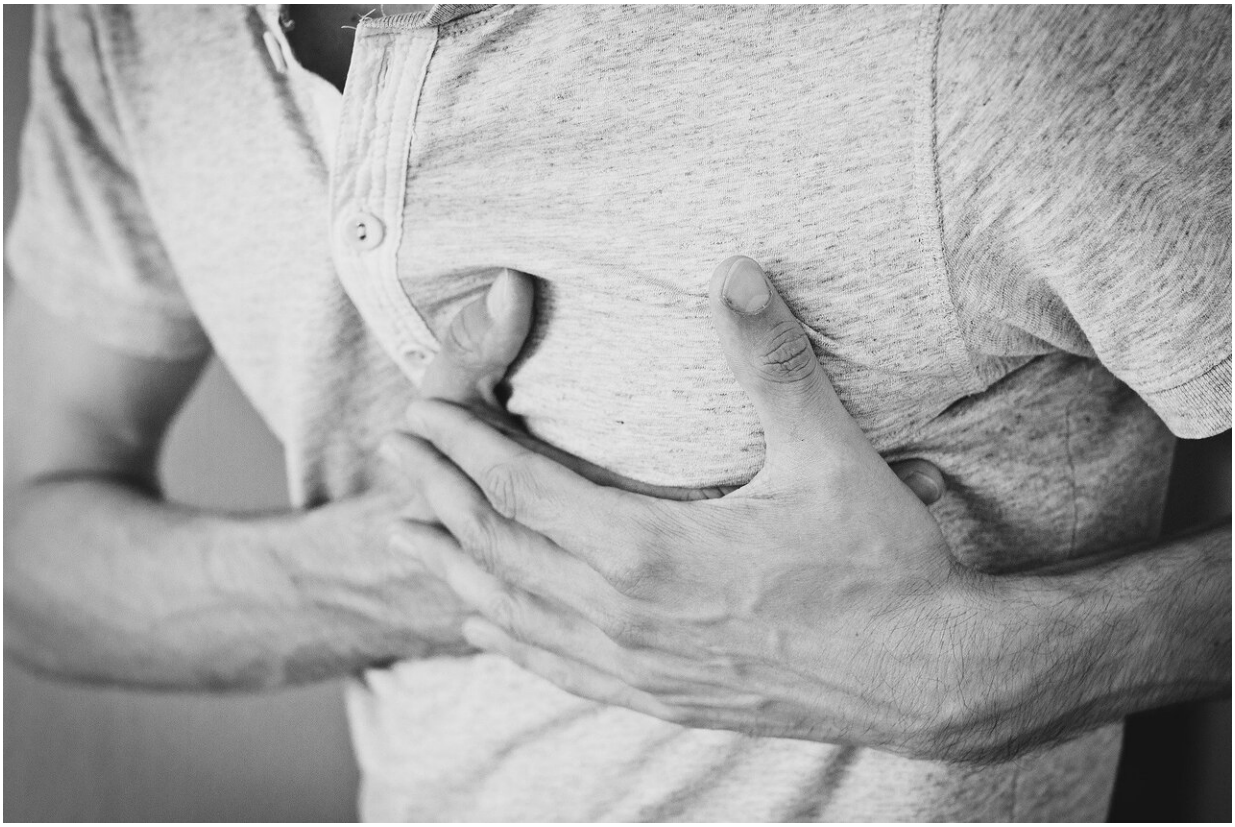
Map of metabolic changes after heart attack holds clues to recovery

May 11 2021



Credit: CC0 Public Domain

Researchers have mapped out the changes in metabolism that occur after a heart attack, publishing their findings today in the open-access *eLife* journal.

Their study in mice reveals certain genes and metabolic processes that could aid or hinder recovery, and might be good targets for treatments to prevent damage after a heart attack.

"Although some studies have looked at how changes in individual body tissues underlie mechanisms of disease, the crosstalk between different tissues and their dysregulation has not been examined in heart attacks or other cardiovascular-related complications," explains first author Muhammad Arif, a Ph.D. student at KTH Royal Institute of Technology, Stockholm, Sweden. "In this study, we performed an integrated analysis of heart and other metabolically active tissues using a mouse model of heart attack and used systems biology approaches to get a systematic picture of the metabolic changes that occur."

Systems biology has aided the discovery of new treatment approaches in multiple diseases. Rather than take systems apart and analyze the components, it involves taking measurements from different cells and tissues and using them to reproduce the system being studied. In this research, the team used a systems biology approach called co-expression networks (CNs) to reveal how the functions of genes in different tissues were linked together.

First, they measured the activity of all the genes in four tissue types: heart, fat, skeletal muscle and the liver in mice that had a heart attack. They compared these with the gene activity in mice that did not have a heart attack to generate sets of differentially expressed genes (DEGs) unique to each tissue. Next, in the co-expression network analysis, they looked at the top 5% of genes that were most strongly connected within the four different tissues. They then used the DEG results to see how those top 5% of genes were altered 24 hours after a heart attack.

They found key clusters of genes that were altered in different tissues after a heart attack. In the heart and muscle, the gene changes tended to

be linked to energy production and muscle contraction. In the liver, the gene changes were related to fat transport and metabolism, and the metabolism of cell-protecting substances such as glutathione.

The team then used this information to build a multi-tissue model of the metabolic response to a heart attack and compared their results with other studies of heart tissue. They found that four genes were consistently altered across all studies. These genes are known to play roles in energy production, muscle contraction and protein production, and at least one of them is being explored as a drug target for cardiovascular disease.

Taken together, the results reveal a downregulation of heart-specific functions and upregulation of fat metabolism and inflammation in the heart, muscle and fat tissue after a heart attack. By contrast, the team saw a different response in the liver where inflammation was reduced.

"Our integrative analysis highlights both common and tissue-specific biological responses to a heart attack across a range of metabolically active tissues," concludes senior author Adil Mardinoglu, Professor of Systems Biology at KTH Royal Institute of Technology, Sweden, and King's College London, UK. "The approach demonstrates a way of using multi-tissue gene activity data to identify changes in biological processes and pathways and systematically explore the effects of a disease. This opens up new opportunities for future research into the pathways identified, and the potential to use a similar approach to understand other complex human diseases."

More information: Muhammad Arif et al, Integrative transcriptomic analysis of tissue-specific metabolic crosstalk after myocardial infarction, *eLife* (2021). DOI: 10.7554/eLife.66921

Provided by eLife