



Uncovering the mysteries behind heart defects

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Until now, the reasons why some children are born with holes in their hearts, or faulty heart valves, have eluded doctors and scientists. Findings published online today in the prestigious PNAS journal may hold at least some of the answers.

“It’s a great tragedy when children need open heart surgery almost as soon as they are born,” said Professor Fabienne Mackay, Director of the Autoimmunity Research Unit at the Garvan Institute of Medical Research. “We are very hopeful that our discovery of the actions of one molecule, CXCR7, may help prevent this surgery in the future.”

CXCR7 is a chemokine receptor. Chemokines are substances in our bodies that help cells migrate to specific parts of the body during its development. They attach themselves to receptors on cells, attracting other cells to that spot. The cells lured towards the chemokine will then develop into brain cells, bone cells, or heart valve cells, depending what the body needs.

“At Garvan we could see there was a chemokine receptor, CXCR7, that we knew nothing about, so we designed a mouse without that receptor to see what would happen. When CXCR7 is genetically ‘knocked out’ of mice, their pups die the day they are born, suffering from catastrophic heart defects.”

“On discovering this, we approached Christine Biben and Richard Harvey, developmental scientists from The Victor Chang Cardiac Research Institute, to see if they could help us understand why. They found that the defect lay in aortic and pulmonary valves. There are usually 3 leaflets that activate those valves, or flaps. In our mice, the valve flaps, which are usually very flexible, were thick and rigid, like bone cartilage. Sometimes the leaflets were so overgrown, that you couldn’t distinguish the structure any more. Interestingly, 50% of our mice also had holes in their hearts.”

“So our mice were basically dying of cardiac failure or cardiac arrest, unable to pump blood through their bodies. To form normal heart valves, they needed migration of endothelial cells to the right structure in the valve. We think CX CR7, and the chemokine that attaches to its surface, could be critical in attracting the endothelial cells that are precursors of the valve – and possibly also the walls of the heart.”

“Knowing that CXCR7 is critical for proper formation of the heart in mice obviously begs the question ‘is it equally critical in humans?’ and we believe it might be.”

“We are working with Westmead Hospital’s Dr David Winlow, who operates on children born with congenital heart defects. Our next step is to look at the genetic make up of patients that are born with congenital heart defects similar to our mice. If our predictions are correct, it may be that drugs can be developed to bypass the missing CXCR7 receptor, small molecules that will activate that downstream mechanism that would lead to a normal heart development.”

“It’s even possible that we might be able to screen families for that mutation, and perhaps give the mother a medication that will prevent her kids from being born with a heart defect.”

Notes to editors

The following paper will be published online in PNAS, a publication by the National Academy of Sciences of the United States of America: Disrupted cardiac development but normal hematopoiesis in mice deficient in the second CXCL12/SDF-1 receptor, CXCR7

ABOUT GARVAN

The Garvan Institute of Medical Research was founded in 1963. Initially a research department of St Vincent’s Hospital in Sydney, it is now one of Australia’s largest medical research institutions with approximately 400 scientists, students and support staff. Garvan’s main research programs are: Cancer, Diabetes & Obesity, Arthritis & Immunology, Osteoporosis, and Neuroscience. The Garvan’s mission is to make significant contributions to medical science that will change the directions of science and medicine and have major impacts on human health. The outcome of Garvan’s discoveries is the development of better methods of diagnosis, treatment, and ultimately, prevention of disease.

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