GROUNDBREAKING ADVANCES IN CARDIOVASCULAR RESEARCH

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Highlighting the numerous scientific breakthroughs we witnessed last year in the cardiovascular field is a daunting task. Between several important discoveries, we selected groundbreaking advancements in three areas of cardiovascular research that hold great promise for the years to come: (i) therapeutic approaches targeting metabolic remodeling in heart failure; (ii) a novel methodology to interrogate gene expression patterns of single cell types; and (iii) the emerging connection between heart failure and cancer.

NEW THERAPEUTIC TARGETS: METABOLIC REMODELING IN CARDIOVASCULAR DISEASE

One of the most arduous challenges of basic research in cardiology is the quest for novel therapeutic approaches to treat heart failure. In fact, in spite of our quite sophisticated understanding of the molecular mechanisms underlying cardiac dysfunction, heart failure therapy has been based for a long time on blockade of neurohormonal activation, ventricular unloading, and heart rate control, the introduction of neprilysin inhibitors was the only innovation in the last 25 years. In contrast, agents directly targeting cardiac myocyte function are not currently available for the treatment of chronic heart failure in the clinical arena.

Targeting deranged cardiac metabolism is emerging as one of the most promising approaches in preclinical models of heart failure, and studies published last year have provided new exciting insights into this field. In particular, numerous cutting-edge studies have further elucidated the relationship between intermediary metabolism and cellular regulatory pathways in the heart and vasculature. An outstanding example is the study by Lehmann et al published in *Nature Medicine*,[1] which demonstrated that the hexosamine biosynthetic pathway has downstream effects on excitation-contraction coupling in cardiac myocytes by inducing posttranslational modifications of proteins involved in calcium handling. As hexosamine biosynthetic pathway activation is observed in response to numerous cardiac stressors, this maladaptive pathway is a potential target for novel therapeutic approaches aimed at ameliorating contractility in the failing heart.

Another example of the detrimental impact of metabolic remodeling on cardiac function was provided by the elegant mechanistic study by Tsushima et al[2] based on a mouse model of lipotoxicity, ie, the accumulation of toxic lipid intermediates in cardiac myocytes. In this setting, an increase in myocardial fatty acid uptake enhanced mitochondrial fission by inducing posttranslational modifications of proteins involved in mitochondrial dynamics. Mitochondrial fission is the process of organelle division that leads to removal of damaged mitochondria and enables metabolic adaptations in response to an elevation in energy demand, as elucidated by another landmark study published last year in *Circulation Research*.[3] However, pathological mitochondrial fission results in fragmentation of the mitochondrial network, thereby leading to cardiomyopathy. The study by Tsushima et al[2] revealed that a key mediator in this maladaptive process is oxidative stress, suggesting that lipotoxicity-induced cardiac dysfunction might be rescued by mitochondria-targeted antioxidant agents. Since lipotoxicity is a hallmark of diabetic cardiomyopathy,[4] and intramyocardial accumulation of toxic lipid intermediates was reported in heart failure patients with and without diabetes,[5] these studies hold great translational value.

Although promising, these mechanistic insights are still far from being tested in clinical trials. In contrast, experimental evidence demonstrating the benefit associated with supplementation with nicotinamide adenine dinucleotide (NAD) precursors might already be sufficient to warrant testing this approach in heart failure patients.[6] A study published in *Circulation*[7] strongly corroborated this model by proving the benefit of NAD augmentation on contractile function in two mouse models of heart failure, namely a genetic mouse model of dilative cardiomyopathy and the widely used model of acute pressure overload by transverse aortic constriction. Intriguingly, supplementation with NAD precursors was also shown to decrease susceptibility to acute kidney injury in mice and humans.[8] However, the mechanisms underlying the beneficial effects of NAD supplementation are far from being fully elucidated. NAD plays a key role in energy metabolism by donating the electrons harvested by Krebs cycle dehydrogenases to the electron transport chain complexes. In addition, NAD is an essential cosubstrate of sirtuins, a family of enzymes catalyzing posttranslational modifications of proteins involved in a variety of cellular functions. Future studies should be aimed at resolving which NAD function(s) is the dominant driver of its cardioprotective activity, a pursuit which will be facilitated by the recent identification of the protein mediating import of NAD precursors inside the cell.[9] In the meantime, this therapeutic approach appears ripe for translation to the clinical arena.

NEW TECHNOLOGIES: SINGLE-CELL RNA SEQUENCING

The development of genome-wide transcriptome profiling has led to great advancements in our knowledge of gene expression landscapes. However, until

recent years, this approach was limited to the analysis of extracts from whole tissue lysates, consequently losing any information regarding individual cellular populations. This limitation was recently overcome due to the development of new methodologies enabling the amplification of small amounts of RNA. The novel technique, coined single-cell RNA sequencing, has enabled researchers to generate unbiased maps of cellular heterogeneity, and represents a potent tool for the identification of molecular mechanisms of disease.

The study by Gladka et al published last year was the first to experiment with this new approach in the adult heart.[10] In this study, single-cell sequencing led to the identification of a new mediator involved in the activation of cardiac fibroblasts in response to injury. By applying the single-cell RNA sequencing approach to the vasculature, Cochain et al investigated the leukocyte infiltrate in murine atherosclerotic aortas.[11] This study identified three distinct macrophage populations, two of which are specifically associated with atherosclerotic plaques, and recognized the existence of a previously unappreciated macrophage subtype. In a back-to-back study, Winkels et al combined single-cell RNA sequencing with mass cytometry, outlining an atlas of the immune cell repertoire in atherosclerotic plaques.[12]

Overall, these studies support the concept that the use of a single marker to discriminate cellular subtypes is a reductive approach, whereas assessing gene expression patterns provides a more accurate picture of cellular heterogeneity and has the potential to unravel new cell-specific pathways associated with cardiovascular disease.

NEW MECHANISTIC INSIGHTS: THE DANGEROUS LIAISON BETWEEN HEART FAILURE AND CANCER

For the last decades, the focus of cardio-oncology has been the prevention of cardiovascular disease in oncology patients and cancer survivors who carry a higher risk of cardiovascular events compared with the general population.[13] In the last years, a previously overlooked connection between heart failure and cancer was unraveled by epidemiological studies reporting a higher risk of incident cancer in heart failure patients compared with individuals without heart failure.[14-16] While many confounding factors can underlie this association, such as the increased medical attention received by patients newly diagnosed with heart failure, a preclinical study by Meijers et al[17] shed light on a novel and intriguing scenario, ie, that heart failure might represent a pro-oncogenic condition. In this study, sham-operated or infarcted mouse hearts were transplanted into the necks of mice carrying a mutated adenomatous polyposis coli gene, making these mice prone to developing intestinal tumors. Compared with mice being transplanted with sham-operated hearts, animals receiving infarcted failing hearts developed

a substantially higher tumor burden due to the release of mitogenic factors from the failing myocardium. As mice receiving heart transplantations in the cervical region retained their own healthy heart, the investigators could demonstrate that the pro-oncogenic activity of the failing myocardium is independent of hemodynamic factors. This study opens up an entirely novel field of research where the challenge will be to elucidate this and possibly additional mechanisms linking heart failure to cancer. For instance, it has been proposed that neurohormonal activation, which is a hallmark of heart failure with reduced ejection fraction, might influence tumor biology via β-adrenergic receptors expressed by cancer cells and the tumor microenvironment, consequently promoting progression and dissemination of neoplasms.[18]

CONCLUSIONS

The field of cardiovascular basic science is evolving at a steady pace, and those discussed here are only three of the exciting advancements made in 2018. We look forward to the upcoming years, which will hopefully witness the translation of these groundbreaking preclinical studies to the clinical arena. ■

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