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Title: Surfing on the Cardiovascular Frontier Wave

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The very first conference of "Frontiers in Cardiovascular Research" took place in the archipelago paradise of Hawaii in the middle of the Pacific Ocean from September 26 to 27, 2013. The venue for the meeting was the Sullivan Auditorium at the University of Hawaii Cancer Center located on the John A. Burns School of Medicine (JABSOM) campus in Honolulu. Although the school is relatively small compared to other medical schools elsewhere, research thrives here on the JABSOM campus. With the flagship Cancer Center and departments dedicated to studying tropical diseases and native Hawaiian health, researchers at JABSOM are working hard to fulfill the mission of serving the diverse population of people that live in Hawaii. Amongst certain sectors of the Hawaiian population, cardiovascular diseases are on the increase. The dedicated team of researchers at the Center for Cardiovascular Research at JABSOM are studying ways to lessen the cardiovascular burden with experts that focus on various areas of cardiac and vascular function. This conference was a perfect venue to exchange ideas and research findings between the European scientists and the cardiovascular researchers at JABSOM who normally work literally on opposite sides of the globe. The collection of concise reviews and original articles presented in this theme issue is devoted to new aspects of cardiovascular medicine with particular emphasis on stress conditions in the heart.

The heart is a high energy-demanding organ that strongly depends on a fatty acid supply to work without interruption for 80 years or more, beating more than 3×10^9 times during this time to pump more than 200×10^6 liters of blood throughout our body´s 100,000 km long blood vessel system. Although it is very well established that cardiomyocytes rely on the different functions of their different types of mitochondria, whose ATP-generating capacity greatly depends on a fatty acid metabolism, only limited data are available on a second fatty acid-driven organelle in these cells, the peroxisome. In their review, Colasante et al. (1) provide comprehensive information on the largely cardio-protective role of peroxisomes and their lipid metabolism, which is regulated by components of the "peroxisome-proliferator-activated-receptor" (PPAR) system. In addition, these authors present new original data on the regional expression of peroxisome-related genes in the heart as well as on the dysregulation of specific PPARs in a mild peroxisomal biogenesis defect. The possible impact of peroxisomal dysfunction on myocardial metabolism, involving the peroxisome-PPAR loop, is discussed.

Based on their recent observations as to the damaging role of extracellular (ribosomal) RNA (eRNA), derived from hypoxic cardiomyocytes in the context of ischemia/reperfusion injury (2), Cabrera-Fuentes et al. (3) now present conclusive data on the strong impact of eRNA on driving macrophages towards the pro-inflammatory M1-phenotype. A variety of inflammatory cytokines become upregulated in mouse bone marrow-derived as well as in human peripheral blood monocytes /

macrophages in response to eRNA, and this process may occur during the progression of atherosclerosis in authentic lesions of the inflamed arterial wall, as previously described by these authors (4). The characterization of the underlying mechanism of this robust phenotype change in macrophages requires further work, particularly as to the response of different tissue-resident macrophages towards the inflammatory agonist eRNA. As part of the innate immune response, the complement system provides all components for opsonization, chemotactic attraction of leukocytes as well as membrane lysis of microbes in the context of an inflammatory response. In their concise review, Vogel et al. (5) present compelling data as to the beneficial therapeutic effects of complement depletion by "cobra venom factor" (a very stable C3 homologue) in different murine vascular disease models. This new experimental approach, involving humanized versions of cobra venom factor, may particularly represent a promising therapeutic strategy to prevent tissue damage in reperfusion injury-related diseases.

In the area of cardiovascular disease, the review by Rose and Hoffmann (6) covers in detail the role of various selenoproteins in regulating oxidative stress in a number of conditions that damage the cardiovascular system such as ischemia-reperfusion, myocardial hypertrophy and Keshan disease. Selenoproteins contain the amino acid, selenocysteine, which in turn contains the essential trace element, selenium, thought to be derived mainly from the diet. Selenoproteins are best known for their function as antioxidant enzymes such as glutathione peroxidase and thioredoxin reductase. The review by Han and Boisvert (7) focusses on the role of one of the quintessential anti-inflammatory cytokines, IL-10, on immune-driven atherosclerosis. They emphasize the importance of macrophages in the pathogenesis of atherosclerosis and the ways in which IL-10 can modulate the essential functions of macrophages such as foam cell formation and cytokine production that are known contributors to the disease process. In another review by Patra et al. (8) efforts to vascularize engineered cardiac tissue are described. The implantation of engineered cardiac tissue may be necessary after a myocardial infarction or during surgical correction of cardiac malformation that may result in loss of valuable cardiac tissue. However, vascularizing such implanted tissue has been a challenge. In describing the various attempts to establish vascularization in implanted tissues, the authors focus in particular on the potential role of extracellular matrices which are traditionally known as supporting structures for tissue scaffold, but are now recognized as having an essential role in angiogenesis. The authors also discuss the latest technology in biomaterial-based approaches to engineering cardiac tissue.

Ischemic heart disease (IHD) remains the leading cause of death and disability worldwide. Therefore, it was pertinent that novel mechanisms of cardio-protection were discussed at the New Frontiers in

Cardiovascular Research meeting. Mitochondria are key mediators of cell survival and death in the setting of acute ischemia/reperfusion injury (IRI), and are therefore critical targets for cardio-protection. In their article, Ong et al (9) investigated the role of the well-known cardio-protective signaling protein kinase, Akt, on mitochondrial morphology - a phenomenon in which mitochondria are able to change their shape by undergoing fusion and fission events, processes which are regulated by mitochondrial fusion and fission proteins and which can influence the susceptibility of the heart to acute IRI (reviewed in ref. 10). Previous experimental studies have shown that mitochondria undergo fission in response to acute ischemia, and preventing this change in mitochondrial morphology using either a genetic or pharmacological approach can attenuate cardiomyocyte death and reduce myocardial infarct size in hearts subjected to acute IRI (11). The authors have found that Akt may exerts its cardio-protective effect by inhibiting mitochondrial fission induced by acute IRI – importantly this cardio-protective effect was reproduced by the cardio-protective cytokine erythropoietin. The mechanism through which Akt modulates mitochondrial morphology is unclear although it may be through the modulation of mitochondrial fission and fusion proteins. Fernandez-Sanz et al. (12) have investigated the contribution of mitochondrial function to the increased susceptibility of the aged heart to the detrimental effects of acute IRI. As the FoF1 ATP synthase has recently been proposed to be a component of the "mitochondrial permeability transition pore" (MPTP, a critical determinant of acute myocardial IRI) (13, 14), these authors investigated the effect of acute IRI on the FoF1 ATP synthase and the MPTP opening sensitivity. They found that components of the FoF1 ATP synthase were oxidized and sensitivity of MPTP opening was increased, and have hypothesized that the oxidation of ATP synthase may underlie this effect.

Although reperfusion is required to salvage myocardium in the ischemic heart in the setting of an acute myocardial infarction, the process of reperfusion itself can induce myocardial injury and cardiomyocyte death – a phenomenon termed "myocardial reperfusion injury" (reviewed in ref. 15). A shift in arginine metabolism from nitric oxide (NO) to polyamine formation may contribute to the impaired myocardial functional recovery at reperfusion. In their study, Schreckenberg et al. (16) have investigated the role of tumor necrosis factor (TNF)-α and the renin-angiotensin system (RAS) in this change in cardiac metabolism. They found TNF-α and the RAS to be responsible for the depressed cardiac function that occurs in the first few hours following reperfusion, providing an insight into the pathophysiology of myocardial reperfusion injury. In the clinical setting ongoing advances in the field of interventional cardiology continue to improve the treatment of obstructive coronary artery disease. In this context, Simsekyilmaz et al. (17) review recent developments in coronary stent technology which have the potential to overcome the problems associated with maintaining stent patency in patients with diseased coronary arteries. Finally, Ferrazzi et al. (18) have applied gene

network analysis in the study of cardiac development with the aim of elucidating the pathophysiology underlying congenital heart defects in order that novel therapeutic targets can be identified to treat cardiac disease. Further, this form of analysis may lead to the understanding of the pathways underlying stem cell differentiation in adult cardiomyocytes in the field of regenerative therapy.

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