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Perspectives

Extracellular Matrix in Cardiovascular Pathophysiology

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Abstract

The extracellular matrix (ECM) actively participates in diverse aspects of cardiovascular development and physiology, as well as during disease development and progression. ECM roles are determined by its physical and mechanical properties and by its capacity to both release bioactive signals and activate cell signaling pathways. The ECM serves as a storage depot for a wide variety of molecules released in response to injury or with aging. Indeed, there is a plethora of examples describing how cells react to or modify ECM stiffness, how cells initiate intracellular signaling pathways, and how cells respond to ECM. This Perspectives article reviews the contributions of twenty-one articles published in The American Journal of Physiology-Heart and Circulatory Physiology in response to a call for papers on this topic. Here we summarize the contributions of these studies focused on cardiac and vascular ECM. We highlight the translational importance of these studies and conclude that the ECM is a critical component of both the heart and vasculature. Readers are urged to examine and learn from this special call for papers.

Keywords: extracellular matrix; myocardial; cardiac; vascular; cardiovascular; matrix metalloproteinases; collagen

The cardiovascular extracellular matrix (ECM) is defined as the hundreds of proteins that comprise the complex scaffold that surrounds cells of the heart and vasculature. In response to a recent call for papers in this journal, twenty-one reviews and original research articles provide additional evidence for the extensive roles that the ECM plays in cardiovascular physiology and pathophysiology. Some articles address ECM in cardiac and vascular cell development and differentiation. Others are focused on the mechanisms by which ECM contributes to heart and blood vessel physiological and pathological responses to aging, stress, or injury. Most address ECM contributions in a diverse array of pathologies, implicating the ECM as a logical translational target.

Cocciolone et al. reviewed elastin formation and maturation, as well as the role that elastin plays in the mechanical properties of the cardiovascular system with emphasis on conduit arteries.(5) There is a nice summary of the roles that deficiencies in elastin fibers have on specific human vascular diseases and how animal models of elastin insufficiency provide avenues to evaluate human disease. Klein et al. report that culturing mouse resistance arteries without tone caused cannulated and pressurized vessels to undergo outward ECM remodeling.(10) Culturing in the presence of vasoconstrictors prevented arterial outward remodeling, indicating the ECM can be structurally modified by tone. In line with this, Knutsen et al. showed that mice with elastin haploinsufficiency have stiffer arteries and reduced cerebral blood flow.(11) When the haploinsufficient animals were treated with the vasodilator Minoxidil, cerebral blood flow was restored and carotid vascular diameter increased to wild type amounts. The changes in vascular mechanics and function persisted for weeks after the treatment ended and were accompanied by differential expression of 127 ECM genes.

The Parker lab performed an unbiased proteomics screen on the ascending aortas from wild type mice and mice with abnormal fibrillin 1 expression that serve as a model for Marfan Syndrome.(20) Transforming growth factor beta (TGFβ) was increased in both young and aged Marfan syndrome mice, while rapamycin independent component of target of rapamycin

(RICTOR) was increased only in the aged Marfan syndrome mice. TGFβ signaling occurred in cultured vascular smooth muscle cells through a RICTOR dependent pathway, affected by β3 integrin and integrin-linked kinase, similar to that found in vivo in Marfan syndrome blood vessels. These results provide new targets for the potential treatment of aneurysms.

Collagen is a major component of the vascular wall and myocardium. Steffensen and Rasmussen summarized current knowledge on single nucleotide polymorphisms in the 13q34 locus that harbors the genes *COL4A1* and *COL4A2,* controlling collagen IV expression in the vascular wall, and report how alterations in these genes are linked to the risk of coronary artery disease, vascular stiffening and atherosclerosis.(24) l. Holzapfel and Ogden describe the microstructural characteristics of collagen, focusing on its relationship with smooth muscle cells as primary components influencing vascular strain and stress.(9) Additional considerations are given to the changes in microstructure of these passive and active components that take place in diseases such as atherosclerosis and aneurysm formation, and the authors provide evidence for the need of computational modeling to better understand ECM roles in vascular diseases.

Caggiano and colleagues tested the effect of changing the local mechanical environment on scar collagen turnover, accumulation, and alignment in Sprague-Dawley rats at 1, 2, 3 and 6 weeks after myocardial infarction (MI) by sewing a Dacron patch to the epicardium to eliminate circumferential strain while permitting continued longitudinal stretching with each heartbeat.(4) They found that collagen in healing infarcts aligned parallel to regional strain and perpendicular to the pre-MI muscle and collagen fiber direction, indicating mechanical environment is a primary determinant of scar alignment.

There were several articles focused on anti-fibrotic and anti-matrix metalloproteinase (MMP) strategies for prevention of adverse remodeling following injury. Using a hydrogel that released tissue inhibitor of metalloproteinase (TIMP)-3 after MI, the Spinale laboratory found that localized delivery of TIMP-3 interrupted adverse post-MI remodeling, underlining the

translational importance of this strategy.(21) Li et al. treated diabetic rats with the natural alkaloid berberine, which down-regulated insulin growth factor 1 receptor expression in cardiac fibroblasts, and subsequently reduced MMP-2 and -9, alpha smooth muscle actin, and collagen I expression in the diabetic hearts.(12) The Bradshaw laboratory examined the role of macrophage-derived secreted protein acidic and rich in cysteine (SPARC) on pressure-overload.(17) They found that macrophages were important for time-dependent increases in SPARC, which enhances postsynthetic collagen processing, insoluble collagen content, and myocardial stiffness.

ECM is an important component of blood vessel remodeling during pregnancy. Ren and colleagues investigated the balance between signaling from soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) on the expression and activity of matrix metalloproteinases and collagens I and IV.(23) The addition of sFlt-1 to pregnant rats simulated preeclampsia, and infusion of PlGF reversed the effects.

The extent of ECM cross-linking determines the stiffness of blood vessels and cardiac tissue. Craighead et al. demonstrated that the ECM cross-linking enzyme lysyl oxidase-like 2 was greater in skin biopsies from middle aged human subjects with essential hypertension compared to young or normotensive controls, while soluble lysyl oxidase (LOX) expression was diminished with hypertension.(7) Brief in vivo pharmacological inhibition of LOX in the cutaneous microvasculature affected the vasomotor responses to vasoconstrictor and endothelium-independent vasodilator agonists only in the normotensives, suggesting that LOX activity plays an important role in the acute control of vascular tone under normal physiological conditions. In response to volume overload in the heart, inhibiting LOX prevented the left ventricular wall stress increase, partially attenuated cardiac hypertrophy, completely blocked increases in fibrotic proteins, including collagens, MMPs, and TIMPs, and prevented the decline in cardiac function.(8)

Changes to ECM structure translate the changes in physiology. Corporan et al. found that in a rat model of severe mitral regurgitation, imbalance in the MMP to TIMP ratio in the myocardium occurred early and contributed to the increase in dilation.(6) Su and colleagues provided evidence of ECM changes in the proximal portion of the pulmonary artery in response to chronic hypoxia, with downstream effects on the mechanical properties of blood vessels in vivo and ex vivo.(25) A decrease in the elastin to collagen ratio was the most prominent structural change and was accompanied by increased measures of pulmonary artery stiffness including pulse wave velocity and moduli of elasticity, changes not observed in the aorta. A better understanding of altered dynamic afterload parameters in pulmonary arterial hypertension should provide new targets for therapy.

Cardiac fibroblasts are the predominant source of ECM, and the Cieslik laboratory review our current understanding of how this cell type transitions over the course of aging.(26) Defective TGFβ signaling enhances activation of the ERK1/2 pathway to activate fibroblasts and stimulate interstitial fibrosis. The Czubryt laboratory investigated how scleraxis transactivates twist1 and snai1 to stimulate epithelial-to-mesenchymal transition during development.(1) Scleraxis was a critical controller of fibroblast genesis and fate in the myocardium, implicating this transcription factor in wound healing and fibrosis following injury. Qin et al. chronically supplemented exogenous humanin in middle-aged mice and found that this can prevent and reverse age-dependent cardiac fibrosis.(22) Aging mice with macrophage overexpression of MMP-9 have increased macrophages at 7 days after MI, which improves diastolic physiology and cardiac remodeling by altering cardiac wound healing.(18)

Ariyasinghe et al. reviewed how microphysiological systems are being engineered to establish direct relationships between distinct features in the ECM and myocardial function with unprecedented in vitro control and resolution.(2) This technology will continue to unravel important ECM features that control myocardial cell and tissue physiology. Likewise, the Ping laboratory used phrase mining to determine the association between ECM and six

cardiovascular pathologies, namely, ischemic heart disease, cardiomyopathy, cerebrovascular accident, congenital heart disease, arrhythmias, and valve disease.(13) This bioinformatics approach utilizing 1M research publication abstracts indicated that 82 ECM proteins associate with all six pathologies. A recent review on myocardial infarction remodeling has also highlighted the importance of ECM, and text mining strategies will uncover previously unidentified or underappreciated targets.(19)

In conclusion, this compendium of ECM articles displays the complexity of this research field and highlights the translational relevance of understanding ECM roles in both normal conditions and during pathophysiological processes (Figure 1). In conjunction with recent guidelines published by AJP Heart on myocardial ischemia and infarction models, measuring cardiac physiology, antibody use, and statistical reporting, this ECM collection will aid investigators new to the field in developing experiments that have strong rigor and reproducibility potential.(3, 14-16) We hope that you enjoy reading these articles as much as we did editing this Call.

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Disclosures. None

Figure Legend

Figure 1. The articles covered in the Extracellular Matrix Call span both physiological and pathophysiological processes and a number of cell types, involve mechanistic studies using deficient and overexpression approaches, and evaluate translational strategies to define ECM roles in the cardiovascular system.

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