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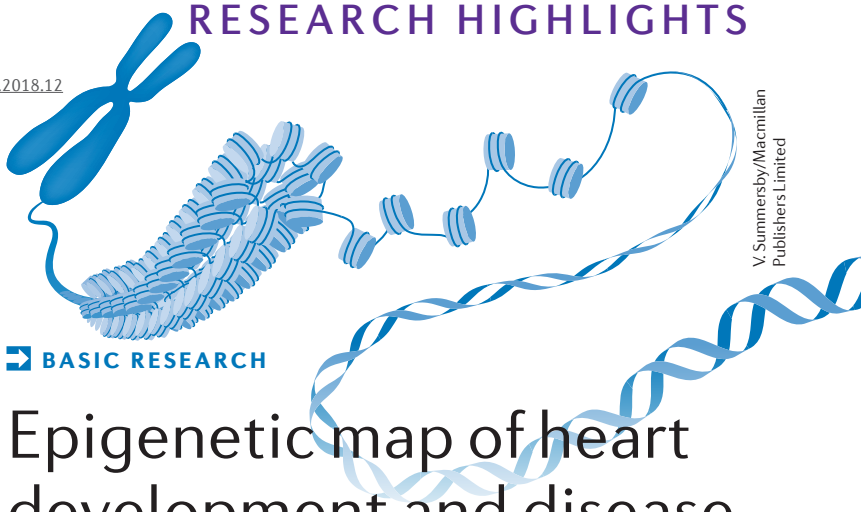

BASIC RESEARCH

Epigenetic map of heart development and disease

Past studies on heart development have provided a better understanding of the transcriptional and epigenetic events that regulate cardiomyocyte (CM) differentiation. However, the mechanisms that control normal gene expression during CM postnatal maturation and homeostasis, as well as the transcriptional and epigenetic changes that drive pathological gene expression in the failing human heart, are not well understood. A new study now reveals that two distinct epigenetic programmes orchestrate CM gene expression during heart development and disease.

Previous studies on the role of epigenetic modifications in heart development and disease used whole tissues owing to technical limitations. "As epigenetic marks are highly cell-type specific, whether epigenetic alterations in disease reflected changes in cell-type composition … or whether the alteration actually occurred in a specific cell type remained unknown," explains lead investigator Lutz Hein. To identify cell-type-specific regulation features, Hein and colleagues used nuclear staining and fluorescence-assisted sorting to isolate CM nuclei from prenatal and postnatal human heart tissues and from heart tissue during heart failure, and performed transcriptomic and epigenomic analyses. The investigators identified genomic regions with promoter-associated features that had different DNA methylation profiles from fetal to adult life. "These findings indicate that the DNA methylome remains dynamic even after CMs exit the cell cycle postnatally," says Hein. DNA methylation was associated with concordant changes in histone marks in these regions, illustrating the tight link between the two epigenetic mechanisms. These epigenetic changes were accompanied by alterations in the expression of neighbouring genes, including increased expression of maturation-associated genes and decreased expression of developmental genes. By contrast, the DNA methylation profile was unchanged in heart failure compared with healthy hearts. However, genes expressed differentially in CMs from failing and nonfailing hearts, such as *CTGF*, correlated with changes in histone marks, indicating that CM gene expression changes during heart failure involve remodelling of histone modifications and not alterations in DNA methylation.

Additionally, the research team identified >100,000 low methylated regions in the noncoding genome of human CMs, located in intronic and intergenic regions and harbouring distal regulatory properties. These regions also had different DNA methylation profiles from fetal to adult life, and were enriched in genetic polymorphisms associated with cardiac diseases such as arrhythmia and coronary heart disease. "This study provides a comprehensive atlas of *cis*-regulatory regions in human CMs … and will help to identify the importance of these genetic variants within the noncoding genome," says Hein, who concludes that a better understanding of the human CM epigenome will also have implications in regenerative medicine.

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ORIGINAL ARTICLE Gilsbach, R. *et al.* Distinct epigenetic programs regulate cardiac myocyte development and disease in the human heart *in vivo*. *Nat. Commun.* **9,** 391 (2018)
FURTHER READING Greco, C. M. *et al.* Epigenetic modifications and noncoding RNAs in cardiac hypertrophy and failure. *Nat. Rev. Cardiol.* **12**, 488–497 (2015)