the reason for the controversy, Kang explains, is that studies using diet to create different omega-6/omega-3 ratios in animal models may introduce changes caused by other dietary factors, such as calories, potentially confounding the results.

One type of animal that naturally produces all fatty acids is the c.elegans roundworm, and in 2004 Kang's group reported that mice transgenic for a c.elegans gene called fat-1 converted omega-6s into omega-3s in their tissues. The current study describes how crossbreeding the fat-1 mouse

with another strain transgenic for the c.elegans gene fat-2, which converts monosaturated fats into omega-6s, can produce mice expressing both c.elegans genes. Called the Omega mouse, this strain produces both omega-6 and omega-3 fatty acids in its tissue.

The crossbreeding protocol produces four different strains within the same litter – Omega mice that express both fat-1 and fat-2, strains that express only one of the c.elegans genes, and a nontransgenic strain expressing neither. Littermates fed a identical diet high in saturated fats and carbohydrates and low in omega-6s had these differences in their muscle tissues:

- nontransgenic mice had an omega-6/omega-3 ratio of 3.6 to 1
- fat-2 mice had a doubling of omega-6s and a 6/3 ratio of 5.2 to1
- fat-1 mice had increased omega-3 levels, decreased omega-6 and a 6/3 ratio of 0.59 to 1
- Omega mice had a fivefold increase in omega-3s and a 6/3 ratio of 0.75 to 1

Even when fed a high-carbohydrate, fat-free diet, both the Omega and fat-2 strains produced significant levels of both essential fatty acids.

"Since our 2004 report on the fat-1 mouse, our lab and many others have been working towards the generation of larger omega-3-producing animals – including pigs, sheep and cows – that could produce meat, milk or other foods rich in this essential fatty acid," says Kang, an associate professor of Medicine at Harvard Medical School. "While there are regulatory issues that need to be addressed, this transgenic approach may help meet the increasing demand for omega-3-rich foods and supplements, and the new Omega mouse model will help us better understand the true importance of the omega-6/omega-3 ratio for human health."

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