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High Resolution Chromatin Mapping in Heart Failure: Some Answers, But More Questions

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The long-standing quest to define the basic mechanisms that are responsible for the development and progression of heart failure has yielded important insights into the myriad of cellular, molecular, and anatomic changes that occur in the failing heart, as well as how these changes are modulated by the use evidence based medical and device therapies that lead to improvements in clinical outcomes. The preponderance of data suggest that clinical heart failure develops in response to a series of complex interactions involving changes in the biology of the cardiac myocyte, changes in the number of cardiac myocytes and/or changes in the composition of the extracellular matrix, which lead collectively to changes in left ventricular (LV) structure and function (reviewed in reference 1). Among the more important changes in the biology of the failing cardiac myocyte are those related to the expression levels for genes that regulate sarcomere function, excitation-contraction coupling, the cytoskeleton and cardiac energetics.[1] Whereas prior studies have identified an important role for activation of specific DNA-binding transcription factors with respect to the dysregulated gene expression profile in heart failure, more recent studies have suggested that histone modifications and changes in chromatin structure may play an equally important role in regulating the transcriptional dynamics of the failing heart.[2, 3] Accordingly, the study by Rosa-Garrido et al in this issue of *Circulation* that examines high resolution mapping of chromatin conformation is of considerable interest.[4]

Rosa-Garrido and colleagues examined changes in chromatin configuration in cardiac myocytes isolated from mouse hearts subjected to transverse aortic constriction (TAC), or hearts subjected to tamoxifen inducible cardiac-specific excision of CTCF, which is a ubiquitous chromatin structural protein. The authors performed genome-wide chromatin conformation capture and DNA sequencing, as well as deep RNA-sequencing, which was used as a functional readout for relevant epigenetic changes. Remarkably, the authors found that cardiac specific deletion of CTCF was sufficient to induce a dilated cardiac phenotype with a reduced LV ejection fraction, increased myocyte hypertrophy and increased myocardial fibrosis. In contrast, mice subjected to TAC developed concentric LV hypertrophy, increased cardiac myocyte hypertrophy and myocardial fibrosis. There was no change in CTCF mRNA or protein expression in the TAC mouse hearts; however, there was increased CTCF mRNA and protein expression in human failing hearts that had been

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supported with a left ventricular assist device. High resolution chromatin mapping showed that the TAC and the cardiac-specific CTCF deletion mice had similar, although not identical changes in the chromatin architecture, including changes in the boundary strength of topologically associating domains (TADs), which are regions of DNA (chromosome neighborhoods) in which physical interactions occur frequently, in contrast to interactions that occur across a TAD boundary, wherein interactions occur relatively infrequently. The investigators also showed that there were changes in the compartmentalization of active chromatin and inactive chromatin segments, which is a measure of genomic accessibility. They then demonstrated that the looping structure of chromatin was altered in TAC and the cardiac-specific CTCF deletion models, and that genes associated with cardiac function were enriched within the reorganized chromatin loops, whereas enrichment of aberrant genes coincided with the loss of chromatin loops. Rosa-Garrido et al also demonstrated that changes in expression levels of several target genes associated with the development of heart failure (e.g. *Nppa* [ANF]) were accompanied by changes in the local chromatin microenvironment.

This well-done study by Rosa-Garrido in the current issue of *Circulation* represents a technical tour de force that annotates important hierarchical changes in chromatin remodeling in the heart following pressure overload, including the interrelationship of TADs, the compartmentalization of segments of active and inactive chromatin, changes in the intermediate structural features of chromatin (i.e. chromatin loops) and how these changes are involved with canonical target genes associated with the development of heart failure. What this study does not tell us is how these changes are related, if at all, to the development and progression of the heart failure phenotype. That is, although the authors provided a detailed road map of the changes in the chromatin microenvironment in the CTCF genetic model and the TAC pressure overload model, these studies did not delineate whether these changes were causally related to changes in cardiac structure and function. In this regard, it is notable that Rosa-Garrido et al demonstrated similar hierarchical changes in chromatin remodeling in the CTGF deletion mice, which developed a dilated LV phenotype similar to that observed in patients with a reduced ejection fraction (HFrEF), and that pressure overloaded TAC mice developed a concentric LV hypertrophy phenotype similar to that observed in patients with heart failure with a preserved ejection (HFpEF). Although the clinical phenotype of heart failure is similar in patients HFrEF and HFpEF, and we refer to patients with both conditions as having hypertrophy and as having heart failure, the hard lesson learned from the last 10 years of clinical HFpEF trials is that the biology of dilated and concentric hypertrophy is vastly different, and that these two forms of heart failure cannot be conflated and cannot be viewed scientifically as the same pathophysiological process. Insofar as similar changes in chromatin remodeling were observed in the experimental models of dilated and concentric hypertrophy, the important and unanswered question raised by the study of Rosa-Garrido and colleagues is whether the observed changes in chromatin remodeling represent a generalized genomic stress response that allows cells to configure DNA in a more dynamic conformation in an effort to preserve cellular homeostasis, or whether instead these changes are disease causing. Further studies will be necessary to address this intriguing question. An important limitation of this study is the use of the TAC model. Although the TAC model is time-honored, and has become a

well-accepted model for studying heart failure, the clinical relevance of TAC models to HFrEF in humans is uncertain, given that the transition from concentric LV hypertrophy to eccentric (dilated) hypertrophy in humans is uncommon, and is usually associated with the development of an inter-current event (e.g., myocardial infarction) when it does happen.[5, 6, 7] In this regard it is unfortunate that the authors did not examine changes in chromatin configuration in the human heart failure samples that were used to measure CTCF mRNA and protein levels, which although descriptive, would have nonetheless provided important insights into whether the observed changes in the chromatin microenvironment observed in the TAC model were relevant pathophysiologically. These limitations notwithstanding, the carefully done and provocative study by Rosa-Garrido and colleagues adds significantly to our understanding of the unrecognized complexity and plasticity of chromatin remodeling in the heart and should provide a useful roadmap to guide and inform future studies in the field.

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