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Flying to the heart of the matter

The first systematic map of heart failure identifies hundreds of genes that regulate heart function

Was it a horror film or a sci-fi spoof? Fans of the 1986 blockbuster “The Fly” have been debating the issue ever since but one point has always been accepted. The underlying idea is plainly too far-fetched to be plausible: man and flies have nothing at all in common and the idea that they could exchange genes is ridiculous. Or is it? The cover story of the scientific journal *Cell* (April 2, 2010) is a paper in which scientists at the Institute of Molecular Biotechnology (IMBA) in Vienna, Austria, report that human hearts and fly hearts are essentially under the control of many of the same genes. Using a model of heart failure in the fly, they present a systematic map of the genes involved in heart disease and heart failure and confirm that one of the control mechanisms they have identified really is associated with heart failure in flies, mice and in man.

500 genes involved in regulation of heart function

Heart disease represents the most common cause of death in Europe and North America but our knowledge of its genetic causes remains scant. In close collaboration with Rolf Bodmer of the Sanford-Burnham Medical Research Institute in La Jolla, California, Greg Neely in Josef Penninger’s group at the IMBA has screened for genes that regulate heart function in the fly. Taking advantage of the in-house fly library VDRC (Vienna Drosophila Research Center), he found nearly 500 genes that when inhibited caused increased mortality when the flies were stressed. Penninger’s collaborators at Strand Life Sciences in Bangalore, India used advanced computer methods to investigate the interconnections between the genes and the result – which looks like a super-complicated version of a city transport system – is the first global map of the genetic interactions behind heart function and heart failure.

From fly to mouse to humans

As Penninger notes, “About 35% of the hits relate to genes that are already known to be involved in heart function, so the method works. But we wanted to see what the other genes do.” One of the ‘novel’ pathways detected was the CCR4-Not complex. This is highly conserved through evolution but the idea that it has a role in the heart was new. Neely was able to confirm that it is involved in heart function in the fly, and Keiji Kuba at the Akita University School of Medicine Global COE in Japan, generated knockout mice for Not3 gene, one of the CCR4-Not components and found that the mice developed severe heart problems when subjected to cardiac stress. What does CCR4-Not do in man? Based on the results of the work in flies, it seemed possible that mutations (variants) around the site of the human *NOT3* gene could be associated with heart disease.

Working with Andrew Hicks and Peter P. Pramstaller of the EURAC-Institute of Genetic Medicine in Bolzano, Italy, and Arne Pfeufer of the Institute of Human Genetics at Technical University in Munich, who are all part of the QTSCD consortium (QT Interval and Sudden Cardiac Death), to explore this possibility using human data from ECG recordings,

this idea was shown to be correct: variants over the region are associated with changes in QT interval, which predispose to sudden cardiac death.

Penninger notes with satisfaction that “Our work on flies has identified a possible cause of human heart disease that the human genetic screens had missed.”

Results may yield clues to future therapies

The result confirms that Neely’s screen in flies can be used to identify genes involved in heart function and heart disease in mice and humans. The screen picked up very many genes, over a hundred of which have no known function. They may also represent candidates for factors that predispose individuals to heart disease. Investigating them will involve a vast amount of work that will be performed in collaboration with groups studying heart function in flies, zebra fish, mice and men. Combining data from all of these models will give an overall picture of heart function under normal and diseased conditions – and presumably important clues to new therapeutic possibilities.

The paper “A global in vivo *Drosophila* RNAi screen identifies NOT3 as a conserved regulator of heart function” by G. Gregory Neely et al. will be published in the April 2, 2010 issue of the journal *Cell*, along with a cover illustration.

About IMBA

The IMBA – Institute for Molecular Biotechnology of the Austrian Academy of Sciences – opened in 2003. It combines fundamental and applied research in the field of biomedicine. Interdisciplinary research groups address functional genetic questions, particularly those related to the origin of disease. The ultimate goal is to implement acquired knowledge into the development of innovative applications for prevention, diagnosis and treatment of disease.

About IMP - IMBA Research Center

A cooperation contract links the Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA) to the Research Institute of Molecular Pathology (IMP), which has operated since 1988 and is supported by Boehringer Ingelheim. Under the name of the “IMP – IMBA Research Center”, both institutes have access to a combined infrastructure in scientific and administrative areas. Together, the two institutes employ around 400 staff from 30 nations and are members of the Campus Vienna Biocenter.

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Illustrations and a video are available at

<http://www.imba.oeaw.ac.at/pressefoto-herzgene>