Unlocking CRISPR: Epigenetics in Cardiac Hypertrophy

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Cardiac hypertrophy is a disease characterized by the enlargement or thickening of the heart muscle, specifically the myocardium (Nakamura & Sadoshima). This condition occurs when cardiomyocytes, or heart cells, increase in size rather than multiplying. The condition is often a response to chronic stressors such as hypertension, heart valve disease, or genetic mutations. In response to these stressors, the heart enlarges its muscle cells to maintain cardiac output. While physiological hypertrophy, such as that seen in athletes, is beneficial, pathological hypertrophy increases the risk of heart failure, arrhythmias, and sudden cardiac death (Frey et al). Symptoms of cardiac hypertrophy include shortness of breath, chest pain, irregular heartbeats, dizziness, and fatigue. According to epidemiological studies, left ventricular hypertrophy (LVH) affects approximately 1 in 5 people, with a higher prevalence in individuals with hypertension (Kahan & Bergfeldt). Patients with LVH are at a fivefold increased risk of cardiovascular events—issues ranging from heart attacks, strokes, heart failure, arrhythmias, and more, compared to those with normal heart structure (Verdecchia et al.). Given the significant health burden of cardiac hypertrophy, researchers are currently exploring novel therapeutic strategies, including epigenetic modifications and CRISPR-based gene regulation.

Epigenetics refers to heritable changes in gene expression that do not involve alterations in the DNA sequence. Think of it as a switch that turns genes on or off. One example is DNA methylation, where small chemical tags, called methyl groups, attach to the DNA. These tags can prevent a gene from being "read" and working properly. For example, in some cancers, certain genes that are supposed to stop tumors from growing get "turned off" because of these tags, even though the DNA sequence itself hasn't changed. This process can be passed down as cells divide but doesn't involve any change to the DNA code itself. *These modifications* regulate how genes are turned on or off in response to environmental and physiological signals. Three primary types of epigenetic modifications influence gene expression in cardiac cells: DNA methylation, histone modifications, and non-coding RNAs. DNA methylation, as mentioned earlier, is when small chemical tags called methyl groups are added to a part of the DNA called cytosine. This usually turns off the gene, stopping it from being used (Liu & Tang). Histone modifications, like adding acetyl or methyl groups, change the structure of the DNA packaging, which affects transcription, a process deciding whether a gene will be “on or off.” Also, non-coding RNAs, such as microRNAs and long non-coding RNAs, help control gene expression by either breaking down messenger RNA (*mRNA*) or stopping it from being used to make proteins, a process termed translation. *These epigenetic mechanisms* play a crucial role in cardiac hypertrophy by regulating key genes involved in heart muscle growth and remodeling. Currently, treatment options for cardiac hypertrophy focus on managing symptoms and reducing cardiac stress. Common approaches include beta-blockers, ACE inhibitors, and lifestyle

modifications such as exercise and dietary changes. However, these treatments do not address the underlying molecular mechanisms driving the disease, highlighting the need for more precise interventions. That is why understanding the regulatory pathways detailed above is essential, as it will aid in developing novel therapeutic solutions, such as CRISPR-based epigenetic editing, to reverse maladaptive changes in the heart. Gene editing technologies like CRISPR (*Clustered Regularly Interspaced Short Palindromic Repeats*) are a revolutionary gene-editing tool that allows scientists to precisely modify DNA sequences (Shi et al). Originally designed for genetic editing, CRISPR has been adapted for epigenetic editing, enabling researchers to control gene expression without permanently altering the genome. For this reason, CRISPR is emerging as a promising tool for cardiac hypertrophy, as the technology has the potential to reverse harmful epigenetic modifications, offering a novel and targeted therapeutic strategy.

Addressing one of the techniques mentioned earlier, DNA methylation plays a key role in controlling gene expression, including in conditions like cardiac hypertrophy. In this condition, certain genes that protect the heart from excessive growth can be turned off by DNA methylation, while other genes that promote abnormal heart enlargement might be turned on. Hypermethylation of genes that are supposed to prevent hypertrophy can worsen the disease, as it silences these protective genes (Xiao et al). The *dCas9-TET system*, for example, removes methylation from specific genes, allowing them to turn back on and restore normal heart function. Think of this as an eraser, one that removes the methyl groups from specific genes. Normally off, genes can be turned back on by this eraser removing chemical tags. This enables them to function properly again. In the case of the heart, this can help restore normal heart function by reversing the changes that caused the heart cells to grow abnormally. On the other hand, the *dCas9-DNMT system* adds methyl groups to genes that should be turned off, preventing harmful gene activation that leads to heart enlargement. This ability to control gene expression in heart cells offers a non-permanent, targeted approach to treat cardiac hypertrophy, potentially improving treatment options without making permanent changes to the genome. As of now, CRISPR-based epigenetic editing has primarily been investigated in mammalian models for treating cardiac hypertrophy. In these studies, techniques such as base editing have been employed to correct mutations associated with hypertrophic cardiomyopathy. For instance, a study with mice that had a specific genetic mutation showed that base editing could fix the mutation in heart cells. In the study, about 68% of the heart cells in the lower part of the heart (*ventricular cells*) were corrected, and 26–39% of the cells in the upper part of the heart (*atrial cells*) were also improved. The intervention led to the prevention of cardiac hypertrophy and normalization of gene expression patterns (Strong). In other words, it suggested that the technique can help fix genetic issues in the heart, and even improve heart function. These findings underscore the potential of CRISPR-based epigenetic editing as a non-permanent and reversible therapeutic approach for cardiac hypertrophy. However, while

these results are promising, further research, including clinical trials, is necessary to fully assess the efficacy and safety of these techniques in humans.

Furthermore, histone modifications, such as acetylation and methylation, play a crucial role in regulating gene expression by altering chromatin structure, which is a particular level of DNA packaging. In cardiac hypertrophy, these modifications can influence the activation or repression of genes associated with heart muscle growth and function. For instance, increased histone acetylation, the process of adding an acetyl group to histone proteins, which consequently loosens the DNA structure, is generally linked to gene activation. By contrast, deacetylation, the removal of acetyl groups from histone proteins, tightens the DNA structure, and thus suppresses gene expression (Kampen & Rooij). Recent advancements in CRISPR/*dCas9* technology have enabled precise editing of histone modifications, offering potential therapeutic strategies for cardiac hypertrophy. The inactive Cas9 (*dCas9*) can be combined with enzymes that modify histones to target specific areas of the genome without changing the DNA itself. For example, when *dCas9* is attached to histone acetyltransferases, it adds acetyl groups to DNA regions, activating protective genes that can help counteract heart muscle growth (Robb). Conversely, when *dCas9* is combined with histone deacetylases, it removes acetyl groups, turning off genes that promote excessive heart growth (Cai et al). The application of these CRISPR-based histone editing tools offers several advantages. They allow for reversible and specific control over gene expression, providing a targeted approach to modulate gene activity without introducing permanent genetic changes. This precision reduces the risk of off-target effects and offers a safer alternative to traditional gene editing methods. Moreover, by directly modifying epigenetic markers, these tools can potentially reprogram pathological gene expression patterns associated with cardiac hypertrophy, paving the way for advanced therapeutic interventions (Kwon et al).

Overall, CRISPR-based epigenetic editing is emerging as a powerful tool for modifying DNA methylation and histone marks, providing a new level of control over gene expression without permanently altering the genome (Kampen & Rooij). This approach holds significant potential for treating complex diseases like cardiac hypertrophy, where precise regulation of gene activity can help restore normal heart function. Unlike traditional gene editing, which introduces permanent changes to DNA, CRISPR-based epigenetic editing offers a reversible and highly targeted method to either activate or suppress specific genes, which is particularly important for cardiac hypertrophy as the condition involves complex, dynamic changes in gene expression that need to be carefully controlled (Pulecio et al). This advantage reduces the risk of unintended genetic alterations and provides a more flexible and adaptable therapeutic strategy. Despite its promise, several challenges must be addressed before CRISPR-based epigenetic therapies can be widely used in clinical settings. Remaining a primary concern are off-target effects, which are unintended modifications to the epigenome that could lead to unforeseen consequences (Cai et al). Such outcomes include mistakenly binding to and

modifying similar sequences elsewhere in the genome, ones that were not desired to change. Additionally, efficient and safe delivery methods are still being optimized to ensure that therapeutic agents reach target heart cells effectively and with minimal side effects (Strong). Furthermore, efficient and safe delivery methods are still being optimized to ensure that therapeutic agents reach target heart cells effectively and with minimal side effects (Pulecio). Personalized medicine is a particularly exciting application of CRISPR-based epigenetic editing. By tailoring treatments to an individual's unique genetic and epigenetic profile, researchers hope to develop more effective and precise therapies for conditions like cardiac hypertrophy and other cardiovascular diseases (Pagliarulo). However, the high cost of such treatments remains a major barrier. For example, the recently approved CRISPR therapy Chevy for sickle cell disease is priced at approximately $2.2 million per patient, while another gene therapy, Lyfgenia, costs around $3.1 million per patient. These costs significantly exceed the estimated lifetime medical expenses for sickle cell disease, which average $1.7 million per patient (Salib). The high price of personalized medicine raises concerns about accessibility and affordability, highlighting the need for strategies to reduce costs and improve widespread availability. In conclusion, while CRISPR-based epigenetic editing holds immense potential for treating cardiac hypertrophy and other complex diseases by precisely controlling gene expression, further research, development, and improvements in delivery methods are essential to fully harness its therapeutic capabilities and make these innovations accessible to a broader population.

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