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Cardiac Fibrosis And Heart Failure Cause Or Effect Advances In Biochemistry In Health And Disease

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Interstitial Fibrosis in Heart Failure

Cardiac Fibrosis And Heart Failure Cause Or Effect Advances In Biochemistry In Health And Disease ***OMB No. 8523946824007 edited by***

CROSS LEILA

Role of Mechanosensitive Ion Channel Trpv4 in Cardiac Remodeling

Springer
This book details the advances in cardiac MRI that have enabled quantitative tissue characterization of the myocardium using myocardial and blood T1 measurements, which have enabled reliable detection of diffuse pathological processes in both the cardiomyocytes and the interstitial cells of the myocardium. Evaluation of the native myocardial and interstitial fibrosis, and measurement of the extracellular volume fraction has allowed an unprecedented opportunity to elucidate the pathology, diagnosis and prognosis of cardiovascular disease. T1-Mapping in Myocardial Disease: Principles and Applications reviews a wide spectrum of significant cardiovascular disease and provides relevant guidance for the clinical implementation of this innovative technique. The specific topics covered include principles of T1-mapping in cardiovascular disease and the role of T1-mapping in hypertensive heart disease and hypertrophic cardiomyopathy, cardiotoxicity from cancer treatment, cardiacfibrosis, left ventricular hypertrophy in aortic stenosis, peri-infarct injury in ischemic cardiomyopathy, and stem cell therapy. This comprehensive coverage of the utility of T1-mapping in cardiovascular diseases will greatly appeal to the entire cardiovascular medicine and imaging communities.
Autopsy, Surgical and Molecular Pathology Steinkopff
Understanding extracellular matrix (ECM) structure and function is important for developing biomedical applications that are as close to ‘native’ as possible. Written by pioneering scientists from all over the world, this book reports research and new developments in the field of collagen structure, function, and biomechanics and discusses the relevance of hyaluronic acid and its therapeutic uses. It gives readers a glimpse of what is current in this area and we hope it piques their interest in learning more about ECM biology.

Myocardial Viability

Cardiac Fibrosis and Heart Failure: Cause or Effect?
In the joint American College of Cardiology /American Heart Association classification system, Stage B heart failure refers to patients with structural heart disease but no symptoms of heart failure. Preventing progression of heart failure in Stage B patients is a central concern to heart failure specialists, so two issues have been devoted to this topic. Part II focuses on screening to identify patients with Stage B HF and monitoring and therapeutic approaches to patients with a diagnosis of Stage B HF.

Cannabinoids in Health and Disease

W B Saunders Company
Rationale: Pathological remodeling of the heart is a hallmark of

chronic heart failure (HF) and these structural changes further perpetuate the disease. Cardiac fibroblasts are the critical cell type that is responsible for maintaining the structural integrity of the heart. Stress conditions, such as a myocardial infarction (MI), can activate quiescent fibroblasts into synthetic and contractile myofibroblasts. G protein-coupled receptor (GPCR) kinase (GRK) 5 is an important mediator of cardiovascular homeostasis through dampening of GPCR signaling, and is expressed in the heart and upregulated in human HF. Of note, GRK5 has been demonstrated to translocate to the nucleus in cardiomyocytes in a calcium-calmodulin (Ca2+-CAM)-dependent manner, promoting hypertrophic gene transcription through activation of NFAT. Interestingly, NFAT is also involved in fibroblast activation. GRK5 is highly expressed and active in cardiac fibroblasts (CFs), however its pathophysiological role in these crucial cardiac cells is unknown. Objective: The aim of this study is to elucidate the role of GRK5 in the activation of cardiac fibroblasts in vitro and cardiac fibrosis after injury in vivo. Methods and Results: We demonstrate using adult cardiac fibroblasts that genetic deletion of GRK5 inhibits Angiotensin II (AngII) mediated fibroblast activation. Fibroblast-specific deletion of GRK5 in mice decreased fibrosis and cardiac hypertrophy after chronic AngII infusion compared to non-transgenic littermate controls (NLCs). Fibroblast-specific deletion of GRK5 was also protective in mice after ischemic injury as they presented with preserved systolic function, decreased fibrosis, and decreased hypertrophy compared to NLCs. Mechanistically, we show that nuclear translocation of GRK5 is involved in fibroblast activation. Conclusions: We present novel data demonstrating that GRK5 is a regulator of fibroblast activation in vitro and cardiac fibrosis in vivo. This adds to previously published data which demonstrates the potential beneficial effects of GRK5 inhibition in the context of cardiac disease.

Experimental and Clinical Aspects Springer

Ischemic heart disease (IHD) is the major underlying cause of myocardial infarction (MI), scarring, and hypertrophy leading to heart failure which is one of the leading causes of death. Cardiac remodeling following induced pressure overload/myocardial infarction is a multiphase reparative process which involves replacement of damaged tissue with physiological (reparative) fibrosis to form scar that limit the expansion of the left ventricle/infarct of the heart. Although therapeutic approaches targeting soluble factor (ex: ACE inhibitors, ARBs, TGF-[beta] inhibitors: Pirfenidone, Halofuginone) signaling is available for the treatment of cardiac fibrosis and hypertrophy, they showed modest efficacy in clinics. Hence, it is indispensable to identify and develop an alternate and novel therapeutics to treat the heart failure. Mechanical cues are indeed necessary to integrate with soluble factor associated signaling to maintain cardiac physiological functions. Of late, TRPV4 has been shown to be mechanosensor and our lab has established that TRPV4 is a key mechanosensor in endothelial cells and cardiac fibroblasts (CF) and plays an important role in cardiovascular pathophysiology. We have recently demonstrated that TRPV4 mediates cardiac fibroblast differentiation into myofibroblasts in vitro. However, the physiological significance of TRPV4 in cardiac remodeling in vivo is not known. Based on our previous findings, we hypothesized that targeting TRPV4 may offer cardioprotection following pressure overload-induced hypertrophy and myocardial infarction. The first aim of the dissertation was to determine whether TRPV4 mediated mechanotransduction preserves the heart integrity and reduce fibrosis in vivo following pressure overload-induced hypertrophy. By inducing pressure overload hypertrophy (TAC), we found that TRPV4 knockout (KO) mice exhibited improved cardia function, decreased myocardial cross sectional area and left ventricular mass when compared with WT. Further, we have also revealed that TRPV4 KO mice hearts showed less cardiac fibrosis compared to WT. To unravel the unexplored integration of soluble and mechanical signaling behind the cardiac fibrosis, the second aim of this dissertation was to delineate the molecular mechanisms by which TRPV4 regulate cardiac fibroblasts differentiation into myofibroblasts. Our in vitro studies revealed that TGF-[beta]1 mediated fibroblasts differentiation was attenuated in TRPV4KO mCF compared WT mCF. Further, both TGF-[beta]1 and a specific activator of TRPV4, GSK1016790A, significantly enhanced pro-fibrotic a-SMA and Col1a1 promoter activities. Importantly, we have dissected the mechanism and found that both TGF-[beta]1 and GSK (TRPV4 agonist) induced TRPV4-dependent activation of the Rho/Rho Kinase pathway as well as a mechanosensitive transcription factor MRTF-A are involved in CF differentiation. To further corroborate the critical role of TRPV4 in cardiac remodeling, the third aim of this dissertation was to ascertain the functional role of TRPV4 in cardio protection following myocardial infarction. We found that after 8 weeks post- MI, significant improvement of cardiac function was observed in TRPV4KO mice compared to WT. Further, we found reduced cardiac fibrosis at infarct and remote zones in TRPV4KO-MI mice compared to WT-MI mice which display enhanced fibrosis at infarct/border zone as well as remote zones. Furthermore, TRPV4KO hearts exhibited decreased cardiomyocyte apoptosis (TUNEL assay) and increased capillary density (CD31 staining) post-MI compared to WT hearts. In conclusion, our results suggest that targeting a mechanosensor TRPV4, protects heart from induced pressure overload or myocardial infarction-induced damage by preserving cardiac structure, function and identifies TRPV4 as a novel therapeutic target for heart failure.

GRK5 IS A NOVEL REGULATOR OF FIBROBLAST ACTIVATION AND CARDIAC FIBROSIS

Cambridge Scholars Publishing

This issue of Heart Failure Clinics, guest edited by Dr. Subha V. Raman, will cover key topics in Cardiovascular Magnetic Resonance. This issue is one of four issues selected each year by our series consulting editor, Dr. Eduardo Bossone. Topics discussed in this issue will include: When to use CMR for patients with heart failure; Quantifying cardiac dysfunction with CMR; CMR in heritable cardiomyopathies; CMR in ischemic cardiomyopathy; CMR in right heart and pulmonary circulation disorders; CMR of myocardial fibrosis, edema, and infiltrates in heart failure; Magnetic resonance-based characterization of myocardial architecture; CMR in valvular heart disease-related heart failure; Pericardial disease with CMR; CMR’s central role in chemotherapy-induced cardiotoxicity; Intracardiac and vascular hemodynamics with CMR in heart failure; Myocardial energetics with CMR; CMR in congenital heart disease: focus on heart failure; and Machine learning in CMR applied to heart failure.

Protective Signaling in the Myocardium Elsevier Health Sciences

Heart failure (HF) is a leading cause of death in the developed world, and its impact is rising due to an increasing aging population (Roth et al. 2017). Despite developments in treatment, the long-term prognosis remains poor with annual mortality rates of 1-2 million (Savarese & Lund 2017). Approximately half of these mortality cases in HF are sudden and they are believed to be the result of lethal arrhythmias (Wilson et al. 2009). Of the numerous pathologies that lead to HF, more than three quarters of patients display antecedent hypertension (Benjamin et al. 2017). In light of this, the progression of hypertension to HF has been studied intensively (A. M. Gerdes et

al. 1996; Doggrell 1998; Aidietis et al. 2007; Drazner 2011) and is characterised by significant structural remodelling such as fibrosis (Ma 1998; LeGrice et al. 2012). While structural remodelling is a hallmark of progression towards HF, its role in arrhythmogenesis remains an area of debate. With this in mind, the principal objectives of this study were to characterise the relationships between electrical dysfunction and multi-scale structural remodelling in the progression towards HF. To investigate the possible electrophysiological variation associated with fibrosis, Wistar Kyoto (WKY) and spontaneously hypertensive rat (SHR) image volume sets consisting of minimal fibrosis and large amounts of fibrosis, respectively were analysed and compared. The two tissue sets were structurally investigated, while computational simulations were conducted to identify any variation in electrical activation. At larger scales, the SHR volumes displayed a marked reduction in fiber rotation in the sub epicardium. In addition, significant tissue connectivity reduction associated with fibrosis was also observed. Finally, electrical activation simulations demonstrated slowing in conduction velocity (CV) in the SHR dataset. Building on this finding, the structural and electrical changes associated with the development of HF was investigated using the hypertensive heart disease (HHD) SHR model in a longitudinal (6, 12, 18 months) paired study. Structural remodelling was captured at the tissue level using multiple morphological measures. Characterisation of the cellular architectural variation was also conducted using a imaging protocol developed in this thesis. This method enabled large high resolution volumes of cardiac cellular arrangements to be acquired without the use of physical sectioning. In addition to the structural measurements, the electrical variation was also quantified using high resolution optical mapping. Furthermore, a novel optical mapping motion artifact reduction tool was developed using a non-rigid deformation technique. The relatively simple tool was able to recover action potentials (APs) from optical mapping datasets in the presence of substantial motion artifact. The majority of these methods were applied to the SHR cohorts. The outcomes of this longitudinal study demonstrated that there were significant differences in structure and electrical activity with age. The most marked changes occurred between 6 and 12 months, showing significant increase in fibrosis, cell dimension, and rate dependent CV slowing /anisotropy and repolarization dispersion. In contrast, while there was an increase in the measures noted above from 12 to 18 months, the differences were less pronounced with a considerable overlap. Arrhythmic susceptibility also increased with age and showed a similar nonlinear trend to that of the other measures. Further to these age related changes, cellular coupling exhibited a clear inverse relationship with the amount of fibrosis. Finally, comparisons of structure and electrical dysfunction demonstrated that the extent and form of fibrosis were associated with rate dependent CV slowing/anisotropy and repolarization heterogeneity. Both these features of electrical dysfunction formed the substrates for increased arrhythmic susceptibility. Overall, the increased electrical dysfunction/arrhythmic susceptibly observed with the progression of HHD towards HF was closely linked with fibrotic influence. This provides significant evidence that structural remodelling plays a major role in electrical instability.

Myocardial Fibrosis and Extracellular Matrix Remodelling in Chronic Heart Failure Elsevier Health Sciences

Clearly presents the pathology of heart disease from fetus to adolescence, integrating histology and macroscopy with effects of treatment.

Tissue Repair and Fibrosis BoD – Books on Demand

This Volume of the series Cardiac and Vascular Biology offers a comprehensive and exciting, state-of-the-art work on the current options and potentials of cardiac regeneration and repair. Several techniques and approaches have been developed for heart failure repair: direct injection of cells, programming of scar tissue into functional myocardium, and tissue-engineered heart muscle support. The book introduces the rationale for these different approaches in cell-based heart regeneration and discusses the most important considerations for clinical translation. Expert authors discuss when, why, and how heart muscle can be salvaged. The book represents a valuable resource for stem cell researchers, cardiologists, bioengineers, and biomedical scientists studying cardiac function and regeneration.

Cardiac Fibrosis and Ventricular Arrhythmogenesis Wiley-Blackwell

Structural and functional abnormalities of the left ventricle and atrium are important prognostic factors in patients with cardiovascular disease. Dysfunction of the left ventricle in heart failure exposes the left atrium to elevated pressures during diastole, which result in adverse left atrial remodelling and impairment. Although the development of systolic left ventricular impairment has been linked with a number of causative factors, the pathophysiological cascade between these initiators of myocardial dysfunction and its overt manifestation has been incompletely characterised. Amongst the proposed intermediaries of systolic heart failure, recent attention has focussed on myocardial fibrosis and ventricular dyssynchrony. Myocardial fibrosis describes the extracellular deposition of collagen in response to an injurious process. This collagen deposition plays an important role in left ventricular remodelling, and may perpetuate myocardial dysfunction. Ventricular dyssynchrony refers to the incoordinate contraction of the ventricles: inter-ventricular dyssynchrony is the temporal uncoupling of left from right ventricular contraction, and intra-left ventricular dyssynchrony pertains to heterogeneity in the time to regional mechanical activation within the left ventricle. Ventricular dyssynchrony has also been implicated in the pathogenesis of systolic heart failure, and its treatment by cardiac resynchronisation has been proven efficacious in selected patients with systolic left ventricular dysfunction. Despite emerging evidence implicating myocardial fibrosis and ventricular dyssynchrony in heart failure, their causal relationship with each other, and their relative importance in the pathogenesis of myocardial dysfunction have been poorly characterised. The aims of this thesis are to 1) characterise the role of myocardial fibrosis and ventricular dyssynchrony in the development of left ventricular and atrial mechanical dysfunction, and 2) examine the importance of myocardial fibrosis and ventricular dyssynchrony in the response to therapy of patients with systolic heart failure using non-invasive imaging approaches. The first study presented in this thesis in Chapter 3 explores the relationship between left atrial mechanical and left ventricular function by evaluating the effects on left atrial mechanical function of eliminating left ventricular function through the temporary induction of ventricular fibrillation in patients undergoing routine defibrillation threshold testing following implantable cardioverter-defibrillator insertion. In this mechanistic study, the dependence of left atrial function on left ventricular function is demonstrated. This finding establishes the context for the subsequent research in this thesis on the effects of left ventricular function on the left atrium in idiopathic dilated cardiomyopathy and cardiac pacing. Chapter 4 presents research investigating the prevalence of myocardial fibrosis and ventricular dyssynchrony in patients with a first presentation of idiopathic dilated cardiomyopathy. The influence of these factors, amongst other recognised prognostic factors in heart failure, on

recovery of left ventricular systolic function is examined. The key finding of this chapter is that myocardial fibrosis and ventricular dyssynchrony are independent predictors of improvement in left ventricular systolic dysfunction amongst these patients. These results relate directly to the chief aims of this thesis. In Chapter 5, abnormalities in left atrial structure and function in patients with a first presentation of idiopathic dilated cardiomyopathy are explored. This research demonstrates that structural and functional abnormalities are prevalent early in the time course of this condition, but that these derangements are reversible following appropriate medical therapy. This chapter extends on the findings of the previous two chapters to illustrate how disease processes primarily affecting the left ventricle can impact upon the left atrium. Chapter 6 aims to further develop the evidence that left ventricular dyssynchrony promotes ongoing left ventricular dysfunction through the study of patients who had been enrolled in a randomised trial of right ventricular apical versus right ventricular outflow tract septal pacing for bradycardia. The major findings of this research are that right ventricular apical pacing is associated with greater ventricular dyssynchrony, poorer left ventricular function and worse adverse left ventricular remodelling than outflow tract septal pacing. Moreover, the adverse left atrial structural and functional effects of right ventricular apical pacing and ventricular dyssynchrony are demonstrated. These results lend support to the theme that ventricular dyssynchrony, in this instance induced by pacing site, adversely influences left ventricular function, which in turn impacts in a deleterious manner on left atrial structure and function. In chapter 7, the final study conducted in this thesis, the intuitive question arising from the findings of chapter 6 is addressed, namely: if induction of ventricular dyssynchrony is deleterious, is its reversal therapeutic? This study randomised patients undergoing cardiac resynchronisation therapy for advanced heart failure to routine simultaneous bi-ventricular pacing, or echocardiographic optimisation of V-V timing during bi-ventricular pacing, with the goal of further reduction in ventricular dyssynchrony. This study was unable to demonstrate a benefit of routine V-V optimisation in recipients of cardiac resynchronisation therapy despite achieving less left ventricular dyssynchrony. A trend towards improved functional status was observed, however. This thesis has led to an improved understanding of the mechanisms underlying the development and perpetuation of left ventricular and atrial dysfunction, and the determinants of their response to heart failure therapy. Work of this nature may allow the identification of novel diagnostic and therapeutic approaches to heart failure in the future.

An Overview of the Heart's Prodigal Chamber

BoD – Books on Demand

The unique biology of cardiac fibroblasts and related cells, such as cardiac myofibroblasts and valvular interstitial cells, distinguish them from other fibroblastic cells, a concept that is only beginning to be widely appreciated. Further, the natural signals that stimulate and inhibit cardiac fibrosis within these cells are not well understood. This volume compiles articles that address the molecular mechanisms that control the synthesis and secretion of the cardiac ECM. The book showcases chapters that highlight discussion of role of Transforming Growth Factor β (TGFβ), an important fibrogenic cytokine and its downstream effectors SMAD in many cardiac diseases. Further, the contributions highlight information to discuss endogenous inhibitors of cardiac fibrosis, as well as advances in tissue engineering specific to matrix in the heart. Finally, discussions of unifying mechanisms of matrix remodeling in valves and myocardium are presented. The mechanisms involved in the stimulation of cardiac fibrosis are not fully understood. In most cases the marginal attenuation of cardiac fibrosis as a result of a given therapy is a beneficial side-effect linked to other primary effects on other cells, especially cardiomyocytes. Very few drugs or agents are known to affect the function and dysfunction of cardiac fibroblasts and myofibroblasts alone. The book helps to translate the information gathered within to allow us to alter the course of fibrogenic events that are typical of cardiac fibrosis, and thereby reduce their burden on the patient and on society itself.

An Organ-Based Guide to Disease Pathophysiology and Therapeutic Considerations Frontiers Media SA

Myocardial fibrosis is associated with vast majority of cardiovascular diseases which is one of the most common disease afflicting adults around the world. During myocardial infarction, myocytes die and are replaced by a specialized fibrotic extracellular matrix (ECM), otherwise known as scarring. The transdifferentiation to myofibroblasts is essential for wound healing of the heart. This cell type influences the secretion of cytokines, deposition of extracellular matrix proteins, structural support, and filling of the mechanical load caused by myocyte necrosis. However, the fibrosis influenced by myofibroblasts can lead to progressive heart failure. Fibrotic scarring presents a tremendous hemodynamic burden on the heart, as it creates a stiff substrate which resists diastolic filling. Fibrotic mechanisms result in permanent scarring which often leads to hypertrophy, arrhythmias, and a rapid progression to failure. Despite the deep understanding of fibrosis in other tissues, acquired through previous investigations, the mechanisms of cardiac fibrosis remain unclear. Recent studies suggest that biochemical cues as well as mechanical cues regulate cells in myocardium. However, the steps in myofibroblast transdifferentiation, as well as the molecular mechanisms of such transdifferentiation in vivo are poorly understood. This dissertation is focused on addressing the limited understanding of myofibroblast transdifferentiation cues and pathways that transduce those cues for cellular response, especially those mechanical in nature. Previously p38 has been reported to govern cardiac myofibroblast fate in response to various cues such as TGFb, substrate stiffness, and mechanical stretch. We investigated the myofibroblast fate regulation through p38 in response to topographic cue. Moreover, YAP was known to lend itself to heart regeneration and myofibroblast phenotype. In this dissertation, we show that p38 and YAP are also responsible for transducing mechanical signals related to topography and works in conjunction to tensin 1 to regulate transdifferentiation to myofibroblast. These results help to

Frontiers Media SA

Recent studies have shown that the heart possesses an intrinsic renin angiotensin system that is controlled by tissue-specific parameters that are activated by biomechanical stress. This book reviews the latest information on the way in which both the plasma and cardiac renin angiotensin systems affect heart function. It covers the cell and molecular biology of these systems, with contributions on renin synthesis, uptake and the intracellular signalling pathways. Particular insight comes from transgenic mouse models in which either mouse or human genes for various components of the renin angiotensin system are expressed. Other topics covered include wound healing as well as the trophic effects of aldosterone. Contains the most recent findings on the renin angiotensin system and the heart Written by an international team of distinguished scientists Covers both the cellular and molecular basis of the renin angiotensin system and the clinical relevance of this research

elucidate the pathway by which mechanical cues are transduced, leading to transdifferentiation. This study has addressed the limited understanding of myofibroblast transdifferentiation by identifying the novel topographic regulation and pathways that transduce such signals. Taken together, this research demonstrates the utility of bioengineering strategies to develop in vitro platforms to better understand the mechanism of cardiac fibrosis which would aid in discovering solutions to assist patients with hearts affected by fibrosis.

Periostin Raven Press

For decades we have known that the overgrowth, hardening and scarring of tissues (so-called fibrosis) represents the final common pathway and best histological predictor of disease progression in most organs. Fibrosis is the culmination of both excess extracellular matrix deposition due to ongoing or severe injury, and a failure to regenerate. An inadequate wound repair process ultimately results in organ failure through a loss of function, and is therefore a major cause of morbidity and mortality in disease affecting both multiple and individual organs. Whilst the pathology of fibrosis and its significance are well understood, until recently we have known little about its molecular regulation. Current therapies are often indirect and non-specific, and only slow progression by a matter of months. The recent identification of novel therapeutic targets, and the development of new treatment strategies based on them, offers the exciting prospect of more efficacious therapies to treat this debilitating disorder. This Research Topic therefore compromises several up-to-date mini-reviews on currently known and emerging therapeutic targets for fibrosis including: the Transforming Growth Factor (TGF)-family; epigenetic factors; Angiotensin II type 2 (AT2) receptors; mineralocorticoid receptors; adenosine receptors; caveolins; and the sphingosine kinase/sphingosine 1-phosphate and notch signaling pathways. In each case, mechanistic insights into how each of these factors contribute to regulating fibrosis progression are described, along with how they can be targeted (by existing drugs, small molecules or other mimetics) to prevent and/or reverse fibrosis and its contribution to tissue dysfunction and failure. Two additional reviews will discuss various anti-fibrotic therapies that have demonstrated efficacy at the experimental level, but are not yet clinically approved; and the therapeutic potential vs limitations of stem cell-based therapies for reducing fibrosis while facilitating tissue repair. Finally, this Research Topic concludes with a clinical perspective of various anti-fibrotic therapies for cardiovascular disease (CVD), outlining limitations of currently used therapies, the pipeline of anti-fibrotics for CVD and why so many anti-fibrotic drugs have failed at the clinical level.

Interstitial Fibrosis in Heart Failure Elsevier Health Sciences

This book is an open access dissemination of the EU COST Action ADMIRE in Aldosterone/Mineralocorticoid Receptor (MR) physiology and pathophysiology. Aldosterone is the major hormone regulating blood pressure. Alterations in blood levels of aldosterone and genetic mutations in the MR receptor are major causes of hypertension and comorbidities. Many of the drugs in clinical use, and in development for treating hypertension, target aldosterone and MR actions in the kidney and cardiovascular system. The ADMIRE book assembles review chapters from 16 European ADMIRE laboratories providing the latest insights into mechanisms of aldosterone synthesis/secretion, aldosterone/MR physiology and signaling, and the pathophysiological roles of aldosterone/MR activation.

Interstitial Fibrosis in Heart Failure Springer

Cardiac Fibrosis and Heart Failure: Cause or Effect?Springer

Hypertensive Heart Disease, An Issue of Heart Failure Clinics Springer

Heart failure is a major contributor to mortality and morbidity, both in Australia and worldwide. Despite significant recent therapeutic advances, many patients ultimately progress to advanced cardiomyopathy. The subsequent burden of end-stage heart failure, with few eligible for cardiac transplantation, necessitates urgent research into the underlying pathophysiology of this important disease. Myocardial fibrosis has previously been identified as fundamental in the development of heart failure, as first described in ischaemic cardiomyopathy. Its importance in non-ischaemic cardiomyopathy has been more recently recognised, with considerable interest in possible therapeutic options to retard progression. In order to further elucidate the consequences of myocardial fibrosis and potential benefits of anti-fibrotic therapies, a non-invasive quantitative method for the analysis of myocardial fibrosis is highly desired. In Chapter 1 of this thesis, I provide an introduction and literature review encompassing the current knowledge of the pathogenesis of heart failure, and the pivotal role of myocardial fibrosis. Chapter 2 outlines the methodology of a novel non-invasive cardiac magnetic resonance (CMR) imaging technique, investigated in this thesis as a potential quantitative assessment of diffuse myocardial fibrosis. In Chapter 3 I report for the first time validation of this CMR imaging technique for the quantification of diffuse myocardial fibrosis. This study compares this prototype CMR sequence in patients with heart failure with control subjects. Additionally, histological confirmation and correlation with diastolic function is reported.Recognising the limitations of comparative histology using endomyocardial biopsy specimens, I then compared histological analysis in explanted hearts with in vivo CMR examination prior to cardiac transplantation. This whole heart analysis allowed not only validation of our novel CMR technique for diffuse myocardial fibrosis, but also for confirmation of an established CMR technique, late gadolinium enhancement (LGE), as representative of regional replacement myocardial fibrosis. Whilst this has been shown to correlate with fibrosis in areas of myocardial infarction, histological validation in non-ischaemic cardiomyopathy is lacking.To extend on my investigation into the consequences of myocardial fibrosis, I studied patients planned for implantation of an internal cardioverter-defibrillator (ICD) for the primary prevention of sudden cardiac death. All patients underwent CMR prior to device implantation, and were followed to monitor for a primary endpoint of appropriate device therapy, with a pre-specified composite secondary endpoint of all-cause mortality, appropriate ICD therapy or cardiac transplantation. Presence of LGE was significantly associated with likelihood of reaching both the primary and secondary endpoints.Finally, in Chapter 6, I report cross-sectional and longitudinal data in a group of patients with non-ischaemic cardiomyopathy. In this study, I present data independently correlating diffuse myocardial fibrosis quantified by CMR with symptoms of heart failure, and both regional and diffuse myocardial fibrosis independently predicting adverse outcomes.Publication of two of these papers has contributed to rapid proliferation of research into this important aspect of heart failure, with both papers highly cited. It is hoped that this doctoral work and ongoing post-doctoral studies will continue to advance our understanding of myocardial fibrosis in heart failure, ultimately with reduction in patient mortality and morbidity.

Engineering Post-infarct Extracellular Matrix Remodeling in Vitro for Understanding Cardiac Fibroblast Fate and Function Oxford University Press

This book provides a comprehensive and up-to-date review of current understanding of periostin and its importance for human health and disease. Periostin is a secretory matricellular protein that has been revealed to play key roles in fibrillogenesis and cell

migration, including metastasis of cancer cells. The production of periostin is upregulated during fibrotic responses and the mechanisms by which it promotes fibrosis have become a focus of interest owing to the potential clinical benefit to be derived from periostin blockade. In this book, readers will find coverage of all aspects, from the basic properties of periostin and its function as a scaffold for assembly of extracellular proteins through to its roles in bone and tissue regeneration, tumorigenesis, myocardial infarction, inflammatory and immune system disorders, and other diseases. Readers will also find the latest information on functions of periostin related to stemness and the application of periostin as a biomarker. It is hoped that the detailed knowledge of periostin and its pathobiological significance provided in this book will aid in the search for effective treatments for currently incurable diseases.

Cellular Interactions in Cardiac Pathophysiology Springer
Ventricular arrhythmias cause most cases of sudden cardiac death, which is the leading cause of death in the US. This issue reviews the causes of arrhythmias and the promising new drugs and devices to treat arrhythmias.

Extracellular Matrix Springer Science & Business Media
This book provides a comprehensive overview of current knowledge of cannabinoid activity in human physiology and points out the importance of endocannabinoid system for the maintenance of human health and treatment of diseases. Each chapter has been organized with the aim to cover basic concepts in the modulation of endocannabinoid system in both physiological and pathological conditions, thanks to the integration of data from experimental animal models and clinical observations. A special focus has been put on the medical use of cannabinoids and on the targeting of endocannabinoid system as new therapeutic strategy for the prevention and treatment of human diseases. Taken together, this book targets a wide audience of basic and clinical scientists, teachers and students interested in gaining a better understanding in the field of cannabinoids.

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