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Understanding the role of the extracellular matrix in cardiovascular development and disease: Where do we go from here?

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For many years, analyses of the heart have focused primarily on the role of the myocytes as the principal cell type that generates force. Analyses of the extracellular matrix (ECM) were deemed important, but primarily relevant only in hypertrophy and after myocardial infarction. Related to the ECM was the role of the fibroblast, the principal cell type that makes the ECM. When analyses of the ECM were performed, the focus was primarily on interstitial collagen. This reductionist approach was also incorporated into the experimental design of in vitro studies that used planar two-dimensional culture systems.

Even though studies to show that the ECM was a three-dimensional network were first presented in the early 1900's,[1] it was not until dramatic scanning electron micrographs in the 1980's showed the three-dimensional structure that we began to appreciate how ECM structure can directly regulate cardiac function. In these studies, however, only myocytes were observed in relation to the collagen network.[2] Most papers cited the studies of Zak and colleagues showing that the number of myocyte was 30% and the non-myocyte population was 70% based on anti-myosin staining and electron microscopy.[3,4] These basic numbers of myocytes and other cell types remained dogma until recently, when Banerjee and colleagues showed that the number of fibroblasts varied dramatically by species, stage of development, and physiological condition.[5] In addition, we now know that fibroblasts form a three-dimensional network within the collagen network to form intimate cell-cell contacts with myocytes, other fibroblasts, and endothelial cells.

At the present time, we know that the heart is a dynamic organ, and physiological function is the result of multiple cellular and acellular components. It is the dynamic interaction of chemical, mechanical and electrical factors generated by the cellular components, together with ECM components, that determine the physiological performance of the heart at various stages of development and in response to pathophysiological signals. Analysis of one

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component in isolation provides only a partial picture of function. Similar trends have evolved with *in vitro* studies, where planar two-dimensional techniques provide a distorted view of various cardiac cell type functions and cells plated on a collagen-only matrix do not allow the function and interactions of other ECM components to be evaluated. Three-dimensional culture techniques using ECM that more completely recapitulates *in vivo* phenotypes will allow us to interrogate the complexity of individual cells, heterotypic cell interactions, and the dynamics of cellular interactions with the ECM.

In this special issue, we have assembled a series of reviews that summarizes past investigations but, more importantly, raises new questions as to the role of the ECM in cardiac function. We have chosen topics and investigators who address these concepts. The major themes of this issue are: 1) ECM in specific diseases and with specific cell interactions; 2) particular ECM components; 3) engineering issues related to ECM; 4) diagnostic potential of altered ECM; and 5) how ECM in other tissues compare and contrast with cardiac ECM. We asked each author to limit his/her review to 5000 words and 50 references, to allow the maximum number of articles and provide the largest topic coverage.

The reviews in this issue focus on the ECM in normal development as well as in response to specific diseases, including hypertension, myocardial infarction, and atrial fibrillation. The following review articles demonstrate the complexity of the interactions between both cellular and acellular components, with emphasis given to the role of the environment on cell function. In addition, future directions are discussed in depth to provide information on the key experiments that need to be performed for us to gain a more complete understanding of ECM roles.

Critical to ECM remodeling is the dynamic interactions between the ECM and the matrix metalloproteinases (MMPs) that break down ECM components; the relationship between MMPs and the endogenous tissue inhibitors of metalloproteinases (TIMPs); and the connection between cytokines and both ECM components and MMPs. The range of topics covered include the dynamics of ECM changes in volume overload (Lucchesi)[6], and ECM regulation by the renin-angiotensin-aldosterone system (Sun)[7] and the inflammation system during myocardial infarction (Frangogiannis)[8], viral myocarditis (Westermann) [9], pulmonary disease (Lagente)[10], and cardiac development (Baudino)[11]. Atrial fibrillation is highly associated with fibrosis, and the role of ECM during atrial remodeling is reviewed here (Sheikh) [12]. The challenges of using ultrasound to monitor the progression of remodeling (Scherrer-Crosbie)[13] and applying diagnostic approaches to evaluate fibrosis in the setting of diabetes (Villarreal)[14] are also covered.

Targeting particular individual ECM components yields specific responses to stress and injury, and we have included discussions on the functions of non-fibrillar collagens (Meszaros)[15], osteopontin (Singh)[16], secreted protein acidic and rich in cysteine (Bradshaw)[17], the matrix metalloproteinases (Lindsey)[18] and the tissue inhibitors of metalloproteinases (Vanhoutte) [19] in this issue.

How the response to injury in other organs may predict cardiac function is covered by unique evaluations of how changes in the skin (Gourdie)[20] and kidney (Kalluri)[21] can inform us about cardiac changes. The idea that the reaction of skin to injury could be used to predict outcome following myocardial infarction or hypertension both alone or in the setting of diabetes is one example of how comparative studies of extracellular matrix among the organs is warranted.

A unique aspect of the ECM in the heart is the presence of continuous cyclic and static mechanical tension. While ECM is altered by changes in mechanical properties and ECM is often evaluated as an end point measurement, ECM changes also initiate many downstream

signaling cascades by altering mechanical conditions in a positive feedback manner (Holmes) [22] and by generating ECM peptides to serve as signaling molecules (Davis)[23]. Many of the articles presented focus on cardiac effects of ECM, but the ECM is also crucial to the normal growth and response to pathological and repair signals in the vasculature (Lehoux)[24]. Central to this theme is the role of edema and fluid dynamics, which is also discussed here (Reed) [25].

In summary, these reviews comprehensively evaluate the current state of understanding of ECM roles in cardiovascular development and disease. More importantly, the set of articles presented in this special issue underscores the challenges that remain before we can more completely understand the dynamics of cardiovascular cellular and extracellular interactions. Areas and common themes that remain fruitful for future research are highlighted in Table 1. Together, this special issue highlights the current themes of cardiovascular ECM and points us in the directions where future research can be focused.

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References

- [1]. Piez KA. History of extracellular matrix: a personal view. *Matrix Biol* Aug;1997 16(3):85–92. [PubMed: 9314158]
- [2]. Borg TK, Johnson LD, Lill PH. Specific attachment of collagen to cardiac myocytes: in vivo and in vitro. *Dev Biol* Jun;1983 97(2):417–23. [PubMed: 6852372]
- [3]. Zak R. Development and proliferative capacity of cardiac muscle cells. *Circulation research* Aug; 1974 35(2)(suppl II):17–26. [PubMed: 4276486]
- [4]. Nag AC. Study of non-muscle cells of the adult mammalian heart: a fine structural analysis and distribution. *Cytobios* 1980;28(109):41–61. [PubMed: 7428441]
- [5]. Banerjee I, Fuseler JW, Price RL, Borg TK, Baudino TA. Determination of cell types and numbers during cardiac development in the neonatal and adult rat and mouse. *Am J Physiol Heart Circ Physiol* Sep;2007 293(3):H1883–91. [PubMed: 17604329]
- [6]. Hutchinson KR, Stewart JA Jr, Lucchesi PA. Extracellular matrix remodeling during the progression of volume overload-induced heart failure. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [7]. Sun Y. Intracardiac renin-angiotensin system and myocardial repair/remodeling following infarction. *Journal of molecular and cellular cardiology*. In Press, Uncorrected Proof.
- [8]. Dobaczewski M, Gonzalez-Quesada C, Frangogiannis NG. The extracellular matrix as a modulator of the inflammatory and reparative response following myocardial infarction. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [9]. Westermann D, Savvatis K, Schultheiss H-P, Tschöpe C. Immunomodulation and MMPs in viral Myocarditis. *Journal of molecular and cellular cardiology*. In Press, Accepted Manuscript.
- [10]. Lagente V, Boichot E. Anti-inflammatory properties of MMP-inhibitors. *Journal of molecular and cellular cardiology*. In Press.
- [11]. Bowers SLK, Banerjee I, Baudino TA. The Extracellular Matrix: At the Center of it All. *Journal of molecular and cellular cardiology*. In Press, Accepted Manuscript.
- [12]. Pellman J, Lyon RC, Sheikh F. ECM Remodeling in Atrial Fibrosis: Mechanisms and Implications in Atrial Fibrillation. *Journal of molecular and cellular cardiology*. In Press.
- [13]. Scherrer-Crosbie M, Kurtz B. Ventricular remodeling and function: Insights using murine echocardiography. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [14]. Maya L, Villarreal FJ. Diagnostic approaches for diabetic cardiomyopathy and myocardial fibrosis. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.

- [15]. Shamhart PE, Meszaros JG. Non-fibrillar collagens: Key mediators of post-infarction cardiac remodeling? *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [16]. Singh M, Foster CR, Dalal S, Singh K. Osteopontin: Role in extracellular matrix deposition and myocardial remodeling post-MI. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [17]. McCurdy S, Baicu CF, Heymans S, Bradshaw AD. Cardiac extracellular matrix remodeling: Fibrillar collagens and Secreted Protein Acidic and Rich in Cysteine (SPARC). *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [18]. Zamilpa R, Lindsey ML. Extracellular matrix turnover and signaling during cardiac remodeling following MI: Causes and consequences. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [19]. Vanhoutte D, Heymans S. TIMPs and Cardiac Remodeling: Embracing the MMP-independent-side of the family. *Journal of molecular and cellular cardiology*. In Press.
- [20]. Palatinus JA, Rhett JM, Gourdie RG. Translational lessons from scarless healing of cutaneous wounds and regenerative repair of the myocardium. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [21]. Hertig A, Gangadhar T, Kalluri R. Renal studies provide an insight into cardiac extracellular matrix remodeling during health and disease. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [22]. Fomovsky GM, Thomopoulos S, Holmes JW. Contribution of extracellular matrix to the mechanical properties of the heart. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.
- [23]. Davis GE. Matricryptic Sites Control Tissue Injury Responses in the Cardiovascular System: Relationships to Pattern Recognition Receptor Regulated Events. *Journal of molecular and cellular cardiology*. In Press.
- [24]. Lemarie CA, Tharaux P-L, Lehoux S. Extracellular matrix alterations in hypertensive vascular remodeling. *Journal of molecular and cellular cardiology*. In Press.
- [25]. Reed RK, Lidén Å, Rubin K. Edema and fluid dynamics in connective tissue remodelling. *Journal of molecular and cellular cardiology*. In Press, Corrected Proof.

Table 1**Key Future Directions for Cardiovascular Extracellular Matrix Research**

1	Systems biology approaches for multi-scale kinetic analyses of growth and response to pathophysiological signals are needed. The multi-scales involve mechanical stimuli at the whole organ level down to the individual cell components, including the overlap and integration of different signaling pathways. Computational analyses will facilitate a systems biology approach by identifying candidate key components, which will reduce system complexity to a manageable level.
2	The downstream effects of ECM turnover in homeostasis and disease need to be evaluated. Using ECM as an input factor and not merely a read out, we need to evaluate matricryptin production and MMP and TIMP signaling functions (as well as other protease systems such as the ADAMs and ADAMTS families) as the beginning stage and determine outcomes when these factors are modulated. This includes using proteomic approaches to identify the full complement of ECM matricryptins produced under a particular disease setting and using <i>in vitro</i> and <i>in vivo</i> functional assays to determine the role of ECM fragments on cardiovascular cell function.
3	The dynamics of the vascular system need to be more completely understood, including the roles of signaling from other organs and the effect of new angiogenesis on coordinated edema responses.
4	The dynamics of ECM assembly and interaction to promote and alter cardiac function need to be considered. Often, research experiments are designed to evaluate one time point, which precludes the examination of the kinetics of ECM and functional changes over the course of disease progression. This concept is particularly relevant in the myocardial infarction, hypertension, and congestive heart failure settings. In addition, collagen is the most abundant and most studied ECM protein family in the cardiovascular system, but other ECM proteins (particularly fibronectin and matricellular proteins) are major regulators that should be considered in more detail.
5	Comparative studies of ECM among the different tissue types, to see how systemic plasma factors could affect common or diverse pathways, are warranted. While studies measuring gene levels will be informative, protein level changes also need to be evaluated given the wide range of post-translational modifications that occur.
6	ECM changes over disease progression, in the presence of other comorbidities such as diabetes and aging, are needed. One size will not fit all, and understanding patient diversity will provide mechanistic insight and will help individualize treatment options.