Microsc. Microanal. 18, 1–2, 2012
doi:10.1017/S1431927611012761

Microscopy AND Microanalysis

Introduction: Extracellular Matrix and Cardiovascular Remodeling—Using Microscopy to Delineate Mechanisms

In January 2011, a Keystone Symposium on "Extracellular Matrix and Cardiovascular Remodeling" was held in Tahoe City, California. The purpose of this meeting was to focus on the general theme of extracellular matrix (ECM) roles in cardiovascular remodeling. The presentations and discussions stimulated by this meeting, which was attended by approximately 160 people, serve as the inspiration for this special section of *Microscopy and Microanalysis*.

This section highlights contributions from that meeting, which focus on controversies and knowledge gaps that still prevent or limit therapeutic translation. The overarching goal of this section is to offer direction and stimulate progress in cardiovascular ECM research. We have selected both contributions that review the literature on specific ECM topics, in addition to individual research contributions. The selection of these contributions demonstrates the diversity and dynamics of both the ECM in general and the remodeling response in specific.

In response to normal growth, as well as a variety of pathophysiological signals, the cardiovascular system undergoes a series of structural and functional adaptations, collectively known as remodeling, that are directed responses to both to the initial stimulus and to the feed-forward changes that result from the precipitating event. Remodeling is driven by the dynamic interaction of ECM combined with changes in the cells of the cardiac and vascular systems, in both qualitative and quantitative terms.

Dr. Goldsmith and colleagues review the role of diabetes in altering ECM structure and function (Law et al., 2012). Their review article is highly relevant to the current clinical setting, where co-morbidities such as diabetes, inflammatory diseases, and aging are frequently encountered. Drs. Daskalopoulos, Janssen, and Blankesteijn summarize what is known about myofibroblasts in the infarct region (Daskalopoulos et al., 2012). Importantly, they also discuss concepts that go against popular opinion, such as the idea that a maintained myofibroblast presence may be required in the healed infarct to maintain an adequate scar and prevent infarct dilation. At the same time, activation of myofibroblasts in the remote region is likely to be detrimental and stimulate adverse remodeling that can progress to congestive heart failure.

Several groups examine how external factors can alter ECM. Ma and colleagues examined the role of MMP-28 in regulating age-related ECM responses (Ma et al., 2012). With age, inflammation increases in the left ventricle, and this increase is exacerbated with MMP-28 deletion. The Gardner laboratory explored the role of smoke exposure on cardiac remodeling during volume overload (Bradley et al., 2012). They found that exposure to cigarette smoke promotes eccentric dilation and cardiac dysfunction in response to a volume overload stimulus and that the mechanism involves disruption of compensatory signaling pathways. These two articles highlight the fact that the context in which the ECM is examined needs to be taken into consideration when interpreting study results.

Another concept that was explored during our meeting is the fact that ECM structure is dependent on interactions with the cellular constituents within a tissue. The Davis laboratory explored how endothelial cell and pericyte interactions with the ECM regulate blood vessel formation (Stratman & Davis, 2012). They show that in disease states, such as diabetes, heterotypic endothelial cell and pericyte interactions are key regulators in vascular basement membrane deposition, which is critical for vessel tube maturation. The Gourdie and Potts laboratories explored how self-organizing tissue constructs can be engineered (Gourdie et al., 2012). Their article describes a novel self-organizing behavior of cellularized collagen I gels that may be useful in wound healing and regenerative medicine. The Baudino laboratory revealed how desmoplakin

Table 1. A Selection of Outstanding Microscopy Based Cardiovascular Extracellular Matrix Research Topics.

1. How do proteases regulate ECM responses to normal physiological processes, such as aging, and pathological processes, such as myocardial infarction, hypertrophy, and failure?
2. How do the components of the ECM contribute to cardiovascular development and responses to injury?
3. How do structural connections between the various ECM constituents and between ECM and cells change during cardiovascular pathologies?
4. What are the advantages and disadvantages of various analytical approaches to quantify changes in the ECM?
5. How do the structural alterations translate to functional changes?

cell-cell interactions mediate cardiac cell functions, including cytokine secretion (Bowers et al., 2012).

How an altered ECM structure influences the mechanical function of the heart in the setting of heart failure was studied by the Leonard laboratory (Leonard et al., 2012). They make the case that there is a need for new theoretical and experimental models to better understand how stresses acting on the ECM and resultant deformations link with altered cardiac mechanical function. Felder and colleagues established a neural network to analyze cytoskeletal images, demonstrated that their approach was 300 times faster than manual classification, and showed that the classification of image regions was both objective and accurate (Felder Derkacs et al., 2012). This approach may help the cardiac ECM field develop high throughput imaging capabilities.

Another concept that was discussed at the meeting is that ECM is not only composed of collagen type I but is a complex interwoven mixture of several ECM components. The McCarthy lab discusses using the glomerular basement membrane as a model system to study the bioactivity of heparin sulfate glycosaminoglycans (McCarthy & Wassenhove-McCarthy, 2012). They conclude from their results and recent literature that the role of heparin sulfate glycosaminoglycans in the glomerular capillary wall remain to be fully resolved, which underscores the need for studies on noncollagen ECM proteins. As more groups are exploring the ECM using systems biology approaches, model systems like this one will have growing importance.

In summary, we present here an overview of the cardiovascular ECM field. The set of articles included in this special section represent the field and highlight the challenges that remain. In addition to reading these articles for their information, our hope is that these articles point out directions that remain to be explored in future research, including topics listed in Table 1.

Acknowledgments

We acknowledge support from NIH NHLBI HHSN 268201000036C (N01-HV-00244) for the UTHSCSA Cardiovascular Proteomics Center and R01 HL075360, the Max and Minnie Tomerlin Voelcker Fund, and the Veteran's Administration (Merit) to M.L.L. and from NIH NHLBI R01 HL085847 to T.K.B.

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