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ONLIFE COMMENTARIES

CARDIOVASCULAR RESEARCH Onlife

Insights into cardiovascular research in Göttingen and Heidelberg: a report by the ESC Scientists of Tomorrow

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Over the last years, the medical faculties in Göttingen and Heidelberg have gained important insights into the pathophysiology of heart failure (HF), cardiomyopathies, and cardiac arrhythmias (*Figure 1*). The scientific interest of researchers at both universities has led to fruitful interactions and collaborations to elucidate cardiovascular pathophysiological mechanisms. Until today, cardiovascular research at both universities has involved interactions between basic science, clinical, and especially translational aspects. Here, we aim to summarize some of the latest cardiovascular research developments from both institutions.

Basic science discoveries in heart failure research

Recently, the group of Professor Johannes Backs from Heidelberg described an unrecognized proteolytic and cardioprotective function of the lipid droplet-associated protein ABHD5.[1] ABHD5 acts *in vivo* and *in vitro* as a serine protease that cleaves the histone deacetylase 4 (HDAC4) and inhibits MEF2-dependent gene expression and glucose handling. Strikingly, virus-mediated gene transfer of the HDAC4 fragment HDAC4-NT in mice was protective against HF. In human hearts from HF patients, ABHD5 was significantly reduced indicating that the protective function of the enzyme was decreased. These findings represent a conceptual advance by connecting lipid metabolism with glucose metabolism through HDAC4 proteolysis and may guide new translational approaches against cardiometabolic disease.

Another modulator of HF progression was recently identified by Doctor Laura Zelarayan from Göttingen and her team.[2] They provide evidence for cardiac-specific inhibition of the Wnt/β-catenin signalling pathway by the Krueppel-like transcription factor 15 (KLF15). It is well known that Wnt-signalling, which is physiologically silenced in the postnatal mammalian heart, is up-regulated in HF and there is hope that inhibition of Wnt-signalling may prevent HF progression. Considering the general importance of Wnt-signalling pathways in different organs, the cardiac-specific inhibition of Wnt pathways by activating KLF15 as shown by Noack *et al.*[2] may provide an interesting novel therapeutic concept.

HF can be caused by cardiac pressure (e.g. aortic stenosis, hypertension) or volume (e.g. aortic or mitral regurgitation) overload, resulting in concentric or eccentric left ventricular remodelling, respectively. It has been shown previously that different pathological pathways are responsible for specific phenotypes. The reactive oxygen species-generating enzyme NADPH oxidase 4 (Nox4) appears to play a protective role against pressure overload-induced cardiac hypertrophy. In contrast, a recent study in *Cardiovascular Research* by Doctor Moritz Schnelle (Göttingen) in collaboration with Professor Ajah Shah (King's College London, UK) has suggested Nox4 inhibition as a potential therapeutic approach in patients with eccentric left ventricular remodelling in response to volume overload.[3] Since Nox inhibitors are currently developed for treatment of other human diseases (e.g. lung fibrosis), the authors highlighted the importance of assessing the potential impact of these drugs on cardiac function in patients with co-existing valvular regurgitation.

In another study from Heidelberg Doctor Patrick Schweizer and his team investigated the role of HCN4 ion channels in HF-associated ventricular remodelling.[4] Physiologically, HCN channels cause the depolarizing 'funny current (I_f)' that contributes to cardiac pacemaking. Interestingly, I_f is up-regulated in ventricular cardiomyocytes from failing and infarcted hearts, but its pathophysiological relevance is unclear. Using transgenic mice ($HCN4^{tg/wt}$) functional consequences of increased I_f could be investigated. Transgenic mice with increased I_f current in ventricular cardiomyocytes ($HCN4^{tg/wt}$) showed a dilated cardiomyopathy phenotype with increased cellular arrhythmogenicity but unchanged heart rate and conduction parameters. Pharmacological inhibition of I_f prevented this effect and protected from ventricular remodelling suggesting that inhibition of HCN4 channels (e.g. with Ivabradine) may represent a novel therapeutic approach in HF patients.

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Basic science discoveries in cardiac remodelling after myocardial infarction

By analysing the secretome of cardiomyocytes, the group of Professor Florian Leuschner in Heidelberg identified PCSK6 as a novel player in cardiac remodelling.[5] After myocardial infarction, reduced oxygen delivery perturbs metabolic and mechanical processes in cardiomyocytes. To investigate interactions between cardiomyocytes after ischaemia, changes in active secretion of proteins from cardiomyocytes were experimentally characterized by combining stable isotope labelling and mass spectrometry. The proprotein convertase enzyme PCSK6 was identified as the most strongly up-regulated secreted factor in hypoxia. Cardiomyocyte-specific overexpression of PCSK6 in mice resulted in increased cardiac fibrosis, suggesting that this enzyme is crucially involved in cardiac remodelling after myocardial infarction.

Basic science discoveries in cardio-oncology

Together with colleagues from Heidelberg and Berlin, Doctor Mariella Bockstahler has discovered pathomechanisms of cardiac side effects caused by immune checkpoint inhibitors (ICIs) that are used to treat metastatic cancer.[6] Surprisingly, an autoimmune response against troponin I was observed in two cancer patients receiving either PD-1 or PD-1L inhibitors who developed ICI-related myocarditis. The autodestructive process and cardiac dysfunction could be reduced using the immunoproteasome-specific inhibitor ONX0914.

Basic science discoveries in atrial fibrillation

The first author of this summary recently employed an adeno-associated virus containing siRNA to inhibit expression of the atrial-specific two-pore domain potassium channel TASK-1 in a pig model of atrial fibrillation (AF).[7] The specific TASK-1 knockdown was shown to significantly reduce the AF burden and prevent electrical remodelling in the atria. These results show that targeted inhibition of TASK-1 expression has a significant antiarrhythmic effect.

In recent years, it has become evident that abnormal diastolic Ca^{2+} release from the sarcoplasmic reticulum (SR) contributes to the development and maintenance of AF. In particular, increased phosphorylation of two proteins regulating SR Ca^{2+} homeostasis seems to be crucial: (i) the type-2 ryanodine receptor (RyR2), mediating Ca^{2+} release from the SR and phospholamban (PLN), which regulates Ca^{2+} reuptake into the SR. A recent study in Circulation by Professor Stephan Lehnart (Göttingen) and Professor Xander HT Wehrens (Houston) uncovered a novel protein-phosphatase 1 subunit, PPP1R3A, which targets PP1 to RyR2 and PLN.[8] In mice, PPP1R3A deficiency promotes RyR2 and PLN hyperphosphorylation, resulting in abnormal SR Ca^{2+} release and increased AF susceptibility. Since PPP1R3A was down-regulated in patients with paroxysmal and long-term persistent AF, the authors suggest that this regulatory subunit may represent a new target for AF therapeutic strategies.

The same group from Göttingen investigated the role of abnormal Ca^{2+} handling in the pathogenesis of atrial cardiomyopathy in HF.[9] In atrial and ventricular cardiomyocytes junctophilin-2 stabilizes the interaction between L-Type Ca^{2+} channels in the plasmamembrane and RyR2 in the SR. It was demonstrated by Brandenburg *et al.* that junctophilin-2 knockdown in mice disrupts the distribution of RyR2, which are normally highly organized in clusters, resulting in impaired atrial contractility. Furthermore, mice lacking junctophilin-2 showed exacerbated atrial dysfunction in response to chronic pressure overload. In contrast, junctophilin-2 overexpression led to protection against pressure overload-induced atrial cardiomyopathy, highlighting junctophlilin-2 overexpression as a disease-mitigating concept to improve atrial dysfunction in HF patients.

Figure 1 Medical faculties in Göttingen and Heidelberg gained important insights into the pathophysiology of HF, cardiomyopathies, and cardiac arrhythmias. Map data: Google, GeoBasis-DE/BKG.

Finally, authors from Göttingen and Heidelberg collaborated in a recent study investigating the pre-existing arrhythmogenic substrate in patients developing AF after cardiac surgery (poAF).[10] The authors elegantly link data obtained on a molecular, cellular and *in vivo* level in patients to provide the first comprehensive analysis of the contribution of cytosolic Ca^{2+} handling abnormalities to the pathogenesis of poAF. In particular, analysis of preoperative echocardiographic recordings revealed that poAF development is associated with impaired atrial contractility. The authors demonstrate that reduced atrial function in these patients is likely mediated by pre-existing abnormalities in cytosolic Ca^{2+}-homeostasis. In addition, Ca^{2+}-handling abnormalities increase the cellular susceptibility to Ca^{2+}-transient and action potential alternans thereby contributing to the arrhythmogenic substrate and predisposing patients to the development of poAF. The authors conclude that atrial contractility may represent an important factor for identification of patients at risk for poAF and targeting Ca^{2+}-handling abnormalities may be a novel mechanistic target to prevent poAF development.

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Authors

Biography: PD Dr Constanze Schmidt, FESC, is a clinical and cellular electrophysiologist at the Department of Cardiology of Heidelberg University. In 2010, after receiving her MD degree at Göttingen University, she started her clinical education in internal medicine and cardiology with focus on electrophysiology at Heidelberg University. In 2017, she established her own lab investigating atrial arrhythmopathy and cellular electrophysiology. As part of her scientific work, she characterized the pathophysiological role of K2P channels in the human heart and identified the K2P channel TASK-1 as an important regulator of the atrial action potential in atrial fibrillation and heart failure. In 2016, she was appointed consultant physician in internal medicine. Her scientific work was supported by Rahel Goitein Straus and Olympia-Morata fellowships of Heidelberg University. Amongst numerous awards, she received the Liselotte-Becht research award (2017) and the Oskar-Lapp research award (2016) of the German Cardiac Society, the best moderated poster award of the ESC (2016) and was selected as finalist for the Heart Rhythm Society young investigator award (2014). Since 2018, she has been a member of the Scientists of Tomorrow of the European Society of Cardiology (ESC).

Biography: Dr Niels Voigt, FAHA, FESC, is professor of Molecular Pharmacology at the Institute of Pharmacology and Toxicology at the Georg-August University Göttingen, Germany. He graduated and received his MD from the University of Dresden in 2007. He worked as a postdoctoral scientist at the Institute of Pharmacology in Dresden, at the Medical Faculty Mannheim, Heidelberg University and at the Institute of Pharmacology at the Duisburg-Essen University. In 2013, he obtained the specialization in Pharmacology and Toxicology. His field of interest is the regulation of ion channels and calcium signalling in the normal and diseased heart. He has received numerous research awards, e.g. the Oskar-Lapp-Research Award (2015) from the German Cardiac Society and the Best of Basic Science Abstracts Award from the American Heart Association (2013). In 2016, he joined the nucleus of the Scientists of Tomorrow of the European Society of Cardiology (ESC).