Mouse study shows fetal heart can grow cells to repair disease damage

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(PhysOrg.com) -- A recent study in mice shows the ability of the fetal heart to grow healthy cells to compensate for cardiac tissue lost to disease. The mice are normal at birth and their hearts function well during their youth. However, these gains can be short-lived. About 40 percent had signs of heart disease in early adulthood, and 10 percent died of heart failure.

Results published in the Oct. 14 edition of *Development Cell* describe the capacity of a mouse heart to repair extensive damage while in the womb, even after all the heart's major cell types and structures have developed. The finding that so many of these mice grew up to have heart disease suggests that some human heart diseases in adults may have originated from damage in the womb. An international group of scientists from Australia, Germany, and the United States conducted the study.

Most organs in developing embryos and fetuses have moderate leeway in changing their growth in response to external and internal influences. However, except for the liver, extensive regeneration of diseased or damaged tissue has not been observed before in mammals. This phenomenon was previously thought to occur only in fish and in amphibians, like frogs and newts.

Timothy Cox, University of Washington (UW) research associate professor in pediatrics and the study's senior author, said, "What's noteworthy about this study is that it suggests that a diseased or damaged heart in a developing embryo can largely repair itself. The mice were

born with normal cardiac function that persisted, according to our monitoring, during the first months of life."

Nevertheless, he added, despite the fetal heart self-repairing and the newborn mice appearing healthy, their hearts started to give out as they entered adulthood.

In addition to his work on congenital disorders at the UW, Cox is a member of the Center for Tissue & Cell Sciences at Seattle Children's Research Institute and a researcher at the UW Center for Human Development & Disability. He moved to Seattle recently from Australia, where he was a researcher in anatomy and developmental biology at Monash University and in biomedical and molecular science at the University of Adelaide.

In their study, the researchers bred mice that had a sex-linked genetic defect that caused a disorder in the mitochondria, or tiny powerhouses, inside their heart cells. Mitochondrial disorders are one of the leading causes of fatal heart disease early in life, and they may possibly contribute to failure of aging hearts as well. The researchers found that most of the male mice with this genetic defect on their single X chromosome, and the female mice with the defect on both their X chromosomes, died midway through gestation.

The researchers assumed that the female mice with the defect on only one X chromosome would have the genetic deficiency in about 50 percent of their heart cells. Females generally have only one of their two X chromosomes activated in each cell. The de-activation of one or the other X chromosome is random. To the researchers' surprise, none of the females carrying both the normal and the defective X chromosome died before birth. Analysis of cardiac tissue from newborn and two-month old female mice showed few cellular changes and no major pathology. Measurements of specific protein marker and of cellular respiration

were normal.

At about the middle of gestation, female embryos with one defective X chromosome had an abundance of heart cells with enlarged and disorganized mitochondria, but also many cells containing normal mitochondria. By the time females of this genetic type were born, their hearts appeared to be remarkably normal.

Additional analysis suggested that this normalcy was likely due to such a proliferation of healthy cells that the proportion of defective cells became smaller and smaller, yet remained resident amongst the predominantly healthy cells. The proportion and the location of these residual defective cells, the authors surmised, might have contributed to heart problems later in life. The heart's conduction system, which helps control the heartbeat, might have become more severely affected than it appeared at birth.

Future research in the area of fetal heart self-repair, Cox said, will probably be geared toward identifying the signals that turn on the regenerative response in healthy heart cells. If these signals could be identified, Cox said, switching them on again might help repair adult heart tissue. Scientists are also interested in when or if the heart loses the capacity to repair itself, and what governs the timing and the mechanisms of this loss.

Researchers also are hoping, he added, to understand why some of the apparently healthy baby mice in this study ended up showing signs of heart disease in young adulthood or dying early from heart failure. This information might someday help pinpoint which children are at risk for heart disease as the enter adulthood.

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