The 10 Most Read Articles Published in *Circulation Research* in 2016

Roberto Bolli, for the Editors

We are pleased to provide the list of the 10 most read original articles published in *Circulation Research* in 2016. We realize that the number of citations is the most conventional parameter used to gauge interest by the readership; however, providing this metric would require a few years, by which time the articles may have lost their novelty and appeal. Consequently, as we have done in the past, we have selected the articles on the basis of the number of Full Text/PDF downloads, which we hope will offer a reasonable estimate of the level of interest among our readers.

Our motivation in compiling this list is multifarious. By highlighting the most popular articles, we wish to direct the attention of our readers to new information that may be of particular interest to a large fraction of the community of cardiovascular scholars. In addition, a synopsis of the most popular articles can be a useful indicator of burgeoning areas of research that are likely to dominate the landscape for years to come. This "honor roll" is also meant to acknowledge the outstanding work of the authors and their efforts in advancing the frontiers of cardiovascular science. Furthermore, we believe that the articles highlighted below represent paradigms of scientific excellence, particularly with respect to the three criteria that we value most at *Circulation Research*: conceptual and/or mechanistic novelty, scientific impact, and methodological rigor. Finally, we hope that this list will provide tangible evidence of the high (and always rising) level of scientific excellence of the work published in *Circulation Research*.

At the top of the list, as the undisputed "winner," is a paper describing the use of human cardiac matrix and human induced pluripotent stem cell–derived cardiomyocytes to engineer functional myocardium (Guyette et al). The "silver medal" goes to a study suggesting that proton pump inhibitors (PPIs) produce dysfunction and senescence of human endothelial cells (Yepuri et al). A close third is a paper reporting a new, simplified method for isolation of cardiac myocytes and nonmyocytes from the adult mouse heart (Ackers-Johnson et al). Other areas of emphasis include stem cell biology (including the largest cardiovascular study of cell therapy in primates published heretofore [Hu et al]), diabetes, circular RNAs, and inflammation in heart failure. As outlined in our editorial manifesto,[1] rapid advances in these fields may transform cardiovascular medicine. We view them as an important focus of the journal, and we are proud of the fact that *Circulation Research* has been at the forefront of the explosive growth of cutting edge research, both at the basic and at the translational levels.

—Roberto Bolli

The following represent a selection of the most read *Circulation Research* articles published between January 2016 and December 2016, presented in their order of publication. Articles were selected based on the number of Full-Text/PDF downloads, adjusted to compensate for differences in the time interval since publication.

From the January 8, 2016 issue:

Bioengineering Human Myocardium on Native Extracellular Matrix

Jacques P. Guyette, Jonathan M. Charest, Robert W. Mills, Bernhard J. Jank, Philipp T. Moser, Sarah E. Gilpin, Joshua R. Gershlak, Tatsuya Okamoto, Gabriel Gonzalez, David J. Milan, Glenn R. Gaudette, Harald C. Ott

Abstract

Rationale—More than 25 million individuals have heart failure worldwide, with ≈4000 patients currently awaiting heart transplantation in the United States. Donor organ shortage and allograft rejection remain major limitations with only ≈2500 hearts transplanted each year. As a theoretical alternative to allotransplantation, patient-derived bioartificial myocardium could provide functional support and ultimately impact the treatment of heart failure.

Objective—The objective of this study is to translate previous work to human scale and clinically relevant cells for the bioengineering of functional myocardial tissue based on the combination of human cardiac matrix and human induced pluripotent stem cell–derived cardiomyocytes.

Methods and Results—To provide a clinically relevant tissue scaffold, we translated perfusion-decellularization to human scale and obtained biocompatible human acellular cardiac scaffolds with preserved extracellular matrix composition, architecture, and perfusable coronary vasculature. We then repopulated this native human cardiac matrix with cardiomyocytes derived from nontransgenic human induced

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pluripotent stem cells and generated tissues of increasing 3-dimensional complexity. We maintained such cardiac tissue constructs in culture for 120 days to demonstrate definitive sarcomeric structure, cell and matrix deformation, contractile force, and electrical conduction. To show that functional myocardial tissue of human scale can be built on this platform, we then partially recellularized human whole-heart scaffolds with human induced pluripotent stem cell–derived cardiomyocytes. Under biomimetic culture, the seeded constructs developed force-generating human myocardial tissue and showed electrical conductivity, left ventricular pressure development, and metabolic function.

Conclusions—Native cardiac extracellular matrix scaffolds maintain matrix components and structure to support the seeding and engraftment of human induced pluripotent stem cell–derived cardiomyocytes and enable the bioengineering of functional human myocardial-like tissue of multiple complexities.[2]

From the February 5, 2016 issue:

Revisiting Cardiac Cellular Composition

Alexander R. Pinto, Alexei Ilinykh, Malina J. Ivey, Jill T. Kuwabara, Michelle L. D'Antoni, Ryan Debuque, Anjana Chandran, Lina Wang, Komal Arora, Nadia A. Rosenthal, Michelle D. Tallquist

Abstract

Rationale—Accurate knowledge of the cellular composition of the heart is essential to fully understand the changes that occur during pathogenesis and to devise strategies for tissue engineering and regeneration.

Objective—To examine the relative frequency of cardiac endothelial cells, hematopoietic-derived cells, and fibroblasts in the mouse and human heart.

Methods and Results—Using a combination of genetic tools and cellular markers, we examined the occurrence of the most prominent cell types in the adult mouse heart. Immunohistochemistry revealed that endothelial cells constitute >60%, hematopoietic-derived cells 5% to 10%, and fibroblasts <20% of the nonmyocytes in the heart. A refined cell isolation protocol and an improved flow cytometry approach provided an independent means of determining the relative abundance of nonmyocytes. High-dimensional analysis and unsupervised clustering of cell populations confirmed that endothelial cells are the most abundant cell population. Interestingly, fibroblast numbers are smaller than previously estimated, and 2 commonly assigned fibroblast markers, Sca-1 and CD90, under-represent fibroblast numbers. We also describe an alternative fibroblast surface marker that more accurately identifies the resident cardiac fibroblast population.

Conclusions—This new perspective on the abundance of different cell types in the heart demonstrates that fibroblasts comprise a relatively minor population. By contrast, endothelial cells constitute the majority of noncardiomyocytes and are likely to play a greater role in physiological function and response to injury than previously appreciated.[3]

From the March 18, 2016 issue:

A Large-Scale Investigation of Hypoxia-Preconditioned Allogeneic Mesenchymal Stem Cells for Myocardial Repair in Nonhuman Primates: Paracrine Activity Without Remuscularization

Xinyang Hu, Yinchuan Xu, Zhiwei Zhong, Yan Wu, Jing Zhao, Yingchao Wang, Haifeng Cheng, Minjian Kong, Fengjiang Zhang, Qi Chen, Jianzhong Sun, Qian Li, Jing Jin, Qingju Li, Lihong Chen, Chen Wang, Hongwei Zhan, Youqi Fan, Qian Yang, Lei Yu, Rongrong Wu, Jie Liang, Jinyun Zhu, Ya Wang, Yiping Jin, Yifan Lin, Fan Yang, Liangliang Jia, Wei Zhu, Jinghai Chen, Hong Yu, Jianyi Zhang, Jian'an Wang

Abstract

Rationale—The effectiveness of transplanted bone marrow mesenchymal stem cells (MSCs) for cardiac repair has been limited; thus, strategies for optimizing stem-cell–based myocardial therapy are needed.

Objective—The present study was designed to test our central hypothesis that hypoxia-preconditioned MSCs (HP-MSCs) are more effective than MSCs cultured under ambient oxygen levels for the treatment of myocardial injury in a large-scale (N=49), long-term (9 months), nonhuman primate (Cynomolgous monkeys) investigation.

Methods and Results—MSCs were engineered to express green fluorescent protein, cultured under ambient oxygen or 0.5% oxygen (HP-MSCs) for 24 hours and then tested in the infarcted hearts of Cynomolgus monkeys (1×107 cells per heart). Hypoxia preconditioning increased the expression of several prosurvival/proangiogenic factors in cultured MSCs, and measurements of infarct size and left-ventricular function at day 90 after myocardial infarction were significantly more improved in monkeys treated with HP-MSCs than in monkeys treated with the control vehicle; functional improvements in normal cultured bone marrow mesenchymal stem cells–treated monkeys were not significant. HP-MSCs transplantation was also associated with increases in cardiomyocyte proliferation, vascular density, myocardial glucose uptake, and engraftment of the transplanted cells and with declines in endogenous cell apoptosis, but did not increase the occurrence of arrhythmogenic complications.

Conclusions—Hypoxia preconditioning improved the effectiveness of MSCs transplantation for the treatment of myocardial infarction in nonhuman primates without increasing the occurrence of arrhythmogenic complications, which suggests that future clinical trials of HP-MSCs transplantation are warranted.[4]

From the June 10, 2016 issue:

Proton Pump Inhibitors Accelerate Endothelial Senescence

Gautham Yepuri, Roman Sukhovershin, Timo Z. Nazari-Shafti, Michael Petrascheck, Yohannes T. Ghebre, John P. Cooke

Abstract

Rationale—Proton pump inhibitors (PPIs) are popular drugs for gastroesophageal reflux, which are now available for long-term use without medical supervision. Recent reports suggest that PPI use is associated with cardiovascular, renal, and neurological morbidity.

Objective—To study the long-term effect of PPIs on endothelial dysfunction and senescence and investigate the mechanism involved in PPI-induced vascular dysfunction.

Methods and Results—Chronic exposure to PPIs impaired endothelial function and accelerated human endothelial senescence by reducing telomere length.

Conclusions—Our data may provide a unifying mechanism for the association of PPI use with increased risk of cardiovascular, renal, and neurological morbidity and mortality.[5]

From the August 19, 2016 issue:

Anti-Inflammatory Effects of Metformin Irrespective of Diabetes Status

Amy R. Cameron, Vicky L. Morrison, Daniel Levin, Mohapradeep Mohan, Calum Forteath, Craig Beall, Alison D. McNeilly, David J.K. Balfour, Terhi Savinko, Aaron K.F. Wong, Benoit Viollet, Kei Sakamoto, Susanna C. Fagerholm, Marc Foretz, Chim C. Lang, Graham Rena

Abstract

Rationale—The diabetes mellitus drug metformin is under investigation in cardiovascular disease, but the molecular mechanisms underlying possible benefits are poorly understood.

Objective—Here, we have studied anti-inflammatory effects of the drug and their relationship to antihyperglycemic properties.

Methods and Results—In primary hepatocytes from healthy animals, metformin and the IKKβ (inhibitor of kappa B kinase) inhibitor BI605906 both inhibited tumor necrosis factor-α–dependent IκB degradation and expression of proinflammatory mediators interleukin-6, interleukin-1β, and CXCL1/2 (C-X-C motif ligand 1/2). Metformin suppressed IKKα/β activation, an effect that could be separated from some metabolic actions, in that BI605906 did not mimic effects of metformin on lipogenic gene expression, glucose production, and AMP-activated protein kinase activation. Equally AMP-activated protein kinase was not required either for mitochondrial suppression of IκB degradation. Consistent with discrete anti-inflammatory actions, in macrophages, metformin specifically blunted secretion of proinflammatory cytokines, without inhibiting M1/M2 differentiation or activation. In a large treatment naive diabetes mellitus population cohort, we observed differences in the systemic inflammation marker, neutrophil to lymphocyte ratio, after incident treatment with either metformin or sulfonylurea monotherapy. Compared with sulfonylurea exposure, metformin reduced the mean log-transformed neutrophil to lymphocyte ratio after 8 to 16 months by 0.09 U (95% confidence interval, 0.02–0.17; P=0.013) and increased the likelihood that neutrophil to lymphocyte ratio would be lower than baseline after 8 to 16 months (odds ratio, 1.83; 95% confidence interval, 1.22–2.75; P=0.00364). Following up these findings in a double-blind placebo controlled trial in nondiabetic heart failure (trial registration: NCT00473876), metformin suppressed plasma cytokines including the aging-associated cytokine CCL11 (C-C motif chemokine ligand 11).

Conclusion—We conclude that anti-inflammatory properties of metformin are exerted irrespective of diabetes mellitus status. This may accelerate investigation of drug utility in nondiabetic cardiovascular disease groups.

Clinical Trial Registration—Name of the trial registry: TAYSIDE trial (Metformin in Insulin Resistant Left Ventricular [LV] Dysfunction). URL: https://www.clinicaltrials.gov. Unique identifier: NCT00473876.[6]

From the September 16, 2016 issue:

Proliferation and Recruitment Contribute to Myocardial Macrophage Expansion in Chronic Heart Failure

Hendrik B. Sager, Maarten Hulsmans, Kory J. Lavine, Marina B. Moreira, Timo Heidt, Gabriel Courties, Yuan Sun, Yoshiko Iwamoto, Benoit Tricot, Omar F. Khan, James E. Dahlman, Anna Borodovsky, Kevin Fitzgerald, Daniel G. Anderson, Ralph Weissleder, Peter Libby, Filip K. Swirski, Matthias Nahrendorf

Abstract

Rationale—Macrophages reside in the healthy myocardium, participate in ischemic heart disease, and modulate myocardial infarction (MI) healing. Their origin and roles in post-MI remodeling of nonischemic remote myocardium, however, remain unclear.

Objective—This study investigated the number, origin, phenotype, and function of remote cardiac macrophages residing in the nonischemic myocardium in mice with chronic heart failure after coronary ligation.

Methods and Results—Eight weeks post MI, fate mapping and flow cytometry revealed that a 2.9-fold increase in remote macrophages results from both increased local macrophage proliferation and monocyte recruitment. Heart failure produced by extensive MI, through activation of the sympathetic nervous system, expanded medullary and extramedullary hematopoiesis. Circulating Ly6Chigh monocytes rose from 64±5 to 108±9 per microliter of blood (P<0.05). Cardiac monocyte recruitment declined in Ccr2−/− mice, reducing macrophage numbers in the failing myocardium. Mechanical strain of primary murine and human macrophage cultures promoted cell cycle entry, suggesting that the increased wall tension in post-MI heart failure stimulates local macrophage proliferation. Strained cells activated the mitogen-activated protein kinase pathway, whereas specific inhibitors of this pathway reduced macrophage proliferation in strained cell cultures and in the failing myocardium (P<0.05). Steady-state cardiac macrophages, monocyte-derived macrophages, and locally sourced macrophages isolated from failing myocardium expressed different genes in a pattern distinct from the M1/M2 macrophage polarization paradigm. In vivo silencing of endothelial cell adhesion molecules curbed post-MI monocyte

recruitment to the remote myocardium and preserved ejection fraction (27.4±2.4 versus 19.1±2%; $P<0.05$).

Conclusions—Myocardial failure is influenced by an altered myeloid cell repertoire.[7]

From the September 30, 2016 issue:

A Simplified, Langendorff-Free Method for Concomitant Isolation of Viable Cardiac Myocytes and Nonmyocytes From the Adult Mouse Heart

Matthew Ackers-Johnson, Peter Yiqing Li, Andrew P. Holmes, Sian-Marie O'Brien, Davor Pavlovic, Roger S. Foo

Abstract

Rationale—Cardiovascular disease represents a global pandemic. The advent of and recent advances in mouse genomics, epigenomics, and transgenics offer ever-greater potential for powerful avenues of research. However, progress is often constrained by unique complexities associated with the isolation of viable myocytes from the adult mouse heart. Current protocols rely on retrograde aortic perfusion using specialized Langendorff apparatus, which poses considerable logistical and technical barriers to researchers and demands extensive training investment.

Objective—To identify and optimize a convenient, alternative approach, allowing the robust isolation and culture of adult mouse cardiac myocytes using only common surgical and laboratory equipment.

Methods and Results—Cardiac myocytes were isolated with yields comparable to those in published Langendorff-based methods, using direct needle perfusion of the LV ex vivo and without requirement for heparin injection. Isolated myocytes can be cultured antibiotic free, with retained organized contractile and mitochondrial morphology, transcriptional signatures, calcium handling, responses to hypoxia, neurohormonal stimulation, and electric pacing, and are amenable to patch clamp and adenoviral gene transfer techniques. Furthermore, the methodology permits concurrent isolation, separation, and coculture of myocyte and nonmyocyte cardiac populations.

Conclusions—We present a novel, simplified method, demonstrating concomitant isolation of viable cardiac myocytes and nonmyocytes from the same adult mouse heart. We anticipate that this new approach will expand and accelerate innovative research in the field of cardiac biology.[8]

From the October 14, 2016 issue:

RBM20 Regulates Circular RNA Production From the Titin Gene

Mohsin A.F. Khan, Yolan J. Reckman, Simona Aufiero, Maarten M.G. van den Hoogenhof, Ingeborg van der Made, Abdelaziz Beqqali, Dave R. Koolbergen, Torsten B. Rasmussen, Jolanda van der Velden, Esther E. Creemers, Yigal M. Pinto

Abstract

Rationale—RNA-binding motif protein 20 (RBM20) is essential for normal splicing of many cardiac genes, and loss of RBM20 causes dilated cardiomyopathy. Given its role in splicing, we hypothesized an important role for RBM20 in forming circular RNAs (circRNAs), a novel class of noncoding RNA molecules.

Objective—To establish the role of RBM20 in the formation of circRNAs in the heart.

Methods and Results—Here, we performed circRNA profiling on ribosomal depleted RNA from human hearts and identified the expression of thousands of circRNAs, with some of them regulated in disease. Interestingly, we identified 80 circRNAs to be expressed from the titin gene, a gene that is known to undergo highly complex alternative splicing. We show that some of these circRNAs are dynamically regulated in dilated cardiomyopathy but not in hypertrophic cardiomyopathy. We generated RBM20-null mice and show that they completely lack these titin circRNAs. In addition, in a cardiac sample from an RBM20 mutation carrier, titin circRNA production was severely altered. Interestingly, the loss of RBM20 caused only a specific subset of titin circRNAs to be lost. These circRNAs originated from the RBM20-regulated I-band region of the titin transcript.

Conclusions—We show that RBM20 is crucial for the formation of a subset of circRNAs that originate from the I-band of the titin gene. We propose that RBM20, by excluding specific exons from the pre-mRNA, provides the substrate to form this class of RBM20-dependent circRNAs.[9]

From the October 28, 2016 issue:

Cardiac Fibroblast GRK2 Deletion Enhances Contractility and Remodeling Following Ischemia/Reperfusion Injury

Meryl C. Woodall, Benjamin P. Woodall, Erhe Gao, Ancai Yuan, Walter J. Koch

Abstract

Rationale—G protein–coupled receptor kinase 2 (GRK2) is an important molecule upregulated after myocardial injury and during heart failure. Myocyte-specific GRK2 loss before and after myocardial ischemic injury improves cardiac function and remodeling. The cardiac fibroblast plays an important role in the repair and remodeling events after cardiac ischemia; the importance of GRK2 in these events has not been investigated.

Objective—The aim of this study is to elucidate the in vivo implications of deleting GRK2 in the cardiac fibroblast after ischemia/reperfusion injury.

Methods and Results—We demonstrate, using Tamoxifen inducible, fibroblast-specific GRK2 knockout mice, that GRK2 loss confers a protective advantage over control mice after myocardial ischemia/reperfusion injury. Fibroblast GRK2 knockout mice presented with decreased infarct size and preserved cardiac function 24 hours post ischemia/reperfusion as demonstrated by increased ejection fraction (59.1±1.8% versus 48.7±1.2% in controls; $P<0.01$). GRK2 fibroblast knockout mice also had decreased fibrosis and fibrotic gene expression. Importantly, these protective effects correlated with decreased infiltration of neutrophils

to the ischemia site and decreased levels of tumor necrosis factor-α expression and secretion in GRK2 fibroblast knockout mice.

Conclusions—These novel data showing the benefits of inhibiting GRK2 in the cardiac fibroblast adds to previously published data showing the advantage of GRK2 ablation and reinforces the therapeutic potential of GRK2 inhibition in the heart after myocardial ischemia.[10]

From the November 11, 2016 issue:

Exposure to Fine Particulate Air Pollution Is Associated With Endothelial Injury and Systemic Inflammation

C. Arden Pope, Aruni Bhatnagar, James P. McCracken, Wesley Abplanalp, Daniel J. Conklin, Timothy O'Toole

Abstract

Rationale—Epidemiological evidence indicates that exposures to fine particulate matter air pollution ($PM_{2.5}$) contribute to global burden of disease, primarily as a result of increased risk of cardiovascular morbidity and mortality. However, mechanisms by which $PM_{2.5}$ exposure induces cardiovascular injury remain unclear. $PM_{2.5}$-induced endothelial dysfunction and systemic inflammation have been implicated, but direct evidence is lacking.

Objective—To examine whether acute exposure to $PM_{2.5}$ is associated with endothelial injury and systemic inflammation.

Methods and Results—Blood was collected from healthy, nonsmoking, young adults during 3 study periods that included episodes of elevated $PM_{2.5}$ levels. Microparticles and immune cells in blood were measured by flow cytometry, and plasma cytokine/growth factors were measured using multiplexing laser beads. $PM_{2.5}$ exposure was associated with the elevated levels of endothelial microparticles (annexin V+/CD41−/CD31+), including subtypes expressing arterial-, venous-, and lung-specific markers, but not microparticles expressing CD62+. These changes were accompanied by suppressed circulating levels of proangiogenic growth factors (EGF [epidermal growth factor], sCD40L [soluble CD40 ligand], PDGF [platelet-derived growth factor], RANTES [regulated on activation, normal T-cell–expressed and secreted], GROα [growth-regulated protein α], and VEGF [vascular endothelial growth factor]), and an increase in the levels of antiangiogenic (TNFα [tumor necrosis factor α], IP-10 [interferon γ-induced protein 10]), and proinflammatory cytokines (MCP-1 [monocyte chemoattractant protein 1], MIP-1α/β [macrophage inflammatory protein 1α/β], IL-6 [interleukin 6], and IL-1β [interleukin 1β]), and markers of endothelial adhesion (sICAM-1 [soluble intercellular adhesion molecule 1] and sVCAM-1 [soluble vascular cellular adhesion molecule 1]). $PM_{2.5}$ exposure was also associated with an inflammatory response characterized by elevated levels of circulating CD14+, CD16+, CD4+, and CD8+, but not CD19+ cells.

Conclusions—Episodic $PM_{2.5}$ exposures are associated with increased endothelial cell apoptosis, an antiangiogenic plasma profile, and elevated levels of circulating monocytes and T, but not B, lymphocytes. These changes could contribute to the pathogenic sequelae of atherogenesis and acute coronary events.[11]

Disclosures

None.

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