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Research reveals molecular mechanism underlying severe anomalies of the forebrain

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Researchers of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch have now identified and described a molecular mechanism underlying the most common malformation of the brain in humans. In holoprosencephaly (HPE), the forebrain (prosencephalon) is only incompletely formed. Here a binding site (receptor) for cholesterol plays a key role. If this receptor is defective, specific signals cannot be received, and the forebrain cannot separate into two hemispheres, as Dr. Annabel Christ, Professor Thomas Willnow and Dr. Annette Hammes have now shown in mice.

Cholesterol has a bad reputation because it may lead to vascular calcification in adults (atherosclerosis) as well as to heart attacks and strokes. However, cholesterol is vital for embryonic development because it controls the development of the central nervous system. The lack of it can lead to severe developmental disorders of the forebrain (prosencephalon), the largest region of the human brain. One in 250 pregnancies does not come to term due to this malformation called holoprosencephaly (HPE). One in 16000 children is born with HPE, of which the mildest form is cleft lip and palate. In severe forms of HPE the affected children do not survive the first weeks of life.

HPE may be due to genetic factors, but environmental factors such as viral infections or alcohol abuse during pregnancy may also cause the malformation. Moreover, the cholesterol metabolism is also frequently disturbed. Thus, patients whose bodies cannot produce cholesterol due to a genetic disorder inevitably have HPE.

As Professor Willnow explained, the human brain develops from the neural tube, a simple tube-like cluster of cells in the embryo. Why defects in cholesterol metabolism lead to a developmental disorder of the neural tube and to HPE is thus far not completely understood. The studies of the Berlin researchers may give a possible clue. They identified a receptor called LRP2 that is formed in the neural tube and can bind lipoproteins, which are the transport form of cholesterol.

Interestingly, this receptor also binds an important signal molecule of forebrain development (sonic hedgehog, abbreviated SHH). As the researchers demonstrated, this lipoprotein receptor drives the accumulation of SHH in the neural tube at a specific site and induces the development of the forebrain structures. The researchers now suspect that cholesterol – directly or indirectly – plays a central role in controlling the activity of this novel receptor and assume that disturbances in cholesterol metabolism lead to a loss of function of this auxiliary receptor for SHH signaling.

More information: LRP2 Is an Auxiliary SHH Receptor Required to Condition the Forebrain Ventral Midline for Inductive Signals. *Developmental Cell*, DOI 10.1016/j.devcel.2011.11.023

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