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The National Institutes of Health (NIH) 2016 Progenitor Cell Biology Consortium (PCBC) and Cardiovascular Tissue Engineering (CVTE) Symposium was held on March 28, 2016 at Birmingham, AL (Figure). Over one hundred scientists, engineers, and trainees attended the symposium hosted by new joint Department of Biomedical Engineering, University of Alabama at Birmingham (UAB). The symposium was part of the NIH National Blood, Heart, and Lung Institute’s PCBC and featured information on the field’s latest accomplishments. The goal of the Symposium was to discuss novel approaches and cell and tissue engineering–based products to repair damaged heart and vasculature. The symposium sessions were aimed at the common topic of advancing the understanding of disease mechanisms and translating the most advanced basic science to preclinical and clinical trials. Because of the word limitation, this report could only highlight some of the presentations from this 1-day PCBC CVTE 2016 Symposums. Many pertinent presentation summaries are not included, yet they certainly merit.

The opening remarks were given by Dr Jianyi Zhang and Dean J. Iwan D. Alexander (School of Engineering, UAB). Following the introductory remarks, 21 speakers presented their research topics in 12-minute lectures. This short presentation format was well acknowledged by the audience.

Cell Therapy Session
Dr. John P. Cooke (The Houston Methodist Research Institute) provided evidence that innate immune activation is essential for nuclear reprogramming to pluripotency, as well as transdifferentiation to another somatic lineage. His group showed that the viral vector for the Yamanaka factors was more than a mere vehicle.1 Stimulation of innate immunity by the viral vector (via TLR3 [toll-like receptor 3] and RIG-1 activation) causes global changes in epigenetic modifiers (eg, suppression of HDAC [histone deacetylases] family members and up-regulation of HAT [histone acetyltransferases] proteins) that increases the probability of an open chromatin configuration. Antagonism of innate immunity abrogates nuclear reprogramming. Similarly, his group has shown that the transdifferentiation of fibroblasts to endothelial cells requires activation of innate immune pathways.2 More recently, his group has preliminary data that innate immune activation of inducible NO synthase results in nitrosylation of epigenetic modifiers that causes a release of suppressive epigenetic mechanisms.

Dr Daniel J. Garry (University of Minnesota) presented his recent works on cardiac progenitors that reside in the adult heart and emphasized that the role cardiac progenitor cells during aging and after injury remains unclear but represents an area of active investigation. He also presented his work on xenogentic organ production for transplantation. He emphasized that the only curative treatment option for chronic heart failure is organ transplantation, which is hampered by the shortage of available organ supply. Furthermore, organ-transplanted patients require lifelong immunosuppression that is associated with damaging side effects. Dr Garry’s group described studies where gene editing and somatic cell nuclear transfer technologies were used to engineer porcine embryos that lack cardiovascular lineages followed by rescue using wild-type GFP (green fluorescent protein)-labeled pig blastomeres to engineer pig:pig chimeras. He concluded that these studies support the hypothesis that humanized organs can be fabricated using human-induced pluripotent stem cells in the gene-edited pigs.

Dr Timothy J. Kamp (University of Wisconsin) described their work on reprogramming of fibroblast into induced cardiac progenitor cells.3 He reported that combination of 11 or 5 cardiac-specific transcription factors along with modulation of canonical Wnt and JAK/STAT signaling enabled reprogramming of adult mouse fibroblasts from heart, lung, and tail tip into induced cardiac progenitor cells. His laboratory expanded these mesoderm-restricted progenitors while maintaining their multipotency and ability to differentiate into different cardiac lineages in vitro. Most importantly, when induced cardiac progenitor cells were transplanted into a mouse heart post myocardial infarction, they differentiated into multiple cardiac lineages and yielded improved cardiac function. He concluded that induced cardiac progenitor cells provide a promising cell source for cardiac regenerative therapy.

Dr Joshua M. Hare (University of Miami) discussed the use of different stem cells for cardiac repair therapy and outlined the results of recent clinical trials of cell-based therapy for chronic heart failure. He then focused on their recent preclinical studies whereby 3 months after ischemia/reperfusion injury, his group injected either mesenchymal stem cells alone or in combination with cardiac-derived stem cells in to the swine hearts.4 Both animal groups showed significant reduction in scar size and increased viable tissue. Most importantly, they observed improvement in ejection fraction, cardiac output, and...
stroke volume only in the combined therapy group. He concluded that beneficial interactions between mesenchymal stem cells and cardiac-derived stem cells form the basis for a novel second-generation cell therapeutic products for cardiac repair.

Dr Hesham A. Sadek (University of Texas Southwestern) group studies mechanisms of cardiomyocyte cell cycle regulation. They recently demonstrated that increased myocardial oxygenation and demand postnatal results in increased energy efficiency of postnatal cardiomyocytes at the expense of their regenerative ability. Specifically, they showed that mitochondrial metabolism induces oxidative DNA damage in cardiomyocytes postnatally, which mediates cell cycle arrest through the activation of DNA damage response. In support of these findings, they recently reported that a rare population of hypoxic cardiomyocytes are protected for oxidative DNA damage and mediate cardiomyocyte turnover within the adult mammalian heart. Current studies are focused on examining the potential role of targeting DNA damage response in cardiomyocytes as a therapeutic strategy for heart regeneration.

Dr Ho-Wook Jun, PhD (UAB) and Young-sup Yoon, MD, PhD (Emory University) presented their work on Bioengineered Stem Cell Therapy. The presentations discussed the development of a novel technique that can enrich cardiomyocytes from cardiomyogenically differentiating mouse and human pluripotent stem cells by using cardiac-specific molecular beacons targeting specific mRNAs that are expressed within cardiomyocytes.

Tissue Engineering Session:
Dr Nenad Bursac (Duke University) described their recent progress in scaling-up human engineered cardiac tissues to clinically relevant dimensions (=40x40 mm²). These large tissue patches were designed to maintain highly advanced electric (velocity of action potential conduction) and mechanical (specific contractile force) properties similar to those previously reported by the same group for smaller engineered tissues. Dr Bursac emphasized the importance of achieving mature electric phenotype and high velocity and spatial homogeneity of action potential propagation in large tissue patches to reduce their vulnerability to arrhythmias. These tissue patches can strongly adhere to epicardial surface without the need for sutures and are currently being evaluated in a porcine model of postinfarction disease.

Dr Beth L. Pruitt (Stanford University) discussed quantitative assays to address open questions of mechanobiology in stem cell–derived cardiomyocytes. She described methods for quantitative experiments in cardiomyocyte biomechanics and mechanotransduction using micromasurement and analysis systems with appropriately tuned mechanical environments and imaging access. She presented results using engineered pluripotent stem cell–derived cardiomyocytes and showed them as promising model systems to study cell mechanoresponse and myofibrillogenesis, disease biophysics, and drug testing. The mechanics of the environment and morphology constraint of the cell couple to provide favorable conditions for force generation and maturation of sarcomere structures. The platforms are being used to study disease mechanisms affecting contractility and the role of force in tissue development and in response to physiological mechanical stimuli.

Dr Milica Radisic (University of Toronto) described a new way to vascularize engineered tissues for the purposes of organ-on-a-chip engineering, tissue engineering, and direct surgical anastomosis. The new vascularization technique is
based on a polymer scaffold with built-in vasculature. The scaffold is termed AngioChip, and it is developed from a synthetic biodegradable elastomer (poly(octamethylene maleate (anhydride) citrate). The design of AngioChip network enabled the researchers to effectively decouple the material choice for the engineered vessel network from the material choice for the cell seeding in the parenchyma, enabling extensive remodeling while maintaining open vessel lumens. The scaffold is assembled using a new 3-dimensional stamping technique that enables the growth of the material sheet by sheet without the use of sacrificial layers. Incorporation of nanopores and microholes in the vessel walls enhanced permeability, permitted intercellular crosstalk, and extravasation of monocytes and endothelial cells on biomolecular stimulation. Vascularized hepatic tissues and cardiac tissues, engineered using AngioChips, were shown to process clinically relevant drugs delivered through their internal vasculature. AngioChip cardiac tissues were also implanted via direct surgical anastomosis to the femoral vessels of rat hindlimbs, establishing immediate blood perfusion. This is the first time direct anastomosis of an engineered microvascular bed was possible without the use of resected vascular beds from another site on the body.

Dr Ibrahim Domian (Harvard Medical School), Dr Brenda Ogle (University of Minnesota), and Dr Eugene Chen (University of Michigan Medical Center) also shared their cutting-edge recent research findings in this session.

Cardiovascular Physiology

Dr Gerald W. Dorn (Washington University) described the importance of mitochondrial fusion and fission in cardiomyocyte development and pathology. He reported that dynamin-related protein 1-mediated mitochondrial fission is necessary for cardiomyocyte hypertrophy, whereas genetic ablation of cardiomyocyte-specific dynamin-related protein 1 evokes mitochondrial enlargement, lethal dilated cardiomyopathy, and cardiac necrosis in adult mice. Furthermore, he described the studies that revealed the important roles of mitofusins 1 and 2 in fetal cardiac development in vivo and early cardiomyocyte differentiation of induced pluripotent stem cells in vitro. Furthermore, he described the importance of mitofusin-2 in switching from carbohydrate-based metabolism to fatty acid-based metabolism in early postnatal development. He concluded that mitochondrial fission and fusion have complex roles on cardiomyocyte calcium signaling, mitochondrial biogenesis, and developmental mitochondrial turnover.

Dr Richard N. Kitis (Albert Einstein College of Medicine) summarized that although accumulating evidence suggests that a substantial portion of the beneficial effects of progenitor cells in various regenerative paradigms is attributable to the molecules they secrete. These paracrine mechanisms contribute to the creation of an appropriate microenvironment, or niche, required for effective tissue repair. The rationale for postulating paracrine effects in cardiac regeneration was initially driven by observations that most exogenously administered progenitor cells fail to engraft, survive, and differentiate—challenging the notion that sustained improvements in cardiac function can be ascribed to the mere presence of these cells. Although beneficial effects of secreted factors on all of these functions have been demonstrated, major questions remain as to their relative magnitudes and which are truly rate-limiting in tissue regeneration. A more precise understanding of this question may provide the basis to engineer progenitor cells to have more favorable paracrine profiles. A related area worthy of further study is how the survival and engraftment of progenitor cells could be promoted genetically or with small molecules. This is not a simple question, however, as classic death molecules, such as caspases, may also play critical roles in cellular differentiation.

University of Alabama investigators Dr Jack M. Rogers, Dr Andrew E. Pollard, Dr Sumanth D. Prabhu, and Dr Ho-Wook Jun presented their recent research findings and did several dynamic roles in this symposium. Postdoctoral research scholars from several frontier research laboratories were also given opportunities to present their work in this symposium.

The organizers of the CVTE 2016 would take this opportunity to express our appreciation and gratitude to all the attendee for their excellent presentations and the active participation in discussions during the meeting. The NIH CVTE 2017 will be on March 2, 2017 at UAB with confirmed presentations by leaders in this field from North America, Europe, and Asia. The organizers sincerely hope that the NIH CVTE symposium will continue to flourish internationally and offer members of the field ample opportunities to collaborate and advance the cutting-edge research on cardiovascular sciences.

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Disclosures

None.

References

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