A map of the human heart after myocardial infarction

Myocardial infarction, or heart attack, is one of the world’s biggest killers. An analysis of spatial and single-cell changes to human tissue after a heart attack provides insights into disease mechanisms and builds a resource for the discovery of therapeutics.

The project

Myocardial infarction, commonly referred to as heart attack, is a leading cause of mortality worldwide. It occurs when one of the arteries that supply blood to the heart is blocked, starving the heart tissue of oxygen and resulting in injury, cell death and inflammation. Acute mortality from myocardial infarction has decreased significantly over the past few decades with the development of minimally invasive procedures to open clogged arteries and restore the blood flow to cardiac tissue. However, the rate of chronic mortality from heart failure after the infarction is still unacceptably high. This is associated with changes to the heart tissue, known as remodelling, that occur after the infarction. The goal of our project was to use advanced genomic technologies to map the remodelling process after myocardial infarction at unprecedented spatial resolution to unravel the cellular and molecular mechanisms involved in heart disease.

The observation

To generate a spatio-temporal map of myocardial infarction and its aftermath, we analysed human heart muscle from the left ventricle at times ranging from 2 to 166 days after infarction. We obtained 31 samples from 23 people who were undergoing heart transplants or the implantation of total artificial hearts or assist devices, and compared them with control tissue from 4 non-transplanted donor hearts. Myocardial infarction generates a central region of cell death (the ischaemic zone) surrounded by an area of cell injury and inflammation (the border zone), and beyond that is nearly normal cardiac tissue (the remote zone; see Fig. 1). We first took 10-µm sections of the specimens to examine the spatial gene expression across the tissue. We also isolated almost 200,000 nuclei from cells in adjacent tissue areas and used them to measure gene expression and chromatin accessibility from single cells. We validated some findings by tissue staining and tracing heart cell fates in mice.

Our approach is unusual in allowing us to integrate different data into a ‘multi-omic’ map of heart disease as it evolves. Our data set allows us to catalogue and map cell types, cell states and various molecular functions in cells, such as the activity of signalling pathways, communication between cells, and transcription factor binding. We can therefore understand how a cell state or active pathway predicts the presence of other states or pathways in neighbouring areas. One striking finding is that the presence of myofibroblasts, which drive fibrosis (the scarring of heart tissue), are predicted by the presence of certain states of immune cells called macrophages, and vice versa.

We calculated the gene-regulatory networks that differentiate distinct states of cardiac cell types, and showed how these map to specific tissue locations. This mapping provided insights into how gene-regulatory programs drive the injury and differentiation of cell types such as cardiomyocytes.

Future directions

Our study provides a comprehensive map showing the gene regulation of human heart tissue before and after myocardial infarction. We released the data through publicly available platforms for interactive exploration. We believe this will ultimately lead to a better understanding of the human heart in both health and disease, and point to new treatment strategies.

Our next step is to select and further investigate some of the mechanisms involved in cardiac remodelling. The ultimate goal is to identify new therapeutic targets and develop drugs to reduce or repair tissue damage. For example, a therapy that works on myofibroblasts to reduce fibrosis might reduce mortality caused by heart failure long after myocardial infarction. This will require more research to work out whether activating or blocking specific pathways affects cardiac remodelling in a way that reduces scarring and improves tissue regeneration.

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This is a summary of:

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The authors deployed cutting-edge spatial and single-cell genomics analyses on precious, rare human cardiac samples from individuals after a myocardial infarction. I see this as likely to be a very important and informative resource for the cardiovascular biology community. More generally, the work contributes to the growing sense of optimism about what these technologies can reveal about pathogenic processes when applied directly to human disease tissue.” (CC BY 4.0)

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Medical textbooks show how myocardial infarction affects localized regions of the heart. Spatial transcriptomics, which provides a tissue map of gene expression, could therefore reveal insights into these regional changes. The current resolution of spatial transcriptomics technology means that every spot contains, on average, five different cells within the heart, but the number of cells per spot can increase tremendously when immune cells enter the tissue. To increase the resolution of the technique, we integrated various ‘omic’ data — spatial gene expression, single-cell gene expression, and single-cell open-chromatin measurements. When combined, this allowed us to map individual cells and cell subtypes, as well as molecular information such as pathway activity and gene regulation. It is extremely difficult to obtain research samples from human hearts shortly after myocardial infarction. We were fortunate to receive samples through a total artificial heart programme in which people with severe myocardial infarction, resulting in severe heart failure, would receive implantation of a mechanical pump.

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FROM THE EDITOR

This is a technically strong paper that uses state-of-the-art tools to provide insights into the spatial changes and trajectories that underlie the response of human heart tissue to myocardial infarction. It will no doubt serve as an important resource for future investigations into the biological changes underlying injury, repair and remodelling in the context of cardiac injury.

Susan Allison, Consulting Editor, Nature