A translational approach to myocardial remodelling

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The concept of cardiac remodelling was initially created to describe the changes in the anatomy of the left ventricle that occur following myocardial infarction.1 Today myocardial remodelling is used to qualify a variety of changes in the bio-physiology of the cardiomyocyte, the volume and composition of cardiomyocyte, and non-cardiomyocyte compartments, and the geometry and architecture of the left ventricular chamber that occur in response to myocardial infarction, pressure or volume overload, cardiomyopathic states, and exposure to infectious or cardiotoxic agents.2

Myocardial remodelling results from modifications that are not necessarily adaptive to the initial insult, but pathological and potentially self-perpetuating in a progressive vicious circle. In addition, the effects of the insult on the final phenotype are modulated by several interfering factors, including senescence, obesity, diabetes, a number of cardiac and systemic humoral factors and, probably, genetics.3 Myocardial remodelling may result in alterations of cardiac energetics, deterioration of both diastolic and systolic function, and propensity for arrhythmias.2 Therefore, myocardial remodelling is a key determinant of the clinical course and outcome of a number of cardiac diseases. This Spotlight Issue is committed to a review of information provided by the intensive research performed in the past few years on mechanisms involved in the development, consequences, detection, and treatment of myocardial remodelling.

An early feature of the maladapted heart is a loss of metabolic flexibility. Metabolic signals regulate fluxes through enzyme-catalyzed reactions in metabolic pathways and regulate transcriptional, translational, and post-translational signalling in the heart. The paradigm is emerging that metabolic remodelling precedes, triggers, and sustains functional and structural remodelling.4 Ingwall5 reviews in this Spotlight Issue the energetic phenotype of remodelled myocardium and discuss in depth the interrelations between a lower metabolic reserve and an impaired contractile reserve. Van Bilzen et al.6 focus their article on the analysis of metabolic interventions that may improve the function of remodelled myocardium. In particular, the authors propose to give priority to those interventions aimed to further stimulate glucose oxidation rather than to normalize substrate metabolism by stimulating fatty acid utilization.

Myocardial remodelling is associated with rearrangement of different subcellular organelles. It appears that Ca2+ handling and Ca2+ interaction abnormalities in the failing heart are due to alterations of sarcolemna, sarcoplasmic reticulum, and mitochondria.7 Dhall et al.8 provide a broad updated view of the mechanisms responsible for changes in the biochemical composition and molecular structure of cardiac subcellular organelles and their detrimental impact on organelle functions and cardiac performance. Willis et al.9 discuss in this issue the dynamic interplay between sarcomere-specific chaperones and ubiquitin-dependent degradation of sarcomere proteins that is necessary to maintain structure and function of the cardiac sarcomere.

Tsutsui et al.10 review in detail the molecular aspects of mitochondrial oxidative stress as a mechanism of myocardial remodelling responsible for heart failure progression. In addition, they also analyse some of the emergent molecular tools aimed at the inhibition of mitochondria-derived oxidative stress in the diseased heart. Hori and Nishida11 discuss the role of reactive oxygen species that are generated in the ischemic myocardium in acute myocardial infarction. Reactive oxygen species stimulate signal transduction to elaborate inflammatory cytokines, which, in turn, activate both kinases involved in cardiomyocyte death and matrix metalloproteinases responsible for disruption of collagen network and hence left ventricular dilatation.12

Apoptosis is an important mechanism in the remodelled myocardium. Subcellular events, most prominently protease activation and mitochondrial leak with cytochrome c release into the cytoplasm, generate a partly energy-depleted state and fragment contractile apparatus/structural proteins. Therefore, not only cardiomyocyte loss, but also energy depletion and contractile protein loss contribute to systolic dysfunction.13 The article by Dorn14 in this Spotlight Issue is focused on apoptosis and discusses the molecular cross-talk between apoptosis and other forms of cell death, e.g. programmed necrosis and autophagy, that occur during the remodelling process of the myocardium. Although morphologically different, pathways regulating these forms...
of programmed cell death are evolutionarily conserved.\textsuperscript{15} Out of the three death pathways, roles for apoptosis and necrosis have been well defined, while the role for autophagy as a potential source of programmed cell death is still controversial.

There is growing recognition that after acute myocardial infarction, inflammatory and fibrogenic responses will take place in both infarcted and non-infarcted myocardium that contribute significantly to ventricular dysfunction.\textsuperscript{16,17} The exact pathways through which myocardial inflammation and fibrosis operate after infarction, as well as the potential mechanisms for their therapeutic modulation, are under investigation. Two articles in the current issue are dedicated to the review of these aspects. Frantz et al.\textsuperscript{18} compile evidence for cellular and humoral factors controlling the inflammatory response that develops in the reperfused, infarcted tissue during its healing. The authors focus their attention on the early cascade of events triggered by the ischaemic injury (i.e. activation of the innate immune system, release of inflammatory mediators, and attraction of inflammatory cells to the site of injury) that lead to the subsequent formation of scar tissue. Sun\textsuperscript{19} pays special attention to fibrosis occurring in the non-infarcted myocardium. In particular, she examines the involvement of locally produced angiotensin II in NADPH oxidase-mediated superoxide anion generation that occurs in the non-infarcted region of the heart as well as the ability of this reactive oxygen species to induce the fibrogenic cytokine TGF-\(\beta\) via NF-\(\kappa\)B activation.

In an attempt to compensate for compromised haemodynamics in heart failure, intrinsic and peripheral responses to mechanical dysfunction occur in patients that alter the expression and function of key ion channels and Ca\textsuperscript{2+} handling proteins, thereby remodelling the cellular action potential and the intracellular Ca\textsuperscript{2+} transient.\textsuperscript{20} In particular, the electrophysiological remodelling renders the heart more vulnerable to ventricular arrhythmias that underlie sudden cardiac death. In their contribution to this Spotlight Issue, Michael et al.\textsuperscript{21} review changes in ion currents leading to cardiac repolarization abnormalities that arise from congestive heart failure and atrial fibrillation. In addition, they analyse how these changes can generate arrhythmogenic substrates by reducing repolarization reserve and explore their potentially important therapeutic implications.

Very few data are available on the role of genetic susceptibility and environmental factors in the initiation and development of the remodelling process. It is accepted that gene mutations may trigger myocardial remodelling in cardiomyopathies such as hypertrophic cardiomyopathy and idiopathic-dilated cardiomyopathy.\textsuperscript{22} Scarce and controversial results have been reported concerning the association of single-nucleotide polymorphisms and haplotypes with the development or phenotypic expression of myocardial remodelling.\textsuperscript{23} Infectious agents or cardiotoxic drugs\textsuperscript{2} may induce remodelling, but virtually no information exists on the role of nutrition. Weber et al.\textsuperscript{24} review macronutrients (i.e. Ca\textsuperscript{2+} and Mg\textsuperscript{2+}) and micronutrients (Zn\textsuperscript{2+}, Se\textsuperscript{2+}, and vitamin D) that might contribute to myocardial remodelling. The authors hypothesize that insufficient dietary intake, inadequate sunlight exposure, excessive excretory losses, and/or a preferential translocation of cations from the intravascular compartment to injured tissues lead to disturbances in nutrient homeostasis. The resulting imbalance can be the basis for oxidative stress and myocardial remodelling.

The identification of cardiovascular biomarkers has been a prolific field in recent years.\textsuperscript{25} In this Spotlight Issue, González et al.\textsuperscript{26} review recent studies performed on small populations of patients with hypertensive heart disease. A panel of circulating molecules were identified that fulfil the criteria of biomarkers of the structural alterations of the cardiomyocyte and the collagen matrix. In particular, the authors examine the usefulness of these biochemical markers in the clinical areas of diagnosis and therapeutic monitoring.

Current therapy of cardiac remodelling is still largely based on the mechanical and neurohumoral hypothesis of heart failure. However, multiple and redundant signalling systems are involved in remodelling. Thus, a paradigm shift may be necessary for the development of novel medicinal therapies.\textsuperscript{27} Landmesser et al.\textsuperscript{18} review the current pharmacological approaches (i.e. interference with the sympathetic nervous system and with the renin–angiotensin–aldosterone system) and potential novel strategies to prevent or reverse remodelling like modulation of nitric oxide pathways, inflammation and proteolysis, oxidant stress, and angiogenesis.

As more detailed molecular information accumulates on myocardial remodelling, the need for new integrative analyses is growing. In this regard, the time has come to approach myocardial remodelling using the tools and methodology of systems biology.\textsuperscript{29} In fact, high-throughput technologies and integrative computational analysis must be applied to construct networks of the interactions between remodelling molecules and signal transduction pathways in order to develop systems models of their functionally integrated biological properties. These systems models can then be incorporated into structurally integrated multi-scale models for both predicting clinical phenotypes and developing novel diagnostic and therapeutic strategies aimed at improving the care of patients with cardiac diseases.

References