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Recent highlights on the mechanistic basis of cardiovascular remodeling from the *International Journal of Cardiology Heart & Vasculature*

The *International Journal of Cardiology Heart & Vasculature (IJCHA)* provides a growing forum for reports on novel candiate biomarkers and their association with clinical outcomes in cardiovascular disorders. An emerging focus is myocardial remodeling, a key unifying feature of many cardiomyopathies like heart failure (HF) and atrial fibrillation (AF). Rhythm monitoring strategies, non-invasive imaging and blood biomarker surrogates to indirectly determine the extent and nature of cardiovascular remodeling processes and their relation to disease evolution are increasingly at the core of clinical research papers submitted to the journal [1–8].

The phase 1 prospective „FIbrosis Biomarker Mirroring Atrial fibRillation severity as a Key of aging (FIB-MARK)“ trial published by Kawaji et al. [9] teamed an inflammatory protein array of peripheral blood from AF patients with assessment of atrial low voltage zone (LVZ). This surrogate fibrosis index was around the same time validated in a proof-of-concept study by Nedios et al. [10] as the best indirect measure of atrial remodeling in patients undergoing AF ablation. In the report by Kawaji et al., interleukin (IL)-17A and interferon (IFN)-γ, respectively, showed the strongest positive and negative correlation with LVZ, suggesting that a raised serum IL-17A/IFN-γ ratio might be of predictive value – and possibly causal relevance – during AF evolution. The report by Nguyen et al. [11] exemplified the emerging role of the gut-heart axis in pro-arrhythmic atrial remodeling. The authors assessed key gut microbe-derived metabolites in plasma of patients participating in the AF-RISK study and linked them to AF risk and disease severity. The microbial metabolite trimethylamine N-oxide (TMAO) was consistently elevated in patients with persistent AF compared to those with paroxysmal AF. In univariate analysis, every unit increase in TMAO modestly, but significantly, raised the odds of having persistent AF. TMAO is formed from the diet-derived precursers betaine, choline and L- carnitine by the action of gut flora and has been implicated in the development of various metabolic, inflammatory and remodeling-associated diseases [12]. Its putative role in development of atrial cardiomyopathy and AF was commented in the accompanying editorial by Gawalko et al. [13]. Mechanistic insight into myocardial remodeling specifically underlying ischemic cardiomyopathy was provided by the case-control biomarker study by Chumkova et al. [14]. The authors assessed prototypical myocardial remodeling mediators and monocyte immunophenotypes together with regional myocardial macrophage distribution in patients undergoing cardiopulmonary bypass surgery. Despite limited sample sizes, the comprehensive study design could convincingly link ischemic cardiomyopathy with a lower abundance of non-classical and transitional monocyte phenotypes, with increased circulating galectin-3 and matrix metalloproteinase (MMP)-9, and finally with altered regional distribution of myocardial $CD68^{+}$ macrophages. Transforming growth factor-β (TGFβ) was not different, suggesting that ischemic myocardial remodeling is more dependent on the extracellular matrix (ECM)-degrading actions of MMP-9 and galectin-3 than on the pro-fibrotic effects of TGFβ. In contrast, the findings of Takahashi et al. [15] question the value of gold-standard biomarkers as surrogate indices for coronary plaque characteristics. The authors found no correlation between a panel of conventional inflammatory serum biomarkers and either the extent or lipid core composition of culprit plaque lesions in patients with acute coronary syndrome and stable angina. This negative finding reinforces the continued need for direct intravascular plaque assessment.

Clinical association studies provide important insight into possible mechansims of cardiovascular pathophysiology, but the causal involvement of biomarkers requires proper validation in well-designed preclinical models. The quality and reproducibility of these model systems are critical for their translational value. A conventional preclinical model system to study myocardial remodeling and HF development is transverse aortic constriction (TAC) in rodents. Patel et al. [16] evaluated various methodological modifications of the core approach, including the size and location of the constriction, the technique used to measure blood pressure as the primary read-out, and the duration of follow-up. The largest and most reproducible increases in systolic and diastolic blood pressures were achieved with a needle size of 24G rather than 22G, placed above rather than between the renal arteries, and with blood pressure measurement performed using the Millar PV catheter system rather than the tail-cuff approach. This constellation of experimental parameters was the only approach to significantly increase heart: body weight (HW/BW) ratio, lower heart rate and elevate left ventricular end systolic pressure (LVESP). Of note, in echocardiography, the QRS and QT intervals were also significantly prolonged with this constellation of experimental parameters, recapitulating additional features of the clinical setting. Soraya et al. [17] applied the pressure-overload TAC model to mice to delineate the cell-specific role of the stress-activated transcription factor ATF3 in maldadaptive cardiac remodeling. Conditional deletion of ATF3 in cardiomyocytes blunted markers of TAC-induced cardiac hypertrophy, specifically HW/BW ratio and re-expression of the fetal gene B-ype natriuretic peptide (BNP) and of Acta1, the cardiomyocyte form of smooth muscle α-actin (αSMA). TAC-stimulated atrial natruretic peptide (ANP) re-expression was not affected. By contrast, TAC-stimulated gene expression of the pro-fibrotic factors TGFβ, the collagens Ia and IIIaI, and Acta2 were essentially normalized. Conditional ATF3 knockout in myofibroblasts did not prevent the TAC-induced increase HW/BW ratio, but significantly suppressed re-expression of BNP, Acta1 and ANP, without affecting gene

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expression of classical pro-fibrotic mediators. These findings suggest ATF3 in cardiomyocytes is essential for fibrosis formation, while ATF3 in myofibroblasts primarily regulates hypertrophy. A narrative review by Kerr et al. [3] comprehensively bundles the available evidence for natriuretic peptides in myocardial remodeling underlying AF, critically appraising the current state of the art on this topic and the critical remaining gaps in knowledge. Specifically, the need for optimal cut-off values in the different clinical settings, and the required screening intervals are discussed, with a view to improve risk stratifaction according to atrial cardiomyopathy and AF progression and improve patient management.

Bukowska et al. [18] examined spontaneously hypertensive rats (SHR), an established preclinical model of stable compensated hypertrophy, for the development of atrial oxido-inflammatory stress and the effect of the novel endothelin (ET-1) receptor antagonist macitentan on this. Unlike the α_1-aderenoceptor antagonist doxazosin, macitentan did not reduce blood pressure over the chronic (8-week) treatment period, but comparably suppressed the lipoperoxidation marker 8-isoprostane, the pro-inflammatory intercellular adhesion molecule ICAM-1 and IL-8, and the phosphorylation of mitogenic kinases p38MAPK and ERK1/2 in atrial myocardium. Neither drug affected myocardial hypertrophy, fibrosis or the expression of major calcium-handling proteins. Unlike doxazosin, macitentan additionally lowered the abundance of vascular adhesion molecule VCAM-1 and phosphorylated nuclear factor kappa B (NFκB), attributed to a mechanism independent of blood pressure-lowering. The accompanying editorial by van Wagoner [19] critically discussed the potential reasons why the inhibitory effect of macitentan on NFκB, a critical pro-inflammatory switch that directs many processes of cardiac remodeling and cardiomyopathy, was not accompanied by preserved atrial myocardial structure.

One major limitation of translating basic science to the clinical setting is that hemodynamics, genetic variability and many other factors vastly distinguish humans from small animals and even from larger mammals [20]. The horse is gaining increasing interest as a physiologically relevant large-animal model of AF, since like the human, the horse can spontaneously develop AF [21,22]. Saljic et al. [23] examined horses with persistent AF and elegantly mapped the cellular composition in different regions of the atrial and *peri*-atrial myocardium. A key observation was that although atrial conduction velocity and contractility were reduced in horses with AF, this was not associated with overt structural remodeling and changes in atrial dimensions. The authors proposed that discrete regions of fibroblast accumulation potentially cause local impairment of electrical cell coupling and conduction in the equine atria. The mechanisms that promote fibroblast accumulation and transdifferentiation to collagen-secreting myofibroblasts in such localised hot spots remain poorly understood. An *in vitro* study by Magaye et al. [24] provided insight into a regulatory sphingolipid loop in cardiac fibroblasts that modulates autocrine TGFβ1 signaling. Sphingolipid research is largely focused on the key end-effectors ceramide and sphingosine-1-phosphate (S1P), the possible role of the intermediates sphingosine (Shp) and dihydrosphingosine (dhSph) has been largely understudied. Magaye et al. found that dhSph (but not Sph) could suppress TGFβ1-induced collagen synthesis and expression of pro-fibrotic genes by suppressing canonical and non-canonical TGFβ1 signaling. This reinforces an earlier report that while S1P mimics many of the pro-fibrotic actions of TGFβ1, dh-S1P, an alternative metabolite of dhSph, rather counteracts the responses to TGFβ1. The initial source of extracellular dhSph that triggers the regulatory loop and the overall biological significance remain to be determined.

Finally, Ijichi et al. [25] examined the novel biodegradable polymer-based Ultimaster™ sirolimus-eluting stent (BP-SES) in a porcine model of stent restenosis. Conventional drug-eluting stents (DES) pose the problem of immediate drug toxicity and over time sustained toxicity and inflammatory reactions due to the stent itself. Controlled and timely resolution of inflammation is therefore essential for appropriate healing and remodeling without overshoot. The elegant study by Ijichi et al. paired optical frequent domain imaging (OFDI) with histology assessment of the stent-associated neotintima in minipigs implanted with a standard bare metal stent (BMS), an everolimus-DES or the sirolimus-eluting BP-SES. After 9 months, the biodegradable polymer SES had led to less inflammation and improved regression of the early neointima that was evident in all groups at 3 months. The benefits of *in situ* stent degradation therefore appear to become particularly evident with longer follow-up and are likely related to improved suppression and/or resoluation of late inflammatory reactions.

In conclusion, here we spotlighted a selection of preclincial studies with potential translational relevance in the context of cardiovascular remodeling. Such basic science reports are a valuable complement for clinical association studies, by providing mechanistic links between plasma biomarkers, local molecular signatures and clincial read-outs of disease progression and treatment outcome.

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