The cardiac stress response – getting to the heart of the matter

Our heart is an organ whose function we often take for granted. But what mechanisms does the heart use on a day-to-day basis to protect itself from stressful situations and to continue operating as it is required to? Professor Erin L. Reineke’s research delves deep into the relationship between cardiac function and metabolism. In particular, Professor Reineke and her group at the Houston Methodist Research Institute are interested in a specific molecule, SRC-2, which appears to regulate our response to cardiac stress.

Cardiovascular disease (CVD) is a major player in health-related deaths in the United States. In many cases, comorbidities of cardiac stress, such as diabetes or hypertension cause persistent changes in the nutrients and hormones circulating the body. In addition to the long-term physical load on the heart, the heart cannot maintain function efficiently. Long-term cardiac stress can arise because of CVD and changes in cardiac metabolism are often the first observed adaptations to cardiac stress. This ties in with the observation that many of the predisposing factors for cardiac stress are metabolic disorders themselves, such as obesity, diabetes and high cholesterol.

During pressure overload to the heart, there is increased demand for ATP (adenosine triphosphate, the energy currency for cells) production by cardiomyocytes. In order to try and fulfil this demand, there is an initial increase in fatty acid oxidation, followed by increased aerobic glycolysis and a corresponding increase in glycolytic gene expression. However, as oxygen becomes scarce, anaerobic glycolysis kicks in, and this leads to accumulation of lactic acid. Bad news for the heart.

The cardiac stress response has a varied molecular signature, depending on the stress and on the genetic background of the animal. This makes identifying key regulators of the stress response very difficult, as we need to try and distinguish them from the background variation and ‘noise’ that we see. If we could identify factors that play a part in coordinating the cardiac stress response, maybe this would provide a way in which to diagnose early stage cardiac stress, before it becomes apparent clinically and at a point when the patient will be more responsive to treatment.

Professor Reineke’s group want to solve several questions, including what cellular proteins sense stress signals and what proteins are responsible for coordinating the subsequent changes in the transcriptional machinery.

FROM THE HEART

Ultimately, heart failure results from changes that occur in the heart after the onset of stress, such as alterations in cellular signalling cascades and gene expression profiles. Three of the main pathways important for the heart to maintain normal functions under stress conditions are those relating to cardiac metabolism, growth and structure. In many cases, changes in the metabolic pathways result from a gene profile that resembles the one seen during foetal development, the ‘foetal gene profile’. This alteration in gene expression is controlled by transcription factors, and the shift away from the adult cardiac gene expression profile is associated with pressure overload, aging and inadequate blood supply. So far, research has identified changes in transcription of only a small set of markers for cardiac stress. However, we don’t know much about the transcriptional regulators for these genes, and even less about possible upstream signals.

OF MICE AND MEN

The steroid receptor (SRC) family of proteins has been well studied for their role in co-activating a number of transcription factors in response to cellular signals. One family member of particular interest to Professor Reineke was steroid receptor 2 (SRC-2). Its role in controlling enzymes of fatty acids and glucose metabolism have already been reported. SRC-2 is a transcription activator; it acts as a large scaffold that allows other proteins to dock, interact or be modified. Therefore, it is perfectly placed to be a signal coordinator during cardiac stress.

Furthermore, previous studies investigating human heart failure had identified SRC-2 as one of only 107 genes that showed altered expression in more than one dataset. Consequently, Reineke and colleagues set about investigating a mouse model that lacked SRC-2, to see what effect it had on the ability of the mouse to cope with cardiac stress. Without SRC-2, the mice could not mount a proper response to left ventricular pressure overload, a phenomenon often seen in persistent cardiac stress. There was a shift in gene expression towards the so-called foetal gene signature in the unstressed hearts of the mice, suggesting involvement of SRC-2 with the adult metabolic gene profile.

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The study also found that SRC-2 was...
important for cardiomyocyte function, as it could control several cardiac transcription factors, including one that is important for maintaining adult cardiomyocyte metabolism. Future projects will continue to investigate other key regulators that may be involved in the cardiac stress response.

Despite these changes, the ability of the heart to function correctly was not impeded. Maybe the hearts of these mice are predisposed to cardiac decline with increasing stress, but it is not a change we see straight away. Meanwhile, this shift towards a foetal gene profile is enough to meet the steady-state energy demands of the heart.

Professor Reineke’s current work focuses on the impact that early metabolic signals may have on the downstream stress response. She hypothesises that the abrogated growth of the walls of the heart, observed in the mice lacking SRC-2, could be a direct result of the metabolic profile of the heart being altered, even before cardiac changes are visible. Ongoing research also investigates the differences that timing makes. Are there different results depending on when the normal stress response is disrupted? And what molecules are responsible for regulation and control of these processes?

AN EARLY WARNING SYSTEM

Imagine if you will, a clinical setting in which patients suspected of having high blood pressure had the potential to lead to more long-term problems, could be treated much earlier. As a result of the research done by the group at the Houston Methodist Research Institute and the findings from their SRC-2 mice, it may become possible to screen patients for the tell-tale early markers of cardiometabolic changes, and to then prescribe a personalised transcriptional therapy, saving the patient’s cardiac gene profile from reaching the point of no return, and therefore from developing full blown CVD.

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