Dirty mice might make better models

By housing laboratory mice in hygienic and specific pathogen free barrier facilities, scientists can tightly control conditions for studying immune system function and disease. However, owing to recent failures in translating findings from mouse models to the clinic, there are growing concerns that mice might not be an appropriate species for modeling human disease. In a recent report, a group led by Stephen Jameson and David Masopust at the University of Minnesota show that, rather than blaming the mice, scientists should start taking into account their facility's housing conditions (*Nature* **532**, 512–516; 2016).

The study's goal was to compare the immune systems of laboratory mice with those of humans, to determine what effects standard barrier facility housing conditions might have on translating mouse models to adult humans. According to Jameson, "Standard lab mice don't reflect important features of the adult human immune system. We wanted to know whether this is because lab animals are shielded from microbes that normal mice encounter in the wild." In their experiments, the researchers focused on studying the composition of memory T cells, which are critical for adaptive immune responses to infections and cancer.

The group compared the immune systems of human newborns and adults with those of 'clean' laboratory mice and wild-caught or 'dirty' pet-store mice. Unlike the human adult immune system—but similar to that of human newborns— lab mice lacked effector-differentiated and mucosally distributed T cells. To determine if this trend in lab mice was due to a lack of challenge by typical environmental microbes, the research group tested T cell types in wild-caught feral mice and pet-store mice. They found that the immune systems of both wild-caught and pet-store mice had significantly higher levels of effector-differentiated T cells, a signature of the human adult immune system. They further demonstrated that, after adding pet-store mice into the cages of lab mice, the immune systems of clean lab mice began to look less like those of human newborns, and more like those of human adults.

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Overall, the results demonstrate the importance of the environment in shaping the makeup and function of the immune system. They also highlight that tight control over lab and vivarium conditions comes with a translational price tag. As said by Masopust, "Utilizing this ['dirty'] model to test vaccinations and therapeutics for cancer or transplantation may better predict how these will perform in humans."

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CONTROLLING MOUSE METABOLISM BY RADIO WAVES

The physiology behind feeding behaviors and metabolism of mammals is complicated, and research on these systems is partly hindered by a lack of tools available to examine how specific cell types in the brain can influence metabolic processes. One brain structure involved in this system, the hypothalamus, contains cells that detect blood sugar; however, this structure is located deep within the brain, making it difficult to study. Recent experiments by Stanley *et al.* (*Nature* **531**, 647–650; 2016) show that, with genetic manipulation, the activity of mouse hypothalamic neurons can be influenced with radio frequency (RF) or magnetic field stimuli from outside of the animals. This novel technique now allows researchers to delineate important relationships between the hypothalamus and metabolic function not possible with previous methods.

Stanley *et al.* began their experiments by developing a virus which, when injected into mouse hypothalamus, causes glucose-sensing neurons to express membrane channels that are activated by specific RF stimuli (465 kHz). The mice used were a special strain to ensure that the virus only affected glucose-sensing neurons. Thus, unlike some other forms of neural stimulation, only specific types of neurons were manipulated.

After virus injection, RF stimulation was applied and the blood levels of metabolic hormones and enzymes were examined. By varying the strength of stimulation, Stanley *et al.* successfully changed the amount of plasma insulin, glucagon, glucose, and expression of a liver enzyme involved in metabolism. The researchers then adjusted their technique to allow them to inhibit, or turn down, the activity of these glucose-sensing neurons. In an additional group of mice, RF stimuli now reversed most of the hormone, enzyme, and blood sugar changes they previously observed with stimulation. Thus, the researchers achieved bidirectional control of these glucose-sensing cells. Additionally, the research team used magnetic field stimulation to confirm that their technique could change the firing activity of these neurons, which couldn't be examined using RF stimuli.

Intriguingly, the group also tested the effects of magnetic fields on feeding behavior of virus-injected mice. When exposed to the strong magnetic fields near an MRI scanner, the mice either increased or decreased food intake depending on the type of virus that was expressed in the hypothalamus. This study demonstrates crucial roles of the hypothalamus in metabolism, and also presents a new method of stimulating and inhibiting neurons deep within the brain for bidirectional control of neurons and animal feeding behavior.

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