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DNA hydroxymethylation controls cardiomyocyte gene expression in development and hypertrophy

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The epigenome -the sum of chemical modifications on both DNA and histone proteins associated with the genome- is a key regulatory mechanism through which gene expression changes take place in heart development and disease. DNA methylation (5-mC), a key repressive mark, has emerged in the last years as a determinant of myocardial gene expression regulation. In contrast, the role of 5- hydroxymethylcytosine (5-hmC) – 5-mC's oxidation product – and of the DNA hydroxylases enzymes is unknown in the context of the heart. We performed hydroxymethylated DNA immunoprecipitation coupled with high-throughput sequencing (hMeDIP-seq) in cardiomyocytes to elucidate the function of this modification in this cell type in normal state and under stress, in particular cardiac hypertrophy induced by pressure overload. Our data indicate that the presence of 5-hmC within the gene-body strongly correlates with gene expression and cooperates with activating histone marks marking cardiac specific genes. Moreover, during hypertrophy a profound genomic re distribution of 5-hmC on distal regulatory regions such as enhancers and repetitive elements takes place. We then dissected the functional role of enhancer-associated hydroxymethylation, defining a subset strongly enriched for 5-hmC. Enhancers harboring 5-hmC strongly influenced the expression of the associated genes and were found in the proximity of many transcription factors known to play a pivotal role in cardiac cells (i.e. Mef2c, Hif1a, Nkx2.5, Hand2). Finally, TET2 knock-down (KD) in fetal cardiac cells led to a large-scale gene expression perturbation, by affecting both gene body and enhancer associated hydroxymethylation. Notably the top perturbed pathways were cell cycle regulation, heart development and cardiac muscle contraction pointing out to TET2 as a major regulator in the specification of the transcriptional profile of cardiomyocytes.

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Computational analysis of the intermolecular interaction driving the self-assembly of collagen

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Collagen self-assembly is an important phenomena generating the biological alloy ECM and the structural/ functional diversity of different tissue types. We explored that how the amino acid sequence determines structure resulted from the self-assembly. Studies investigating the collagen intermolecular interactions are mostly based on the experimental host-guest peptides representing small part of collagen alpha chain and their pairwise interaction. By the combination of given protein primary structures and the programming language Python, we investigated the three main types of interaction including hydrophobic, polar, and electrostatic between molecules by taking the physicochemical properties of side chains in a certain range. D-periodic staggered arrangement of collagen molecules in fibrils is clarified by taking the amino acid sequence and calculating the corresponding interaction sliding one molecule to another. Our amino acid based computational analysis provides a wide range of application to investigate the sequence effect on the structure and to understand the characterization of interactions and stabilization of other fibrillar macromolecules.

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