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Epigenetic Regulation of the Cardiovascular System: Introduction to a Review Series

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Our genes code for the building blocks of our body, and variations in our genome predispose us to distinct traits, including disease. To add complexity to the interpretation and regulation of our genetic code, the DNA packed into the chromatin forming our chromosomes is modified by factors that alter its expressivity but without changing its sequence. These factors are referred to as epigenetic factors. A recent definition states: “An epigenetic trait is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence.”¹.

Many factors are involved in establishing epigenetic traits, including DNA methylation, histone variants, chemical modification of histones, position of nucleosomes, and three-dimensional organization of genes in the nucleus, for example. These modifications often act in concert to alter the expression of genes, or to effect allele-specific inheritance. Epigenetic regulation can be established cell-autonomously, through intercellular signaling, and by environmental influences. All cells in the body are subject to epigenetic regulation, and thus understanding this important layer of regulation is key to elucidating mechanisms of cardiovascular development, physiology, and disease.

This review series in *Circulation Research* will explore recent advances in epigenetic research, with an outlook toward the cardiovascular system. The reviews will explore the current state of the art and will focus on the exciting future of epigenetic research as it relates to the cardiovascular system.

Epigenetic regulation is commonly considered to include the chemical modification of histone residues that accompany regulated gene expression. Many have noted that the definition of epigenetics quoted above implies heritability of a phenotype through either mitosis or meiosis. At first glance, this might seem to exclude the changes in histone modifications that are established during gene regulation, but are thought to be transient due to histone turnover. However, some of these changes are in fact actively maintained², and thus histone modifications can be included in a broader definition of epigenetics.

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To enact a concerted phenotypic program during differentiation, or remodeling in disease, several broad programs of gene expression must be co-regulated. Epigenetic regulation through histone modifications is an important aspect of this co-regulation³. The unstructured tails of histones—the proteins that assemble into the nucleosomes around which chromosomal DNA is wound—are subject to myriad chemical modifications, including acetylation, methylation, phosphorylation, ubiquitinylation, and sumoylation. In combination, these modifications are thought to result in a histone “code” that is read and translated into signals for activation or repression of associated genes^{3, 4}. For example, certain histone modifications are most often associated with repressed genes, and others with active genes.

The widespread coordinated deployment of particular histone modifications ensures a stable and efficiently enacted regulatory mechanism that can be targeted to specific sets of genes. In embryonic stem cells, to cite a notable example, most developmentally relevant transcription factor genes are silenced by the imposition of a repressive histone code^{5, 6}; this is thought to ensure that embryonic stem cells remain pluripotent. Another example is the epigenetic repression of the entire HoxD cluster and its gradual activation by the removal of repressive histone modifications⁷. The Hox locus is also the site of an exciting regulatory link between long non-coding RNAs (lincRNAs) and the establishment of histone modifications at specific loci⁸. The function of lincRNAs in recruiting chromatin modifying complexes^{8, 9} provides an attractive mechanistic link between cis- and trans-regulation within the genome at the level of histone modifications.

It will be of considerable interest to determine whether similar broad regulatory mechanisms are involved in cardiovascular biology. Some clues indicate that this might be the case. The histone methyltransferase WHSC1 interacts with an important cardiac transcription factor, Nkx2-5, to regulate the normal development of the heart¹⁰. Jarid2, also known as Jumonji, is an integral component of the Polycomb repressor complex, which deposits repressive histone marks^{11–13}. Jarid2 has long been known to function in heart development^{14, 15}, but its mechanism of action was unknown. Thus, epigenetic regulation is likely to be as important a mechanism for the cardiovascular system as it is in other systems, and it is likely to have important and widespread roles in normal physiology as well as in disease. A review in this series by Ching-Pin Chang and colleagues will explore in detail the role of epigenetic and chromatin-based regulation of cardiovascular development and physiology.

The techniques used to study the epigenome are complex. Thanks to the emergence of high-throughput technologies, it is now possible to efficiently and completely evaluate on a genomic scale the epigenetic modifications that accompany the status of a cell¹⁶. Currently, most technologies involve immunoprecipitation of chromatin associated with specific epitopes, such as histone modifications, histone variants, or DNA methylation, followed by the identification of the associated DNA sequences by hybridization to microarrays, or more commonly now by direct sequencing. New sequencing platforms, while not widely available, allow the scaling down of these techniques, so that smaller samples such as those one would obtain from a human cardiac biopsy can provide equivalent rich information. These new sequencing chemistries also allow, for example, direct measures of DNA methylation¹⁷, which will enable the mapping of this important epigenetic mark on an unprecedented scale. Other exciting developments involve the study of three-dimensional organization of genes in the nucleus, forming interchromosomal transcription “factories”. The three-dimensional organization of chromosomal segments is thought to be regulated by epigenetic mechanisms, and is emerging as an important means to coregulate widely separated genes¹⁸. Keji Zhao and colleagues will review current and future approaches for studying epigenetic modifications.

Epigenetic changes are also thought to be at the root of cellular reprogramming, the process by which a differentiated cell type can be induced to adopt an alternate cell fate. The most well-known and spectacular example of this is the generation of induced pluripotent cells (iPS cells) from fully differentiated somatic cells^{19, 20}. iPS cells are functionally similar, if not identical²¹, to embryonic stem cells, and the spectacular change in status from a “terminally” differentiated somatic cell to a fully pluripotent cell involves epigenetic reprogramming of the DNA methylation of pluripotency genes, amongst certainly many others. The recent elucidation of the mechanism of these changes in DNA methylation will open the door to a broader understanding of mechanisms of reprogramming as well as regulation by DNA methylation²².

Other forms of reprogramming have been described, including the induction of insulin-producing pancreatic beta cells from exocrine cells²³ and the generation of functional neurons from skin fibroblasts²⁴. In the cardiovascular system, the ability to generate new cardiomyocytes, endothelial cells, or smooth muscle cells from other cell types would be of considerable benefit for strategies aimed at regeneration of diseased cardiovascular tissues. Approaches to reprogramming somatic cells into cardiovascular cell types have not yet been described, but the promise offered by the success in reprogramming other cell types brings hope that this avenue will be broadly successful in the near future. In this series, Deepak Srivastava and Shinya Yamanaka will review this exciting field.

In summary, the field of epigenetics has provided important insights into broadly applicable aspects of differentiation, physiology, and disease in many contexts. Large-scale research efforts, in the form of large consortia and funding initiatives, are being deployed to further understand epigenetic regulation. As epigenetics research expands its horizons toward the cardiovascular system, our understanding of cardiovascular biology will be greatly enhanced. Importantly, since epigenetic regulators are mainly enzymes whose functions can be altered by natural and designed compounds, epigenetic regulation of the cardiovascular system may emerge as an exciting and important arena for drug development.

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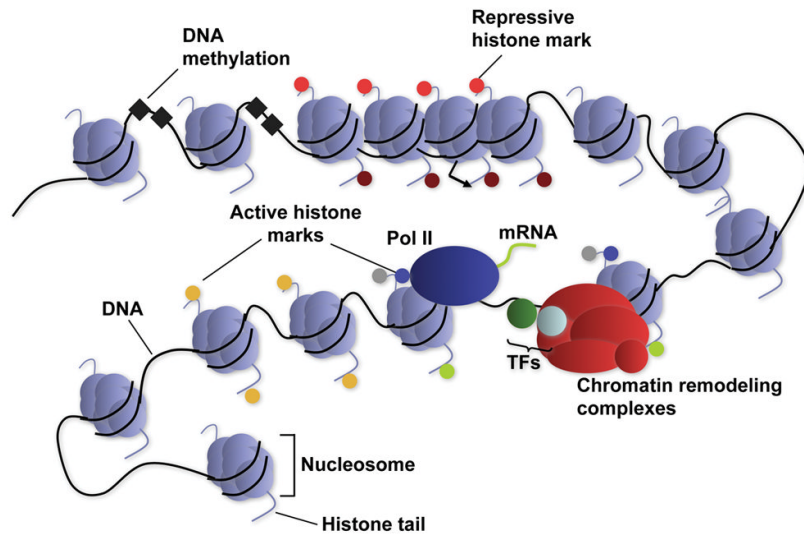


Figure.
Diagrammatic representation of chromatin, and chromatin-mediated gene regulation. TFs: transcription factors.