Molecular Therapy
Nucleic Acids
Commentary

Inflammation attenuating lncRNAs in diabetic cardiomyopathy

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INTRODUCTION

Diabetic cardiomyopathy refers to cardiac structural and functional impairments associated with hyperglycemia and obesity in patients with cardiovascular disease. Clinical outcomes are significantly worst for cardiovascular patients with diabetes and obesity compared with non-diabetic patients. At the core of adverse cardiac remodeling in the diabetic heart are molecular and functional changes in cardiomyocytes that promote hypertrophy, fibrosis, and metabolic rewiring. Clinical management is generally limited to glycemic control, without addressing the underlying cause of cardiomyocytes impairment in patients with diabetes. In most cases, the presence of diastolic dysfunction that progresses to heart failure with preserved ejection fraction (HFpEF) is undetected and further complicates clinical management in patients with diabetes. Consequently, there remains a need for development of novel therapies that can resolve molecular and functional impairment of cardiomyocytes in patients with diabetes. In this respect, Xie and colleagues identify long non-coding RNA (lncRNA) ZNF593-AS as a novel target for attenuating diabetes associated with adverse remodeling in the heart.[1] Prolonged inflammatory response seems to promote secondary adverse changes in the diabetic heart, and the findings that ZNF593-AS salutary effects are linked to dampening of cardiac inflammation are intriguing and potentially open new avenues for the development of therapies for diabetic cardiomyopathy.

lncRNAs have emerged as regulators of physiological and pathological changes in the heart. lncRNAs are a group of heterogeneous RNA transcripts with more than 200 nucleotides that are not translated into functional proteins but can interact with DNA, RNA, and microRNAs (miRNAs) via base pairing or chemical interactions, thus carrying more impact than miRNAs. Ishii et al. were the first to identify lncRNA MIAT in the pathophysiology of myocardial infarction.[2] Similar studies have shown that increased expression of lncRNAs is linked to cardiac hypertrophy via modulation of epigenetic signaling pathways. Alternatively, lncRNA H19 can metabolically reprogram cardiomyocytes to promote cell-cycle reentry.[3] In the diabetic heart, dysregulation of lncRNA-governed signaling mechanisms contributes to the development of diabetic cardiomyopathy. Recent work by Qi and colleagues found the lncRNA HOTAIR to be downregulated in the myocardial tissue of patients with diabetic cardiomyopathy.[4] Another lncRNA, KCNQ1OT1, was found to be elevated in the serum of patients with diabetes and is associated with increased cardiac fibrosis in streptozotocin-induced diabetic mice.[5] lncRNA H19 was found to be downregulated in the myocardium of diabetic rats, decreasing miR-675 and increasing cardiomyocyte apoptosis.[6]

The study by Xie and colleagues identified a novel role for lncRNA ZNF593-AS in the progression of diabetic cardiomyopathy.[1] lncRNA ZNF593-AS was found to be reduced in leptin receptor-deficient db/db mice and high-fat diet (HFD)-induced obese mice. Loss of lncRNA ZNF593-AS in the heart, using a 3-pronged approach based on lncRNA ZNF593-AS global knockout mice, db/db, and streptozotocin-induced diabetic mouse models treated with a GapmeR for lncRNA ZNF593-AS, showed increased diastolic and systolic dysfunction, impaired contractility, and increased apoptosis in response to HFD administration. It is important to point out that all the 3 approaches were not cardiac specific and that the effects associated with loss of lncRNA ZNF593-AS may be due to a global reduction in lncRNA ZNF593-AS. Nevertheless, the authors do not find any changes in kidney or liver function and serum levels of blood glucose or hepatic metabolic parameters, suggesting a cardiac effect rather than an indirect effect. Interestingly, body weight is increased in ZNF593-AS knockout (KO) mice, but blood glucose levels are not significantly different compared with wild-type animals fed HFD or normal chow even after 6 months. On the other hand, both db/db and streptozotocin models show significantly elevated body weight and blood glucose levels. Therefore, it would be important to note in case of the ZNF593-AS KO mice that there is a baseline ZNF593-AS loss without elevated blood glucose, while in the db/db and streptozotocin models, ZNF593-AS is silenced after mice become hyperglycemic. The authors further confirm the pathophysiological role of ZNF593-AS by developing transgenic mice overexpressing lncRNA ZNF593-AS in the cardiomyocytes under myosin heavy-chain 6 promoter. These mice exhibit increased cardiac systolic and diastolic function and reduced apoptosis in response to HFD administration for 6 months. Delivery of lncRNA ZNF593-AS in the heart using AAV9 with cardiomyocyte-specific troponin T promoter provides further evidence for increasing lncRNA ZNF593-AS in the heart as a beneficial strategy that attenuates HFD-induced cardiac dysfunction.

Heart failure progression is significantly exacerbated by activated inflammasomes in the diabetic heart, while blocking inflammasome formation attenuates inflammation and cardiomyopathy in type 1 diabetes.[7] Cardiac inflammation is known to trigger

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the cGAS-STING signaling pathway that binds to the transcription factor interferon regulatory factor 3 (IRF3) in response to hyperglycemic stress.[8] Blockade of cGAS-STING attenuates inflammatory response in the heart and progression of diabetic cardiomyopathy.[9] Therefore, targeting the IRF3-cGAS-STING pathway and attenuating the NLRP3 inflammasome in cardiomyocytes may carry therapeutic benefit in slowing the progression of diabetes-induced adverse remodeling. To test this hypothesis, Xie and colleagues conducted bulk RNA sequencing on palmitic acid-treated cardiomyocytes to mimic hyperglycemic stress *in vitro*.[1] They found that lncRNA ZNF593-AS overexpression significantly downregulates IRF3-associated genes. Mechanistically, lncRNA ZNF593-AS binds and blocks IRF3 mRNA, suppressing IRF3 phosphorylation and activity. Gain or loss of function of lncRNA ZNF593-AS in transgenic mice and *in vitro* cell models, respectively, directly modulates nuclear translocation of IRF3 and its ability to regulate expression of pro-inflammatory cytokines in cardiomyocytes under hyperglycemic stress, in concurrence with the literature showing nuclear translocation of IRF3 essential for regulating expression of pro-inflammatory cytokines. Furthermore, the authors found an increased ratio of pIRF3/IRF3 and decreased lncRNA ZNF593-AS levels in samples from patients with heart failure combined with diabetes, providing a strong translational correlation between lncRNA ZNF593-AS and the IRF3 signaling pathway.

This work contributes to the growing field of lncRNAs in cardiovascular biology and, more specifically, diabetic cardiomyopathy. The rational and effective experimental design combining gain- or loss-of-function approaches for lncRNA ZNF593-AS in mouse models of hyperglycemia provides strength and confidence in the findings. Nevertheless, lncRNAs are known to target multiple signaling pathways,[10] which can diminish the effects, warranting further in-depth characterization of molecular signaling pathways in diabetic cardiomyocytes. Interestingly, lncRNA ZNF593-AS overexpression increases contractility in the diabetic heart under hyperglycemia stress.

Questions remain, and it is critical that the findings are not over-interpreted and moved forward with caution. Whether the positive inotropic effect of lncRNA ZNF593-AS can be extended to diabetic models with myocardial ischemic injury to mimic patients with diabetes at risk of ischemic events requires further testing. Chronic inflammation associated with the release of pro-inflammatory cytokines and chemokines is one of the hallmarks in patients with diabetes. The authors suggest that lncRNA ZNF593-AS attenuates IRF3-associated release of pro-inflammatory cytokines from cardiomyocytes in the diabetic heart. However, the broader implications of changing cardiomyocyte secretion under diabetic stress and its effect on the composition of immune cell subset or fibroblast to myofibroblast transition remains unknown. Moreover, does dampening of the inflammatory response compromise ischemic injury resolution in the diabetic heart?

Overall, the findings by Xie et al. contribute toward the delineating of a novel role played by lncRNAs in modulating cardiac inflammation in the diabetic heart to attenuate adverse remodeling and progression of diabetic cardiomyopathy. This work opens the door for targeting cardiac inflammation as a viable strategy for preclinical studies using models of diabetic cardiomyopathy as well as ectopic use of other lncRNAs regulating inflammatory signaling pathways in cardiomyocytes or immune cell types in the diabetic heart.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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