From fruit fly wings to heart failure -- why Not(ch)?

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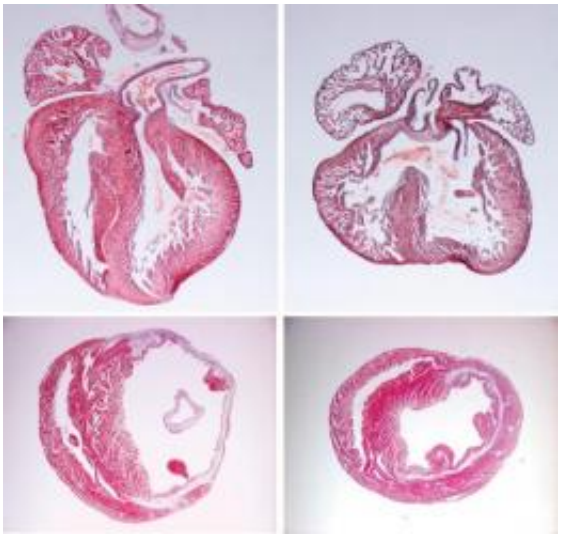

These microscopy images demonstrate the effects of Notch signaling on the hearts of newborn mice (top) and of adult mice after a heart attack (bottom). In a normal neonatal heart (top left), the two major heart chambers (ventricles) are clearly separated by tissue (septum). But when Notch signaling was inactivated in an embryo's heart muscle cells, the septum between the ventricles of the newborn mouse's heart was incomplete. The same defect commonly occurs in humans with congenital heart disease, often leading to circulatory distress. In the images of adult hearts (bottom), healthy tissue is shown in red and damaged tissue in blue. Normally (bottom left), a heart attack causes extensive tissue damage to the left ventricle (right-hand cavity), but mice in which Notch was reactivated after the heart attack had reduced tissue damage (bottom right) and improved cardiac function. Credit: Kratsios/EMBL

Almost a century after it was discovered in fruit flies with notches in their wings, the Notch signalling pathway may come to play an important role in the recovery from heart attacks. In a study published today in *Circulation Research*, scientists at the European Molecular Biology Laboratory (EMBL) in Monterotondo, Italy, are the first to prove that this signalling pathway targets heart muscle cells and thus reveal its crucial role in heart development and repair.

The Notch pathway is a molecular mechanism through which cells communicate with each other. Scientists in Nadia Rosenthal's group at EMBL used sophisticated genetic mouse models to uncover critical roles for this pathway in heart muscle cells. When they inactivated Notch specifically in the heart muscle precursor cells of early mouse embryos, the scientists discovered that the mice developed heart defects.

Curiously, increasing Notch signalling in the heart muscle cells of older embryos had the same detrimental effect, uncovering different requirements for Notch as development proceeds.

"The cardiac malformations we observed are characteristic of Alagille syndrome, a human congenital disorder," said first author Paschalis Kratsios. "Therefore, our findings could help to explain the cardiac symptoms associated with Alagille syndrome and related forms of congenital heart disease."

Intriguingly, the scientists were able to improve the cardiac function and survival rate of adult mice that had suffered heart attacks by re-activating Notch, suggesting new therapeutic approaches to help the heart recover from damage.

"Overall, these results highlight the importance of timing and context in biological communication mechanisms" Nadia Rosenthal concludes: "Our findings also lend support to the notion that, in certain situations,

redeployment of embryonic signalling pathways could prove beneficial for tissue regeneration in the adult."

Source: European Molecular Biology Laboratory (news : web)