Without second wave of brown fat, young mice can't live without mama

February 7 2012

For all those who have wondered where they'd be without their mothers, a study reported in the February *Cell Metabolism* puts a whole new spin on the question. Mice whose mothers pass along a mutant copy of a single imprinted gene can't keep themselves warm and die soon after leaving the comfort of the nest. The findings also reveal that the babies require a second round of heat-generating brown fat to survive.

"When that second wave is delayed, it gets them in the end," said Anne Ferguson-Smith of the University of Cambridge.

The findings also show how "exquisitely sensitive" animals can be to seemingly subtle molecular-level effects that change the dose of particular genes, say Ferguson-Smith and first author of the study Marika Charalambous.

Imprinted genes do different things depending on whether they came from your mother or your father and are especially important in mammalian growth and development. The genes are normally programmed in eggs or sperm to be turned off or on, leaving embryos and offspring with half as much of the gene's product as they would have if both copies were on.

Ferguson-Smith and her team are really interested in understanding the importance of this type of regulatory control in the mammalian genome —and they think understanding what those genes do is a good place to start. Earlier studies showed that complete loss of imprinting in a small

cluster of genes on chromosome 12 produced mice that die before they are born.

The mice in the new study carry a mutation in this same spot, but the animals are rather unique in that the maternally inherited gene (which is normally switched off) is switched on—but only a little bit.

"The protein-coding genes on the maternal chromosome are usually off," Ferguson-Smith said. "But here they are on by about 30 percent." While the mice that die before birth have 200 percent expression of the gene, the mutants in the new study have 130 percent. They still die, but not as early.

"In the mutant, the rather modest overexpression of this gene at a critical time doesn't completely compromise brown fat, but it causes a delay in its timely formation right before weaning," Charalambous says. At that stage, even normal animals are especially vulnerable. They are beginning to roam and find food on their own but are still very small, and mutants with compromised brown fat cannot maintain their body temperatures.

Not only are the mutant animals lacking in brown fat, but they also make too little thyroid hormone, which is important for brown fat to function. As a result, the animals fail to thrive and die. The researchers also showed that mutant mice could be rescued by simply placing them on a heat mat.

"This was a real detective story," Ferguson-Smith said. "It took a lot of time to work out what was happening."

This one particular cluster of imprinted mouse genes is also a model for the importance of genetic variation in regulatory regions throughout the genome, the researchers say.

"Studies of genetic variation associated with human disease are revealing that most variation occurs within intergenic regulatory regions rather than in coding sequences," the researchers wrote. "Whilst the model we describe was generated by genetic manipulation, it illustrates how a regulatory mutation influencing gene dosage can have a dramatic effect on whole body physiology."

Provided by Cell Press