Genetic cause of heart valve defects

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This image shows Dr. Elvira Mass, Dr. Dagmar Wachten and Prof. Dr. Michael Hoch (from left). Credit: (c) Volker Lannert/Uni Bonn

Heart valve defects are a common cause of death in newborns. Scientists at the University of Bonn and the caesar research center have discovered "Creld1" is a key gene for the development of heart valves in mice. The researchers were able to show that a similar Creld1 gene found in humans functions via the same signaling pathway as in the mouse. This discovery is an important step forward in the molecular understanding of the pathogenesis of heart valve defects. The findings have been published in the journal *Developmental Cell*.

Atrioventricular septal defect (AVSD) is a congenital heart defect in which the heart valves and cardiac septum are malformed. Children with Down's syndrome are particularly affected. Without surgical interventions, mortality in the first months of life is high. "Even in adults, unidentified valve defects occur in about six percent of patients with heart disease," says Prof. Dr. Michael Hoch, Executive Director of the Life & Medical Sciences (LIMES) Institute of the University of Bonn.

For years, there have been indications that changes in the so-called Creld1 gene (Cysteine-Rich with EGF-Like Domains 1) increase the pathogenic risk of AVSD. However, the exact molecular connection between the gene and the disease was previously unknown. A research team from the LIMES Institute and the caesar research center in Bonn has now shown, in a mouse model, that Creld1 plays a crucial role in heart development. Researchers at the University of Bonn switched off the Creld1 gene in mice: "We discovered that the precursor cells of the heart valves and the cardiac septum could no longer develop correctly," reports Dr. Elvira Mass from the LIMES Institute. This was an important indication that Creld1 is required at a very early stage for the development of the heart.

In embryonic development, the heart develops as the first organ

"In the embryonic stage, the heart develops as the very first organ. It pumps blood through the vascular system and is essential for supplying other organs of the body with oxygen and nutrients," reports the cooperation partner, Dr. Dagmar Wachten who directs the Minerva research group "Molecular Physiology" at the caesar research center and is engaged in research involving cardiac development. The research team discovered that the Creld1 gene controls the development of heart valves via the so-called calcineurin NFAT signaling pathway. The heart valve defects in mice lacking the Creld1 gene ultimately led to insufficient oxygen supply to the body, causing the mouse embryo to cease development after approximately eleven days.

Potential starting point for improving diagnostic measures

The research team anticipates that the findings can be carried over to patients. With regard to cardiac development, mice and humans are very similar and the Creld1 gene and the calcineurin/NFAT signaling pathway likewise function analogously in both species. "Our results contribute to a better

understanding of the molecular basis of heart development and, in the medium-term, to improved diagnosis of unidentified heart valve diseases," explains Prof. Hoch. Interestingly, the calcineurin/NFAT signaling pathway is not only active in the heart but also in immune cells. In transplant medicine, it has to be suppressed over the long-term by drugs such as cyclosporine A so that transplanted organs are not rejected. "Within the scope of the ImmunoSensation Excellence Cluster, we are currently investigating the mechanism of action of Creld1 in immune cells," says Prof. Hoch, who is convinced that it will also be of importance in transplant medicine in the future.

More information: Murine Creld1 controls cardiac development through activation of calcineurin/NFATc1 signaling, *Developmental Cell*, DOI: 10.1016/j.devcel.2014.02.012

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