'Supermodel' mouse reveals mechanisms that regulate metabolism, researchers find

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Dr. Bruce Beutler is a Professor of Immunology at the University of Texas Southwestern Center for the Genetics of Host Defense. Credit: UT Southwestern

A lean "Supermodel" mouse type has revealed the potentially critical role played by a largely unknown gene that regulates metabolism, findings that could provide new insight into diseases ranging from diabetes to obesity, a new study by UT Southwestern Medical Center researchers suggests.

The Supermodel mouse's phenotype – the physical characteristics that

result from its gene makeup – include being very small in size, with an unusual body form caused by abnormal distribution of fat, said Dr. Zhe Chen, Assistant Professor of Biophysics, and Dr. Bruce Beutler, Professor of Immunology, with UT Southwestern's Center for the Genetics of Host Defense. The mouse phenotype is nicknamed "Supermodel."

"This mouse is important because it has revealed a new regulatory protein that's very important for normal metabolism, but was never known to exist before," said Nobel Laureate Dr. Beutler, Director of the Center for the Genetics of Host Defense. "The implications of the work may be felt in diabetes and obesity research, the study of wasting in chronic disease, the study of muscle cell function, and perhaps other fields."

While at the Scripps Research Institute, Dr. Beutler developed a mouse mutagenesis program, which at UT Southwestern has become the largest and most technologically advanced in the world. The new mouse phenotype was discovered in the lab's colony of mutant mice several years ago, but the mutation was discovered and studied entirely at UT Southwestern, in a collaboration that also involved researchers Dr. William Holland, Assistant Professor of Internal Medicine, Dr. Aktar Ali, Assistant Professor of Internal Medicine, and John Shelton, lab manager in Internal Medicine. Together, they found that a mutation in a gene called *Samd4*, about which almost nothing was known in mammals, results in the abnormally lean mice, which also have diminished insulin responses to glucose and arginine.

"Whereas many heritable obesity phenotypes are known, lean phenotypes are comparatively uncommon. Yet they can reveal critical checkpoints regulating energy balance," the researchers said.

The mice seem to waste energy, consuming excessive oxygen and

producing a commensurately higher amount of CO2, despite being relatively inactive. Much of the fat in these mice seems to be abnormal, similar to "brown fat" of hibernating species.

The findings, appearing in the *Proceedings of the National Academy of Sciences*, may be explained by the apparent involvement of Sterile alpha motif domain containing protein 4 (Samd4) in a specific cell signaling pathway, which tell cells how to interact, called mTORC1. mTORC1 is a master regulatory complex that governs aspects of energy balance, including metabolism, development, autophagy (cell recycling), and other processes in cells.

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