

AUGUST 10, 2007

Hidden Quality Control System Keeps Mothers from Producing Toxic Milk

Throughout human history, mother's milk has been regarded as the perfect food. Rich, nutritious and readily available, it is the drink of choice for tens of millions of human infants, not to mention all mammals from mice to whales.

But even mother's milk can turn toxic if the molecular pathways that govern its production are disrupted, according to a new study by Howard Hughes Medical Institute (HHMI) researchers at The Salk Institute for Biological Studies.

Writing in the August 2007 issue of the journal *Genes & Development*, a group led by HHMI investigator Ronald M. Evans reports that female mice that are deficient in the protein PPAR gamma produce toxic milk. The milk that had been nutritious instead causes inflammation, growth retardation and loss of hair in nursing mouse pups.

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- Ronald M. Evans

"We all think of milk as the ultimate food, the soul food for young animals," said Evans. "The quality of that milk is also something that is genetically predetermined."

In essence, the new finding reveals a genetic program for ensuring that mother's milk is the wonder food it is hailed to be: "We stumbled onto a hidden quality control system. Milk has to be a very clean product. It seems there is a whole process the body uses so that milk is scrubbed and doesn't have anything toxic in it."

Evans said the finding was unanticipated, discovered when his group engineered mice to be deficient in PPAR gamma, a protein that helps regulate

the body's sugar and fat stores. Mouse pups developed growth retardation and hair loss when they nursed on mothers who lacked the gene to produce PPAR gamma in blood cells and cells that line the interior of blood and lymph vessels.

“It's one of those unexpected observations,” Evans explained. “It tells you the mother can transmit quite a bit more than nutrition through the milk.”

Evans's group found they could reverse the toxic effects of the milk by letting the affected mouse pups nurse on a mother without the genetic variation in PPAR gamma.

Further studies showed that the mouse mothers with the PPAR-gamma deficiency produced milk with oxidized fatty acids, toxic substances that can prompt inflammation.

Evans and his colleagues showed that they could reverse the toxic effects of the milk by administering aspirin or other anti-inflammatory agents. “If you suppress the inflammation, the hair grows back,” said Evans.

PPARs are a widely studied family of nuclear receptors, proteins that are responsible for sensing hormones and other molecules. They work in concert with other proteins to switch genes on or off and are intimately connected to the cellular metabolism of carbohydrates, fats and proteins.

Although their discovery came as a surprise, Evans said it should have been obvious that there would be a mechanism in place to ensure the quality of milk.

“We should have realized there is something very special about it,” he said. “The reason we haven't heard about toxic milk is because there is a system that keeps it clean. It is logical and should have been anticipated.”

In Evans's view, PPAR gamma's role in ensuring the quality of mother's milk is likely to be a fundamental feature of evolution.

Lactating mothers, he noted, are not protected from inflammation, yet the milk they produce must be a pristine product: “Healthfulness in the body or products of the body is due to a (genetic) program, a process designed over the course of evolutionary history to maintain health.”

PPAR gamma's role in cleansing milk is “a very straightforward variation on how this system controls both lipid metabolism and inflammation. It's the secret of keeping them apart. That may be the reason the whole system exists,” Evans said.

In the human population, there are variants in the genetic program that governs PPAR gamma, which alters the fate of sugar and fat in the body. The system is already the target of anti-inflammatory drug therapy used to manage conditions such as diabetes.

Co-authors of the new *Genes & Development* article include Yihong Wan, Ling-Wa Chong and Chun-Li Zhang, all of The Salk Institute; and Alan Saghatelian and Benjamin F. Cravatt of The Scripps Research Institute.