Effects of T-Type calcium channel re-expression after heart attacks

Heart diseases such as coronary heart disease (CHD) are the primary cause of death worldwide. Myocardial infarctions (MI), also known as heart attacks, are often a consequence of CHD that can have dangerous effects on the body functioning of affected individuals. **Shavonn Harper**, PhD candidate at Temple University of the Commonwealth in Philadelphia, has been conducting extensive research into the effects of heart diseases and has recently been investigating the consequences of T-Type calcium channel re-expression in the heart, which can occur after heart attacks.

As the leading cause of death worldwide, cardiovascular diseases are the key focus of a substantial amount of research carried out by scientists around the globe. Achieving a better understanding of both the causes and consequences of heart diseases is crucially important to finding ways to prevent and counteract them. Coronary heart disease (CHD) is a common type of cardiovascular disease that can lead to heart attacks. Heart attacks can have serious physiological consequences and investigating these can help to find new ways to treat them and keep them under control.

CORONARY HEART DISEASE (CHD) AND ITS CONSEQUENCES

Coronary heart disease (CHD) is a heart disease that occurs when a substance called plaque is formed and builds up inside coronary arteries. Coronary arteries are important for the functioning of the body, as they supply oxygen-rich blood to the heart muscle. Build-up of plaque inside these arteries, called atherosclerosis, generally occurs over a period of several years. The plaque formed can either break open or harden, both of which can have adverse consequences on the functioning of the heart.

If the plaque breaks, a blood clot can form in its surface, which might partly or completely block the flow through the coronary artery. If it hardens, it can narrow the coronary arteries and reduce the flow of oxygen-rich blood to the heart. Obstruction or cessation of this flow of blood to the heart can lead to angina, chest pain or discomfort, or myocardial infarction (MI). If the flow is not promptly restored, heart attacks can lead to death or serious health issues.

THE EFFECTS OF MYOCARDIAL INFARCTION

After a heart attack, individuals can experience the death of myocytes within the affected area, which are the muscle cells responsible for making the heart contract, as well as the enlargement of surviving myocytes, and loss of the ability of the heart muscle to contract. Patients who survive a heart attack can develop congestive heart failure (CHF), a condition in which the heart cannot pump enough to meet the body's needs, which has limited treatment options. Existing treatments for individuals who experienced MI tend to focus on opening the blocked coronary vessels, lowering blood pressure, or trying to alter the heart's rate and force of contraction. These, however, are not always successful and the rates of progression to heart failure or death after MI are still extremely high.

DEVISING ALTERNATIVE TREATMENTS

As existing treatments are often unable to consistently tackle and treat the grave health consequences of MI, a number of research studies are trying to devise other alternative therapies. A growing amount of research is focusing on exploring the molecular changes

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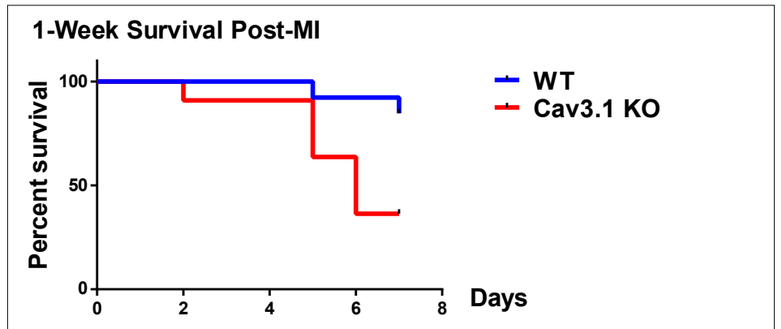
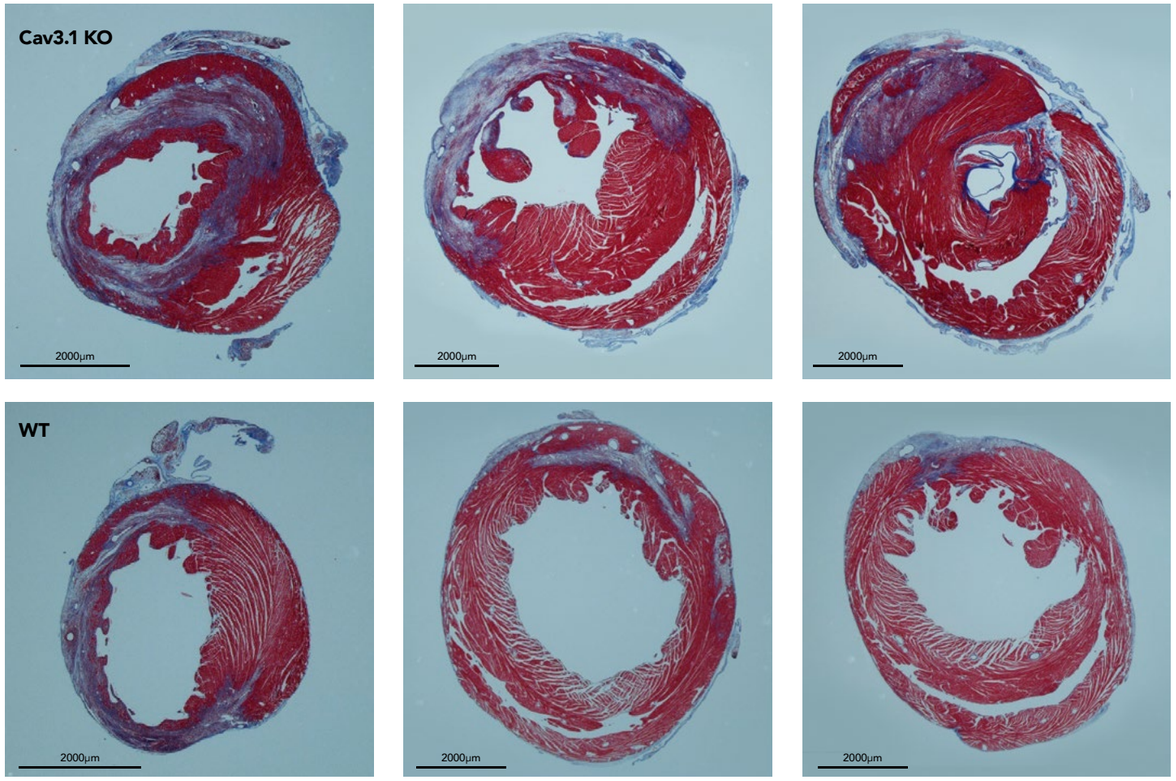


Percent survival for Cav3.1-/- mice (n=12) and C57Bl/6 WT mice (n=13) 1 week post myocardial infarction



that occur during and after MIs. These include altered levels of troponin T (proteins released when the heart muscle has been damaged) other changes in protein expression, and modulation of ion channels, single proteins or protein complexes that form channels to facilitate the movement of ions through the membrane.

Manipulating the cell's signalling pathways and cytokines, substances that are secreted by cells in the immune system and that display altered activity after MI, could be an effective therapeutic strategy to improve cardiac function, preventing the transition of patients' physiology that leads to heart failure. These studies are backed by the idea that prompting a more effective repair of the heart after heart attacks could improve cardiac function and decrease the likelihood of heart failure.

T-TYPE CALCIUM CHANNEL RE-EXPRESSION

Shavonn Harper has conducted a number of studies investigating cardiovascular physiology and mechanisms of cardiac repair after injury. Her current research is focusing on the role of the T-type calcium channel (TTCC) in the heart after MI episodes. TTCCs are voltage-activated ion channels that allow calcium ions to enter cells. In particular, she is investigating the role of a particular type of calcium channel called Cav3.1.

This research could lay the foundation for the development of new therapies to preserve cardiovascular functions in patients who have suffered from a heart attack

TTCCs are expressed in a number of body tissues throughout development and are particularly important to facilitate processes such as cell proliferation, the process through which cells increase in number, and differentiation, the process that allows cells to become more specialised in a specific function, as well as cell growth and death.

After birth, these channels are generally no longer expressed within the contractile cells of the heart, but they can often be re-expressed after injury, including after MI episodes.

Harper and her colleagues are carrying out experiments on mice to study the response of the heart to injury in absence of this particular TTCC channel. Her studies are testing whether mice that lack the Cav 3.1 subunit respond poorly to cardiac stress and whether this could be a result of alterations in the properties of muscle cells or in the ability of stem cells, undifferentiated cells that act as a repair system for the body's tissue, to facilitate cardiac repair.

Q&A

When and how did you decide to focus your research on the mechanisms of cardiac repair after injury?

The heart has always fascinated me, and heart disease remains an important topic for research because it affects millions of people and is the leading cause of death worldwide. As I entered graduate school, I was drawn to the research in Dr Steven Houser's laboratory using a novel stem cell therapy to treat the heart after injury. I could not pass up the opportunity to understand the underpinnings of cardiac repair mechanisms and a potential novel therapy to treat heart disease. Our initial results with the Cav3.1 KO mouse shifted our focus away from the effect of Cav3.1 on stem cells to understanding other mechanisms affecting the repair of the heart in this model.

How important is it to develop alternative treatments for the adverse physiological consequences of MI?

Despite the advances we have seen in clinical care and the ongoing research efforts to improve outcomes after MI, cardiovascular diseases remain the number one cause of death worldwide. Currently, patients that experience an MI are treated by restoring reperfusion to the heart using techniques such as percutaneous coronary intervention or coronary artery bypass graft surgery. They are also given medications to help improve cardiac function. However, the annual death rate for survivors of MI remains high at 5% according to WHO.

What is the most prominent evidence you collected so far that suggests TTCC might play a part in cardiac repair after heart attacks?

We initially wanted to use a permanent occlusion model of myocardial infarction in our Cav3.1 knock-out mice. However, within one week 100% of the male mice and approximately 70% of the female mice with a confirmed MI died. Strikingly, approximately 85% of wild type mice survived to one week. When using the milder and more clinically relevant ischaemia-reperfusion model, there is no longer a difference in survival, but these mice also have more injury to their hearts as observed by increased scar size at one week.

How could your findings inform medical practice in future?

There are multiple subunits for T-type calcium channels. The two forms that are prevalent in the heart are Cav3.1 and Cav3.2. These two subunits seem to play different roles in the injured heart. Gaining a better understanding of how each of these isoforms contributes to cardiac repair or injury can allow for the development of more specific therapies targeting the channels. Manipulation of the expression of these channels could improve cardiac repair and function after injury.

What are your planned next steps in terms of research and investigation?

I will be completing my thesis work at the end of the year. I will continue studying mechanisms of heart failure and cardiac repair during a post-doctoral fellowship in the lab of Walter Koch, another leader in the cardiovascular research field.

INITIAL PROMISING RESULTS

Harper's project is still in its early stages, but already shows promising results. The mice that lack the Cav 3.1 subunit have decreased survival after myocardial infarction. They also have more cardiac hypertrophy and more fibrosis after ischaemia and fewer proliferating cells in the infarct and border zones after MI. Her future studies hope to explore TTCCs further, in order to gain a better understanding of their role after MI and investigate whether their expression in cardiac myocytes and reparative cells might be essential for cardiac repair. By determining the mechanisms by which the re-expression of TTCCs influences the response of the heart after MI, her research could lay the foundation for the development of new therapies to preserve cardiovascular functions in patients who suffered from a heart attack.

Detail

RESEARCH OBJECTIVES

Shavonn Harper's research interest is in cardiovascular physiology, particularly coronary heart disease, the leading cause of death in the world. Her research into T-Type calcium channel expression will lay the foundation for novel therapies for patients who have suffered from a myocardial infarction.

FUNDING

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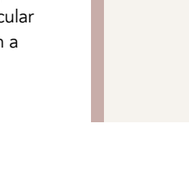

BIO

Shavonn Harper is a PhD candidate working in the lab of Dr Steven R. Houser at the Lewis Katz School of Medicine at Temple University. She received her Bachelor of Science from Ursinus College. Her primary research interest is cardiovascular physiology with a focus on mechanisms of cardiac repair after injury.

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