

Gender Switch?

MICE THAT CAN NO LONGER DETECT PHEROMONES BECAUSE OF A SINGLE GENE DELETION CROSS THE BOUNDARIES OF TYPICAL GENDER BEHAVIOR.

Female mice do not usually initiate sex or mount their partners. Yet a subset of mutant females, studied by HHMI investigator Catherine Dulac and her Harvard research team, has upended the world of lab mouse intercourse.

Dulac's study suggests that sexual behavior in mice is not exclusively connected to inherent differences in the male and female brain. Instead, she found that gender roles become strikingly fluid when the mice are unable to detect pheromones.

Mice detect pheromones through a chemosensory organ called the vomeronasal organ (VNO), located in the nasal cavity. The VNO requires a specific ion channel called TRPC2 to function. When Dulac and colleagues Dr. Tali Kimchi and Jennings Xu bred TRPC2 knockout male and female mice, the mutant mice ignored chemical cues that generally produce gendered behavior. Male knockouts showed a lack of aggression toward other males, and mounted male and female mice indiscriminately. Female knockouts exhibited typical male behavior, such as attacking intruding males, pelvic thrusting, and soliciting sex by using their noses to poke other mice in the rear.

"There's a major finding here," says Dulac. "Sex-specific behaviors were assumed to be controlled by sex-specific neurons. We found that the brains of animals in a given species may have

male and female components controlled by a switch. That switch is sexually dimorphic and modulated by pheromones."

Dulac is careful to clarify that olfactory cues impact sexual behavior in mice much more than in humans. Like other primates, people lack vomeronasal organs and perceive the world mostly through vision. But Dulac insists that focusing on the fact that her study pertains to olfaction is missing the point. It is the *switch mechanism*, independent of the sensory modality, that could apply to several other species, she says. "We are shattering the dogma on the male and female brain and the major importance of testosterone."

Dulac hopes that her findings will provide a fresh outlook for everybody in her field. Next, she plans to focus on whether the male knockout mice demonstrate typically female behavior. "There are some species of rodents in which the father exhibits parental behavior," she explains. "Maybe there's something there." ■

—SHELLEY DUBOIS



A female mouse shows surprising behavior by pursuing another female.

IN BRIEF

of other genes and triggers cell suicide, called apoptosis, in damaged cells.

MicroRNAs, no more than a couple of dozen nucleotides long, regulate a broad array of physiological and developmental processes. Researchers knew that microRNA levels decrease in human cancers, but they knew little about the significance of that decrease, says Hannon.

The team, working with mouse models, compared gene activity between cancerous p53 knockout cells and normal cells. Their studies revealed that p53 directly targets and switches on the genes for the miR-34 microRNA family. When these genes were turned on in cells, researchers saw an increase in apoptosis as well as cell senescence, a kind of "genetic death" in which cells lose the ability to replicate. The miR-34 genes also regulate many target genes involved in the cell division cycle.

"There has always been a hole in the p53 pathway, and people have been looking for genes that code for regulatory proteins to fill that hole," says Hannon. "That hole may well be filled by microRNAs."

NEW CLUE INTO HOW DIET AND EXERCISE ENHANCE LONGEVITY

The traditional prescriptions for a healthy life—sensible diet, exercise, and weight

control—extend life by reducing signaling through a specific pathway in the brain, according to HHMI researchers who discovered the connection while studying long-lived mice.

HHMI investigator Morris F. White at Children's Hospital Boston and his colleagues published their findings July 20, 2007, in *Science*.

The researchers sought to understand the role of the "insulin-like" signaling pathway in extending life span. This pathway governs growth and metabolic processes in cells throughout the body. Insulin and insulin-like growth factor-1 activate the pathway when they switch on proteins inside the cell called insulin receptor substrates (Irs).

When scientists knocked out one copy of the *Irs2* gene in mice, the animals lived 18 percent longer than control mice. When they removed both copies of the gene, the mice were more active as they aged, and their glucose metabolism resembled that of younger mice.

White speculates that the insulin-like signaling pathway in the brain might also promote age-related brain diseases such as Alzheimer's disease, Huntington's disease, and general dementias. "It might be that, in people who are genetically

predisposed to these diseases, too much insulin overactivates *Irs2* in the brain and accelerates disease progression," he says.

PROTEIN SUPPRESSES PROSTATE CANCER METASTASIS

HHMI researcher Richard O. Hynes at the Massachusetts Institute of Technology and others have shown in mice that a protein whose function is lost in a broad array of cancers normally suppresses prostate cancer metastasis. Testing for loss of the protein, called Protein 4.1B, could help clinicians predict which cancers are likely to spread.

The team published their findings in the July 31, 2007, issue of the *Proceedings of the National Academy of Sciences*.

To test how loss of Protein 4.1B affected tumors in living animals, the researchers implanted clumps of human prostate cancer tumors into the prostates of mice. From these mice, the researchers isolated variants of prostate cancer cells with different metastatic potential. A genetic comparison of the cells revealed that the highly metastatic cells had lost Protein 4.1B gene activity. Furthermore, when the researchers suppressed the Protein 4.1B gene in poorly metastatic cells, those cells became highly metastatic.