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Possible drug target for obesity treatment a no-brainer: study

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Scientists at the University of North Carolina at Chapel Hill School of Medicine have discovered a gene that when mutated causes obesity by dampening the body's ability to burn energy while leaving appetite unaffected.

The new research could potentially lead to new pharmacologic approaches to treating obesity in humans that do not target the brain, according to study senior author Yi Zhang, Ph.D., Howard Hughes Medical Institute investigator and professor of biochemistry and biophysics in the UNC School of Medicine. Zhang is also a member of the UNC Lineberger Comprehensive Cancer Center.

The findings also add new knowledge to the burgeoning field of epigenetics, in which heritable changes in gene expression or physical appearance are caused by mechanisms besides changes in the underlying DNA.

The gene in question encodes for a specific epigenetic factor, an enzyme called Jhdm2a. In 2006, Zhang showed that Jhdm2a was able to demethylate, or remove, a methyl group from one of four histone proteins bound to all genes. Because they are so intimately associated with DNA, even slight chemical alterations of histones can have profound effects on nearby genes.

The new study focused on a line of so-called "knockout" mice that lacked the Jhdm2a gene. Zhang found impairment in two molecular

signaling pathways important for normal function in brown fat tissue and muscle cells. Both pathways exert a major influence on metabolism, the body's conversion of food to energy. Without the enzyme, the mice had reduced metabolisms, becoming visibly obese.

To Zhang's knowledge, this is the first mouse model to exhibit obese traits that do not resulting from an alteration in appetite, which is largely a brain function. "Given that this gene is not expressed in the brain, any drug that targets this gene would not have an effect on brain function," he said. "Therefore, we are really looking for a pure effect on metabolism."

With that in mind, Zhang anticipates that the study, published online February 4, 2009 in the journal *Nature*, could be of great interest to pharmaceutical companies eager to develop new anti-obesity drugs aimed at a novel, new molecular target expressed in non-brain tissues.

Zhang said his group will continue to look for more detailed mechanisms involved in how the enzyme regulates the relevant genes and changes in the metabolic rate.

"My lab has a long-term interest in identifying histone-modifying enzymes," said Zhang. "Three years ago, we discovered the jumanji family of histone demethylase, which is a huge family and brought big interest in the field to study this group of genes."

That body of work has contributed significantly to a new understanding that mutations in epigenetic factors such as histone demethylase enzymes can have profound physiologic effects. The team had already zeroed in on the Jhdm2a enzyme, showing in a 2007 Nature publication that the Jhdm2a gene is highly expressed in mouse testes and plays an important role in spermiogenesis, the final step in the production of a functional sperm cell. Male mice with the gene knocked out were infertile.

That discovery has provided researchers with a new potential cause for male infertility, just as the current study shows that the same genetic defect leads to obesity in both male and female animals, shedding new light on the role of epigenetics in regulating metabolism.

"So this gene has at least two biological functions," Zhang said. "One is control of spermiogenesis; the other is control of metabolism."

This finding was not necessarily expected by the researchers. "Nobody could have predicted that this gene had this particular function in regulating metabolism," Zhang said. "The histone-modifying enzymes actually have broad effect - every gene is packaged by histones. Therefore, when modifying histones, you can't necessarily predict what function will be affected."

In addition to being obese, the Jhdm2a knockout mouse also developed other characteristics related to human metabolic disorder, such as hyperlipidemia (raised lipid levels) and insulin resistance. Whether the mouse results will be mirrored in humans remains to be seen. "We don't know whether this gene is defective in some of the obese or metabolic syndrome patients - those are things that need to be investigated," Zhang said.

One of the lines of research Zhang and his colleagues will pursue is to conduct experiments with "conditional" knockout mouse models, in which the gene of interest is functionally removed from specific tissues, such as, in this case, brown fat or muscle tissue. According to Zhang, "that way we can ask specific questions and can pinpoint the specific tissue or cell types…then we can also pinpoint the specific molecular mechanism."

Source: University of North Carolina School of Medicine