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Is obesity a ciliopathy, triggered by malfunctioning primary cilia?

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Is obesity a ciliopathy, a disorder such as polycystic kidney disease (PKD), which is triggered by a defect in the microscopic hair-like cilia that protrude from virtually every cell of humans and other vertebrates?

University of Alabama, Birmingham (UAB) researchers told the American Society for Cell Biology (ASCB) 2011 Annual Meeting in Denver on Dec. 6 that mutations in primary cilia may scramble signaling pathways in the hypothalamus, the appetite-regulating region of the brain, and trigger chronic obesity.

Their preliminary findings suggest that mutated primary cilia are unable to dock the melanin concentrating hormone (MCH) receptor, a key control on appetite.

Levels of another appetite suppressing hormone, leptin, seems to play a secondary role in obese mice modeling a primary cilia defect, they reported.

To explore the relationship between cilia and obesity, the researchers, Nicolas Berbari, Ph.D, Bradley Yoder, Ph.D., and UAB colleagues, turned to genetically modified mice models of Bardet-Biedl syndrome (BBS), which is characterized by obesity.

A rare genetic disorder in humans, BBS is a ciliaopathy linked to defects in the proteins that function in primary cilia. Its symptoms include cystic kidneys, blindness, mental deficits, and extra toes and fingers.

Unable to regulate their feeding behavior, the BBS model mice became obese. The researchers noted that mutant mice lost leptin sensitivity when obese but saw the mice regain leptin sensitivity as their diet was restricted and their weight fell to normal levels.

These results indicated that leptin sensitivity in BBS mice models is a secondary consequence, not the cause, of the BBS animals' obesity, said Berbari.

Berbari and colleagues then turned their attention to other potential appetite regulating pathways.

In previous research in the Ohio State University lab of Kirk Mykytyn, Ph.D., Berbari had showed that the MCH receptor, another player in appetite regulation, localizes in primary cilia in normal brain cells known to regulate feeding behavior.

In normal brain cells of the hypothalamus, the MGH receptor occurs in the primary cilia. However, in the BBS mutant mice, Berbari reported that the MCH receptor was unable to enter the cilium..

The new research findings about the MCH receptor underscore the role primary cilia may play in obesity, said Berbari, who noted that unraveling the complex signaling roles of primary cilia may improve scientific understanding of other human behaviors including learning, memory, and mood.

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