MedicalXpress

Important clue to understanding the pathogenesis of ciliary disorders

July 22 2010

A research team led by Dr. Heiko Lickert of Helmholtz Zentrum Muenchen has pinpointed a gene that is essential for the physiologically correct disassembly of cilia. Errors in the regulation of cilia assembly are implicated in a variety of human syndromes. Until now, however, the consequences of faulty cilia disassembly have not yet been elucidated. The findings are reported in the current issue of the prestigious journal *Developmental Cell*.

Scientists led by Dr. Heiko Lickert, research group leader at the Institute of Stem Cell Research of Helmholtz Zentrum München, have identified the first gene shown to regulate cilia disassembly in a living organism. If the gene is defective, double and forked cilia develop - thus the name Pitchfork. The consequences of the mutation include typical defects in the left-right asymmetry of body organs and heart failure.

The functional investigations were conducted primarily on the mouse model, together with the Institute of Developmental Genetics and the Department of Protein Analytics of Helmholtz Zentrum München. However, Dr. Lickert and his collaboration partner Nicolas Katsanis of Duke University in the U.S. were also able to show mutations in the Pitchfork gene in patients with ciliary diseases. In humans, the substitution of merely one amino acid in the Pitchfork protein can lead to an inversed position of all internal organs (situs inversus), to kidney and liver diseases, but also to severe heart defects. "Our study" Dr. Lickert said, "provides a new entry point to understand and categorize ciliary disease."

Cilia are hair-like cell protuberances, 5 to 10 µm long and 250 nm thick, which are present in almost all human or animal cells. They function like antennas in the cells and play a pivotal role in the perception of the cellular surroundings and signal transduction.

Defective cilia usually have genetic causes and severe consequences: In recent years more than 30 diseases could be traced to ciliary dysfunctions. These ciliopathies affect numerous organ systems and show diverse clinical symptoms, but the molecular and cellular basis for this is not yet understood. The resulting disorders include developmental defects such as polycystic kidney, liver and pancreas diseases (incidence 1:800) and also heart defects and adiposity. An increased risk for common diseases such as diabetes or cancer is also very probable. Despite the far-reaching significance of cilia, many aspects of the biology of these organelles are not yet known and many questions remain to be answered. These include the regulation of the body's own processes (homeostasis), signal transduction between cells, organ and embryonic development, and the assembly and disassembly of cilia in the different phases of the cell cycle.

More information: Kinzel D. et al.: Pitchfork regulates primary cilia disassembly and left-right asymmetry. Developmental Cell 2010; 19(1) pp. 66 - 77; DOI:10.1016/j.devcel.2010.06.005

Provided by Helmholtz Zentrum München