In mice, anxiety is linked to immune system

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(PhysOrg.com) -- In the first study ever to genetically link the immune system to normal behavior, scientists at Rockefeller and Columbia universities show that mast cells, known as the pharmacologic bombshells of the immune system, directly influence how mice respond to stressful situations. The work, to appear this week in the *Proceedings of the National Academy of Sciences* and to be highlighted in *Science*, chips away at the increasingly stale idea that the two most complex systems in the body have entirely separate modes of operation.

Eight years ago, scientists from Columbia University discovered that mast cells travel to the brain from other organs early on in development. "We now knew that mast cells resided in the brain but we didn't know their function," says Rockefeller University's Donald Pfaff, head of the Laboratory of Neurobiology and Behavior. "But we know that they synthesize a large number of important chemical mediators that could potentially have severe neurophysiological effects."

Since then, mast cells have been associated with several behaviors and conditions. For example, the number of mast cells and anxiety levels in mice have been shown to ebb and flow with the onset of stressful conditions, including asthma and food allergies. Lethargy has also been associated with an excess of mast cells. "However, we have now been the first to manipulate mast cells genetically and pharmacologically and show an immediate behavioral effect," says Pfaff.

In their work, Pfaff and postdoc Ana Ribeiro, and the Columbia team, led by senior author Rae Silver and graduate student Kate Nautiyal, bred

mice that lacked mast cells and compared their behavior in stressful situations to the behavior of mice that had a full or a moderate arsenal of mast cells. The researchers observed how willing the mice were to navigate open and lit environments and high spaces, which mice find anxiety-producing. In the wild, if a mouse is down in its own burrow, it's not visible to predation. But if it's bold, that is, if it has low anxiety, it will go out where it can potentially be seen by predators and hunted.

The results were striking. When the researchers placed the mice in an elevated maze with four long arms -- two simulated a canyon and the other two a cliff -- mice that lacked mast cells preferred to stay in the canyons, entering and investigating the doors to the cliffs significantly fewer times than mice with mast cells. When placed in a square box, mast cell-deficient mice preferred to scuttle against the walls, and were more hesitant to venture out to the center of the box than mice with mast cells. They also defecated more, a physiological sign of anxiety. However, the genetically different mice did not show differences in overall arousal or locomotion, suggesting that their behavioral changes were specific to their anxious state.

To confirm the behavioral and physiological differences among the genetically different mice, the researchers conducted an additional experiment. In mice that had mast cells, they used a drug that prevents sack-like granules in mast cells from busting open and releasing the array of mood and immune regulators they contain, such as serotonin, histamine, and various biochemical mediators. When the researchers targeted the drug to work specifically on mast cells in the brain, rather than in other organs, the mice showed much higher levels of anxiety-like behavior during the tests, but showed no difference in other tested physiological responses.

"The two most complicated and highly integrated systems in the body – the immune system and the nervous system – have been shown to be

linked," says Pfaff. "We now show that mast cells in the brain link these two systems at the level of behavior."

Provided by Rockefeller University