Recent Developments

Recent Developments in Cardiovascular Research: The goal of “Recent Developments” is to provide a concise but comprehensive overview of new advances in cardiovascular research, which we hope will keep our readers abreast of recent scientific discoveries and facilitate discussion, interpretation, and integration of the findings. This will enable readers who are not experts in a particular field to grasp the significance and effect of work performed in other fields. It is our hope and expectation that these “Recent Development” articles will help readers to gain a broader awareness and a deeper understanding of the status of research across the vast landscape of cardiovascular research—The Editors.

Recent Developments in Vascular Biology

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The field of vascular biology has transformed dramatically in recent years as new research has elucidated complex roles of novel proteins, stem/progenitor/hematopoietic cells, and miRNAs as well as redox signaling in vascular development, vascular tone regulation and disease in preclinical models and clinical settings. Review of this body of work highlights seminal findings and new developments that emphasize and illuminate underlying principles and historical connections. In the 1980s, there was the frenzied search for the identity of the Endothelium-Derived Relaxing Factor (EDRF; ie, NO). In the 1990s, the elucidation of myriad EDHFs (hyperpolarizing factors, eg, H₂O₂, K⁺, arachidonic acid metabolites) expanded endothelial cell complexity beyond NO. In the 2000s, the endothelial cell generation and overall cardiovascular effects of H₂S were hotly pursued. In the 2010s, the role of the peri-vascular adipose tissue (PVAT) derived relaxing and contractile factors in vascular regulation under physiological and disease promoting conditions (eg, diet-induced obesity, metabolic syndrome) has emerged as a new integrative vascular issue of importance because of the obesity epidemic.

Vasodilation Mechanisms – Still Relevant

Critically important mechanisms continue to be sources of interest and renewed research. Indeed, the panoply of endothelial-derived factors that regulate vascular tone continues to grow, and identifying new ones will only enhance our understanding of the diverse factors that regulate vascular tone and blood flow in context-dependent ways. As elucidated in the article by Zhang et al, entitled “H₂O₂-induced dilation in human coronary arterioles: role of protein kinase G dimerization and long-conductance Ca²⁺-activated K⁺ channel activation,” redox-mediated VSMC K⁺-channel opening ultimately leads to relaxation and dilation in coronary blood vessels. Similarly, PPAR-γ stimulated Regulatory G-protein S 5 (RG5S)-control of Protein Kinase C-mediated opening of calcium-activated BKCa channels also leads to VSMC relaxation in arterioles. If that is not enough, K⁺, BKCa, or inward rectifying K⁺-channels along with the Na⁺/K⁺-ATPase are effector targets of acidosis or reactive hyperemia in arteriolar dilation, respectively. Thus, there has been a resurgence of research into the largely metabolism-driven (such as in exercise) and K⁺-channel-mediated regulation of arterial smooth muscle tone abounds. In another study, “Vascular bioactivation of nitroglycerin is catalyzed by cytosolic aldehyde dehydrogenase-2,” Beretta et al, shed new light on a longstanding controversy regarding the mechanism of nitroglycerin (GTN) bioactivation in VSMC. Superseding the historic roles of both aortic GSTs and mitochondrial ALDH2, their findings suggest that cytoplasmic ALDH2 is the important player in blood vessels, a fresh perspective that could provide a new biochemical target with the potential to combat nitrate tolerance—this adds a new integrative vascular issue of importance because of the obesity epidemic.

Vascular Imaging – Not your Father’s (or Galileo Galilei’s) Microscope

Not to be outdone by detailed vasoregulatory mechanisms, increased attention has been given to vascular imaging, and in recent years, several articles describing new vascular imaging approaches and their applications in a variety of physiological and pathophysiological settings have been published. For example, one of the more difficult tasks of imaging coronary blood flow (especially in mice) is accomplished by Krueger et al in “Visualizing regional myocardial blood flow in the mouse”—a straightforward title for a not so ordinary feat that involves the use of 15-μm fluorescent microspheres with unprecedented spatial and temporal resolution. Second, a “Novel genetic approach for in vivo vascular imaging in mice” by Bartelle et al is quite simply amazing as mice expressing the Biotag-BirA transgene are injected with various “avidinated” probes and then imaged with near infrared, ultrasound, and MRI as appropriate. Similarly, Thuneman et al is available at http://circres.ahajournals.org

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took the advice of Bartelle et al, to heart by making transgenic mice that express a cGMP sensor (cGi500) that when bound elicits fluorescence resonance energy transfer (FRET) for visualization of blood vessels in vivo. This technical accomplishment could be used, for example, in visual assessment of true nitrate tolerance that is a result of impaired GTN bioactivation in SMC. Nanotechnology has also gained an imaging foothold via two like-minded articles featuring potent nuclear imaging methods for cell-type–specific targeting in atherosclerotic plaques.21 These were: “Nanobodies targeting mouse/human vcam1 for the nuclear imaging of atherosclerotic lesions” by Broisat et al, which utilized technetium-99 m (99 m)Tc-labeled, anti-VCAM1 nanobody for noninvasive detection of mouse and human VCAM122; and, “Polymeric nanoparticle PET/MR imaging allows macrophage detection in atherosclerotic plaques” by Majmudar et al, where 13-nm polymeric nanoparticles consisting of crosslinked-dextran radiolabeled with zirconium-89 are imaged and colocalized with CD11b+ cells in plaques.23 These new applications are powerful techniques that will not only revolutionize the way we visualize and interpret changes in vascular wall dynamics that regulate blood flow and vascular wall remodeling, but could also better our understanding of the early, causal, and deleterious modifications that ultimately promote endothelium dysfunction, atherosclerosis and aneurysm.

Atherosclerosis to Aneurysm: Acts of Remodeling

Since Virchow’s day, our model of atherosclerosis is continually updating and recent articles add more of the same.24 From the works, “Lack of neutrophil-derived CRAMP reduces atherosclerosis in mice”25; “Bone marrow-specific deficiency of nuclear receptor Nur77 enhances atherosclerosis”26; and, “Deficiency of ATP-binding cassette transporters A1 and G1 in macrophages increases inflammation and accelerates atherosclerosis in mice,”27 we see important roles for specific proteins expressed in bone marrow-derived hematopoietic (and inflammatory) cells that dramatically alter the progression of atherosclerosis, and as such, these are potentially new targets for suppression of atherosclerotic growth. Moreover, ‘remodeling of the vascular wall’ is a frequently used catch-all phrase; however, current studies are attempting to more precisely define the temporal and spatial relationships (eg, “outside in” versus “inside out”)28 between critical events such as VSMC phenotypic switching and proliferation (eg, see “MicroRNA-663 regulates human vascular smooth muscle cell phenotypic switch and vascular neointimal formation”29; “MAPK phosphorylation of connexin 43 promotes binding of cyclin E and smooth muscle cell proliferation”30; “Quaking, an RNA-binding protein, is a critical regulator of vascular smooth muscle cell phenotype”31) and calcification (eg, “Smooth muscle cell-specific runx2 deficiency inhibits vascular calcification”32, “Prelamin A accelerates vascular calcification via activation of the DNA damage response and senescence-associated secretory phenotype in vascular smooth muscle cells”33) that lead to development of atherosclerotic plaques and/or aneurysm formation. The latter pathology is associated with a new circulating biomarker that could be useful for aneurysm prognosis34 to aid more directed treatment35 as described by Marshall et al in “Thoracic aortic aneurysm frequency and dissection are associated with fibrillin-fragment concentrations in circulation.” Similarly, a potential role of a miRNA is explored in “miR-29b participates in early aneurysm development in Marfan syndrome” by Merk et al with miR-29b suppressing elastin gene and augmenting apoptosis and MMP2.36 Finally, the article “Transient exposure of neonatal female mice to testosterone abrogates the sexual dimorphism of abdominal aortic aneurysms” by Zhang et al37 offers an especially compelling reminder of the powerful influence sex hormones have on cardiovascular disease risk.38

Angiogenesis/Arteriogenesis — From EPCs to miRNA

Although treatments to stop and reverse pathogenic growth processes are certainly crucial, methods that can promote new vascular growth, ie, angiogenesis and arteriogenesis, without tumorigenesis, are equally useful in tissue/organ recovery following ischemia-reperfusion–related injury. Many excellent works have addressed this topic, and it is no surprise that several of these have highlighted mechanisms that influence stem/progenitor cell biology and function. For example, “β2-Adrenergic receptor stimulation improves endothelial progenitor cell-mediated ischemic neangiogenesis”39 shows EPCs have intact β-adrenergic receptors that not only promote EPC migration, proliferation, and tube formation but also augment blood flow restoration in murine models of hindlimb ischemia. The intact endothelium itself is no passive partner in new blood vessel growth40 as shown by Sweet et al41 in “Endothelial Shc regulates arteriogenesis through dual control of arterial specification and inflammation via the notch and nuclear factor-k-light-chain-enhancer of activated B-cell pathways”; and likewise by Yin et al42 in “Induction of vascular progenitor cells from endothelial cells stimulates coronary collateral growth”. Additionally, a series of reports implicate one or more miRNAs in regulating angiogenesis such as miR-10 in zebrafish43; antagonistic action of miRNA-223 44; as well as miR-10A* and miRNA-21 in EPCs,45 which identify potential targets of shRNA, antagonirs, etc. Finally, in additional integrative works that emphasize cellular interdependence and crosstalk in angiogenesis, two articles by Renault et al,46,47 “Gli3 regulation of myogenesis is necessary for ischemia-induced angiogenesis” and “Desert hedgehog promotes ischemia-induced angiogenesis by ensuring peripheral nerve survival” reveal that within the complex milieu of injury and regeneration, proangiogenic factors derive inputs including cardiomyocytes and peripheral neuron Schwann cells, to promote proper and efficient revascularization.

Summary — A Few Good Years

There are nearly 60,000 miles of blood vessels in the human body and their function, or dysfunction, can have long-lasting implications for the quality and quantity of life. In the wake of the diabetes and obesity epidemics, it becomes especially important that we better understand vascular dysfunction because these diseases have a particularly profound effect on cardiovascular health. In fact, vascular insulin resistance
is one of the earliest events to occur in metabolic syndrome and precedes both endothelial dysfunction and atherosclerosis as well as other vascular defects.48 Several recent studies stand out in this regard and have identified promising vascular targets for intervention in diabetes and obesity. For example, Estrada et al show in “STIM1 restores coronary endothelial function in type 1 diabetic mice” that hyperglycemia-induced endothelial injury can be reversed by overexpressing the ER protein STIM1 to regulate ER calcium flux.49 On a more holistic level, Spinetti et al in “Global remodeling of the vascular stem cell niche in bone marrow of diabetic patients: implication of the microRNA-155/FOXO3a signaling pathway” implicates bone marrow-derived stem/progenitor cells as targets of diabetes (an effect reversed by miR-155) that may ultimately limit vascular repair and regeneration. Bringing us full circle is Sansbury et al who show that overexpression of eNOS (and subsequent NO effects) offsets diet-induced obesity in mice ultimately indicating that the “antique EDRF” still has a place in the 21st century.

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**References**


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