METABOLISM

Deer mice bring genetic diversity to metabolic research

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Research with conventional laboratory mice has revealed much about the specific molecular players and signaling cascades that contribute to various metabolic conditions. But inbred mice can be less useful when trying to understand the role of genetic variation in disease. Inbred mice are more or less the same genetically; humans, far from it.

Hippokratis Kiaris and his lab at the University of South Carolina (USC) had been using *Mus musculus* to study endoplasmic reticulum (ER) stress and the ensuing unfolded protein response (UPR), which contribute to the development of a number of metabolic diseases, including diabetes mellitus and hepatic steatosis (aka, fatty liver disease). But to understand how UPR varies among individuals, they needed to bring some more individuality to their rodent experiments.

About three years ago, they started working with outbred *Peromyscus maniculatus* deer mice from the Peromyscus

Genetic Stock Center at USC. The Center has maintained and distributed outbred stocks of deer mice for over thirty years, and the animals remain genetically diverse. In their first research paper with deer mice, published recently in *Disease Models and Mechanisms*, Kiaris and his colleagues took an initial look at variation in UPR in different animals.

Their methodology was one typical of working with lab mice, though it did have to be adapted to the more distant relative—deer mice aren't just a different species, they're a different genus from *Mus*, Kiaris notes. The researchers established fibroblast cultures from 85 pubescent deer mice (43 male and 42 female), profiled UPR and its variability between cultures when the cells were treated with a chemical that causes ER stress, and then monitored phenotypes as the same animals aged and were fed a high fat, high sugar diet.

There was a lot of variability in UPR between individual animals but the

response was coordinated, and its intensity predicted susceptibility to disease later on. Deer mice with more intense UPR profiles were more likely to develop fatty livers and signs of insulin resistance than those with a weaker UPR. That “mechanistically tells you the power of the UPR as a modulator of disease outcomes systemically,” says Kiaris.

From here, the lab wants to identify the specific molecules involved in the UPR based on the deer mouse analysis and then study those further back in lab mice, which are easier to genetically manipulate at the moment. The lab mice too will serve as controls to confirm whether what is observed in deer mice extends to another species, Kiaris says, before they turn their attention to humans.

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