New insights into the development of the heart

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Viewed from the outside, our body looks completely symmetrical. However, most internal organs – including the heart – are formed asymmetrically. The right side of the heart is responsible for pulmonary circulation; the left side supplies the rest of the body. This asymmetry allows the heart to do its job effectively. In a study on zebrafish embryos, the researchers Dr. Justus Veerkamp and PD Dr. Salim Seyfried from the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch have now shown how the left and right sides of the heart develop differently. Their findings were published in the journal *Developmental Cell*.

A protein called Nodal plays an important role in the development of asymmetry. In an early stage of heart development, Nodal is formed on the left side and triggers a multi-step signaling cascade that enables the cardiac progenitor cells on this side to migrate faster. The researchers were able to observe the migration of the cardiac progenitor cells in the zebrafish embryos in vivo. Since the embryos are transparent it is possible to view each single cell using the microscope.

While analyzing the individual proteins involved in the asymmetric development of the heart, Dr. Veerkamp and Dr. Seyfried encountered a surprise: Previously, scientists had assumed that another signaling molecule, the protein Bmp, triggered cell migration on the left side of the heart and, as a consequence, must be very active there.

Current studies, however, show just the opposite: Bmp reduces the

motility of the cells that form the heart. The protein Nodal regulates this process by activating the enzyme Has2. This in turn restricts Bmp activity on the left side. Thus, the cells of the left side of the heart migrate faster and ultimately form a functional, asymmetric heart.

However, when the researchers modulated the experiments so that individual proteins of the signaling cascade were expressed at elevated or decreased levels, the cardiac cells showed subtle differences in "random walk" cell motility rates. This resulted in the development of hearts that were completely symmetrical or whose sides were laterally inverted.

Many of these malformations of the heart in zebrafish embryos are also known in humans. Often asymmetric disorders not only affect the heart but also other organs such as the spleen. It may be missing or two spleens may be present. Depending on the severity of the malformations, the problems of the affected individuals vary in seriousness. It is also possible that the processes identified by the researchers are also involved in the development of diseases in which cell migration plays a role.

More information: Unilateral dampening of Bmp activity by Nodal generates cardiac left-right asymmetry
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