New target identified for repairing the heart after heart attack

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Billions of cardiac muscle cells are lost during a heart attack. The human heart cannot replenish these lost cells, so the default mechanism of repair is to form a cardiac scar. While this scar works well initially to avoid ventricular rupture, the scar is permanent, so it will eventually lead to heart failure and the heart will not be able to pump as efficiently as

before the damage caused by heart attack.

Zebrafish, a freshwater fish native to South Asia, is known to be able to fully regenerate its heart after damage due to the formation of a temporary scar as new cardiac muscle cells are formed. Professor Paul Riley and his team at the University of Oxford have been striving to understand and compare the composition of the cardiac scar in different animals as part of ongoing efforts to investigate whether it can be modulated to become a more transient scar like that of the zebrafish, and therefore potentially avoid heart failure in heart attack patients.

To do so, the researchers used three different models of studying heart repair and regeneration; the adult mouse heart, which behaves in a similar way to the human heart, the neonate mouse heart, which can regenerate up to 7 days after being born before losing that ability as the mouse ages, and the zebrafish which can regenerate the heart up to adulthood through forming a transient scar.

Professor Paul Riley said: "Efforts to treat heart attack with cell replacement strategies to-date have largely failed with disappointing clinical trial results. One reason for this is the local environment into which the new cells emerge: a cytotoxic mixture of inflammation and fibrosis which prevents their engraftment and integration with survived heart tissue. Consequently there is an urgent unmet clinical need to condition the local injury environment for efficient replacement of lost tissue. Major targets for this are the immune cells which invade the heart after injury causing inflammation, and the process of scar formation itself (fibrosis) during which immune cells signal to myofibroblasts to deposit collagen."

The team focused their efforts on studying the behaviour of macrophages, cells normally associated with inflammation and fighting infection in the body, when exposed to the three post-injury

environments. They extracted macrophages from each model to examine their gene expression. In both mouse and fish macrophages, they found that they were showing signs of being directly involved in the creation of the molecules that form part of the cardiac scar, and particularly collagen, which is the main protein involved.

BHF CRE Intermediate Transition Research Fellow and Lead Researcher Dr. Filipa Simões said "This information is important and quite striking because up to today, only cardiac myofibroblasts have been implicated in directly forming a scar in the heart."

"To further investigate whether macrophages were in fact directly contributing to the scar, we transplanted these macrophages into both fish and mouse hearts that had been previously injured, where collagens have been tagged with Green Fluorescent Protein (GFP) as a way of tracking gene expression. We looked 3 weeks later, the time point where the scar has been deposited, and we were very surprised to see that part of the scar formed was green in its composition, which really showed that macrophages can upregulate collagens, export them to the extracellular matrix and deposit into the scar."

"We have identified a new evolutionarily conserved role for macrophages that is really challenging the current dogma that myofibroblasts are the sole cells contributing to the cardiac scar, that we believe could also be applied to the human heart."

"To effectively repair the heart, broadly speaking you need two things: one, you need to modulate the permanent scar into a transient scar and two, you need to replenish all the heart muscle cells and blood vessels that have been lost through injury. Our study helps to address the first part of the problem as we identified macrophages as a new player in depositing the scar. However, before we are able to move to clinical trials and help heart attack patients, we need to carry out more

fundamental basic research to try and deeply understand the mechanism by which macrophages can contribute to the scar."

The study is funded by the British Heart Foundation (BHF). Professor Jeremy Pearson, Associate Medical Director at the BHF, said: "Our hearts struggle to repair themselves following the damage caused from a heart attack. This can lead to heart failure, an incurable condition with worse survival rates than many cancers. We urgently need to find ways to repair the heart when it's damaged.

"Macrophages are an important part of our immune system, removing dead and dying cells and helping to repair damaged tissue. By showing that macrophages produce collagen, a key part of scar tissue, this research could lead to new ways to enhance repair after a heart attack."

The full paper 'Macrophages directly contribute collagen to scar formation during zebrafish heart regeneration and mouse heart repair' can be read in *Nature Communications*.

More information: Macrophages directly contribute collagen to scar formation during zebrafish heart regeneration and mouse heart repair, *Nature Communications*, DOI: 10.1038/s41467-019-14263-2

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