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REVIEW

Hyperglycemic memory in diabetic cardiomyopathy

Jiabing Zhan, Chen Chen, Dao Wen Wang (✉), Huaping Li (✉)

Division of Cardiology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China; Hubei Key Laboratory of Genetics and Molecular Mechanisms of Cardiological Disorders, Wuhan 430030, China

Abstract **Cardiovascular diseases account for approximately 80% of deaths among individuals with diabetes mellitus, with diabetic cardiomyopathy as the major diabetic cardiovascular complication. Hyperglycemia is a symptom that abnormally activates multiple downstream pathways and contributes to cardiac hypertrophy, fibrosis, apoptosis, and other pathophysiological changes. Although glycemic control has long been at the center of diabetes therapy, multicenter randomized clinical studies have revealed that intensive glycemic control fails to reduce heart failure-associated hospitalization and mortality in patients with diabetes. This finding indicates that hyperglycemic stress persists in the cardiovascular system of patients with diabetes even if blood glucose level is tightly controlled to the normal level. This process is now referred to as hyperglycemic memory (HGM) phenomenon. We briefly reviewed herein the current advances that have been achieved in research on the underlying mechanisms of HGM in diabetic cardiomyopathy.**

Keywords diabetes; diabetic cardiomyopathy; hyperglycemic memory

Introduction

Diabetes is one of the major diseases that threaten human health, with a global prevalence of 4%–17%. According to a 2019 report of the International Diabetes Federation, 351.7 million people of working age (20–64 years) had diagnosed or undiagnosed diabetes worldwide. This number is expected to increase to 417.3 million by 2030, bringing a heavy medical and economic burden to the society. A recent epidemiological research showed that the prevalence of diabetes among Chinese adults has reached 11.6%. Diabetes can cause various severe complications involving many vital organs, such as heart, brain, kidneys, and eyes. Among them, cardiovascular complications result in the highest rate of disability and mortality, accounting for nearly 80% of deaths due to diabetes complications. Framingham *et al*. have demonstrated that the incidence of heart failure is substantially higher in patients with diabetes than that in patients without this disease, with a twofold increase in males and a fivefold increase in females compared with age-matched individuals. In fact, diabetes can indirectly lead to heart failure by promoting hypertension and coronary heart disease [1]. Although diabetic vascular dysfunction is considered as the leading cause of heart failure in patients with diabetes [2], recent studies have established that diabetes is an independent risk factor of heart failure, even after controlling for coronary artery disease and hypertension [3–5].

The concept of diabetic cardiomyopathy was proposed as early as 1974 by Robert I. Hamby. It was defined as the appearance of abnormal myocardial structure and performance in the absence of hypertension, coronary heart disease, severe valvular disease, and other conventional cardiovascular risk factors in individuals with diabetes [6]. Subsequent studies have found that diabetic cardiomyopathy is characterized by cardiac diastolic dysfunction and vascular/microvascular function impairment in the early stage, systolic dysfunction in the later stage, and clinical heart failure, with pathological features that include cardiac hypertrophy, interstitial fibrosis, increased capillary basement membrane thickness, capillary microangioma, and decreased capillary density in the end stage [7–9]. Notably, the typical definition of diabetic cardiomyopathy comprises structural and functional abnormalities of the myocardium in patients with diabetes without coronary artery disease or hypertension [10]. Obviously, this type of

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Correspondence: Dao Wen Wang, dwwang@tjh.tjmu.edu.cn;
Huaping Li, huapingli_tj@126.com

cardiomyopathy should also be present in patients with diabetes with coronary artery disease and/or hypertension, although separately assessing the contribution of diabetic cardiomyopathy to overall ventricular dysfunction in such cases is difficult [11]. Clinically, requiring the absence of coronary artery disease, hypertension, or any other form of cardiac disease when a diagnosis of diabetic cardiomyopathy is made seems unrealistic. Therefore, researchers have recently proposed that "diabetic cardiomyopathy" should be defined as "cardiac abnormalities not wholly explained by other cardiovascular or non-cardiovascular causes and likely to be due to diabetes" [12,13].

Although the pathological mechanisms underlying diabetic cardiomyopathy has not been precisely described thus far, several mechanisms have been speculated to account for the progress of diabetic cardiomyopathy, including decreased mitochondrial respiration and pyruvate dehydrogenase activity, accumulation of free radical species, and malfunction of cardiac contractile and intracellular Ca^{2+} regulatory proteins [14]. Interestingly, diabetes seems to abolish the effect of "female advantage" in cardiovascular system, and it is presented as a more serious impairment of myocardial electromechanical function and more prominent neuroregulatory system disorders in women patients suffering from diabetic cardiomyopathy compared with age-matched men [14]. The prevalence of diabetic cardiomyopathy is increasing in parallel with the increase in the number of patients with diabetes around the world, but no effective or targeted treatment specific for diabetic cardiomyopathy has been developed to date, prompting the research community to devise new therapies that target different pathways [15,16].

Hyperglycemia has long been believed to be a major factor that contributes to the development and progression of diabetic cardiomyopathy by activating multiple signaling pathways, such as the protein kinase C (PKC), MAPK, NF-κB, SGLT2, O-GlcNAc, and CREM signaling pathways, which subsequently leads to cardiac structural remodeling, cardiomyocyte apoptosis, and activation of systemic and tissue RAAS [8,17]. Thus, glycemic control has been considered as one of the most important therapeutic approaches in the prevention and treatment of diabetes complications [18–23]. However, multiple recent large-scale studies have revealed that intensive glycemic control fails to improve the overall cardiovascular outcomes in patients with diabetes. A meta-analysis conducted by Turnbull *et al*. analyzed several clinical trials (ACCORD, ADVANCE, VADT, and UKPDS) and concluded that intensive glycemic control does not reduce myocardial infarction events and is insufficient to lower the risk of heart failure in patients with diabetes [24,25]. These studies suggested that patients with diabetes are still prone to cardiovascular complications even after intensive blood glucose control, indicating that transient hyperglycemia stress persists, a condition that is now referred to as "hyperglycemic memory" (HGM) phenomenon. In this review, we will summarize the underlying mechanisms of HGM that have been recently revealed. Thus, this study will provide a theoretical and experimental basis for the development of new strategies for diabetic cardiomyopathy.

Advanced glycation end products

Advanced glycation end products (AGEs) are a heterogeneous group of molecules produced by Maillard reaction, in which the reactive carbonyls in glucose, fructose, or their metabolites, such as methylglyoxal and deoxyglucosone, nonenzymatically react with the amine groups in proteins, nucleotide bases, or fatty acids, followed by further modification, such as dehydration, oxidation, rearrangement, or other reactions, to finally form AGEs [26,27]. Accumulation of AGEs and upregulation of AGE receptors (RAGEs) promote the onset of diabetic cardiomyopathy in streptozocin (STZ)-induced diabetic mice, whereas treatment with the AGE formation inhibitor benfotiamine ameliorates cardiac dysfunction [28]. AGEs induced by hyperglycemia might alter the functional properties of many important proteins, including vital matrix components. For example, AGE formation in type IV collagen induces an irregular crosslink of these molecules instead of generating the normal network-like structure by enzyme lysyl oxidase [29]. AGE formation in laminin decreases its binding to type IV collagen and heparan sulfate proteoglycan (HSPG), resulting in the absence of HSPG in the basement membrane of glomeruli and a compensatory overproduction of other matrix components in diabetic rats [29]. These alterations in extracellular matrix together reduces the compliance of the heart, leading to diastolic dysfunction. Aside from matrix components, AGEs can further directly activate multiple signaling pathways or bind to specific cell-surface receptors, such as RAGEs, a process that subsequently promotes the progress of various pathological changes, such as inflammation, production of reactive oxygen species (ROS), autophagy, or apoptosis, leading to cardiac remodeling and cardiac dysfunction [29].

Accumulated AGEs contribute to different pathological changes in diverse cell types and organs. Oldfield *et al*. [30] found that in fibroblasts, AGE/RAGE signals stimulate the expression of the inflammation-related gene TGF-β and promote the proliferation of fibroblasts and the synthesis of matrix proteins. Excessive collagen deposition leads to myocardial fibrosis and a decrease in cardiac compliance and function [30]. Jin *et al*. [31] suggested that AGE stimulation remarkably increases RAGE expression in macrophages, promotes macrophage differentiation to M1 phenotype, and enhances the expression of several proinflammatory mediators, such as IL-6, TNF, and the

NF-κB pathway. Notably, by secreting multiple proinflammatory cytokines and via intercellular interactions, activated macrophages can further promote the proliferation and secretion of fibroblasts. Bucala *et al*. [32] found that AGEs can quench nitric oxide (NO), the major active constituent of endothelium-derived relaxing factor, both *in vitro* and *in vivo*. They further confirmed that endothelium-dependent relaxation of ascending aorta in diabetic rats is damaged by the accumulation of AGEs in endothelial cells. Accordingly, inhibition of AGE formation by aminoguanidine, a hydrazine-like compound, ameliorates vasodilatory impairment by preserving endothelium-derived NO [32]. Schmidt *et al*. [33] found that the exposure of cultured human endothelial cells to AGEs can induce the expression of vascular cell adhesion molecule-1 (VCAM-1). Therefore, it might accelerate atherogenesis by enhancing the interactions between endothelium and circulating monocytes.

With regard to AGEs in cardiomyocytes, a recent study revealed that AGE exposure impairs the binding of FK506 binding protein 12.6 to ryanodine receptor 2 (RyR2), causing elevated intracellular calcium concentration, decreasing mitochondrial membrane potential, and inducing cell apoptosis in myocardium and cultured myocytes [34]. The expression levels of cytochrome c and active caspase-3 in rat myocardium and primary myocytes are also elevated by AGE exposure, which together with calcium imbalance, result in cardiac dysfunction [34]. Similarly, glycations of RyR2 and sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA2a) are increased in the hearts of patients and rats with diabetes, leading to perturbed SR Ca^{2+} cycling and cardiac dysfunction [35,36]. Moreover, AGE accumulation activates PKC in an ROS-dependent manner, triggering mitochondrial dysfunction and subsequent cardiac cell death [37].

Additionally, the AGE-modified form of low density lipoprotein (LDL) reportedly considerably impairs plasma clearance in patients with diabetes in line with decreased LDL receptor binding activity, leading to an elevated circulating LDL level, which is an important mechanism for dyslipidemia, endothelial dysfunction, and accelerated atherogenesis [38]. Zoltowska *et al*. [39] demonstrated that AGE-modified LDL remarkably enhances platelet aggregation by 32%–44% in response to aggregating agents, such as thrombin, collagen, and ADP, and stimulates cholesterol esterification in monocytes, thereby further contributing to intravascular thrombosis and endothelial dysfunction.

The late stages of Maillard reaction to form AGEs are reportedly irreversible [40], whereas multiple AGE-modified proteins, such as glycated fibrinogen and collagen, are stiffer and less susceptible to biological degradation [41,42]. Therefore, the persistence of accumulated AGEs even after glucose normalization may at least partially explain the HGM phenomenon via various pathways in multiple cell types (Fig. 1), and further studies should attempt to increase the turnover of these abnormally accumulated AGEs and AGE-modified proteins to restore intracellular and circulating physiologic environment.

MicroRNAs

MicroRNAs are a class of small noncoding RNAs that are 19–25 nucleotides in size that commonly regulate the post-transcriptional silencing of target genes [43]. Mature

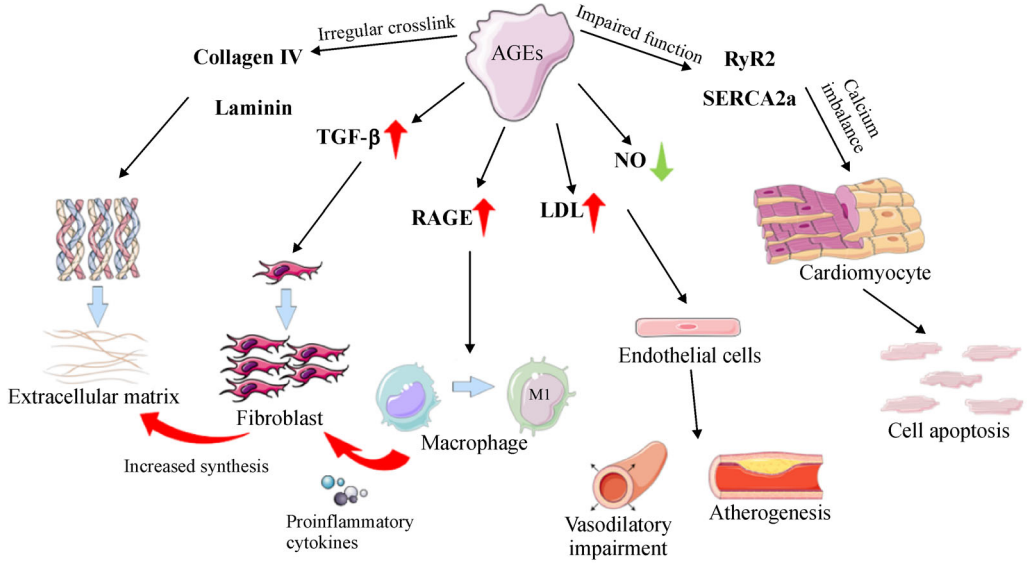

Fig. 1 AGEs promote the process of diabetic cardiomyopathy via various pathways in multiple cell types.

microRNAs usually mediate the silencing of target genes by binding to the 3′ untranslated region of the target mRNA within RNA-induced silencing complexes, resulting in mRNA degradation or translation inhibition [44]. A single microRNA can target hundreds of mRNAs and influence the expression of numerous genes that might be functionally related [45]. In cardiovascular diseases, microRNAs are reportedly involved in the pathological processes of fibrosis/antifibrosis, hypertrophy, mitochondrial fission, apoptosis, lipid deposition, and oxidative stress [46–48].

Several studies have attempted to identify the roles of miRNAs in the HGM phenomenon. Zhong *et al*. [46] distinguished three differentially expressed microRNAs (miR-125b, miR-29a-3p, and miR-146a-5p) in the aortas of diabetic rat, regardless of insulin treatment. They further revealed the direct regulatory effects of miR-125b on TNF-induced protein 3 (TNFAIP3) and those of miR-146a-5p on TNF receptor-associated factor 6 (TRAF6) and IL-1 receptor-associated kinase 1 (IRAK1) in human aortic endothelial cells (HAECs). Consistently, the protein levels of these three target genes (TNFAIP3, TRAF6, and IRAK1) are persistently altered in response to transient hyperglycemia, but these changes can be restored by miR-125b inhibition or miR-146a-5p overexpression [46]. Strycharz *et al*. [49] suggested that even a transient exposure to high glucose levels during adipogenesis might induce changes in miRNA expression in mature adipocytes, and the expression profiles are similar to those exposed to chronically high glucose levels. Peng *et al*. [50] found that high glucose levels induce sustained upregulation of miR-204 and downregulation of sirtuin1 lysine deacetylase (SIRT1) in retinal pigment epithelial cells, both of which contribute to endoplasmic reticulum stress and subsequently to cell apoptosis. These changes can last after replacement with normal glucose levels.

Costantino *et al*. [51] discovered that 316 microRNAs are dysregulated in the heart of STZ-induced diabetic mice compared with those in the controls, among which 209 are upregulated and 107 are downregulated by $>$ 2.0-fold. Interestingly, 268 of those dysregulated microRNAs remain altered even after reverting to normoglycemia by insulin treatment. Subsequent ingenuity pathway analysis revealed that a large proportion of these persistently dysregulated miRNAs are involved in processes related to apoptosis (miR-320b, miR-378, and miR-34a), fibrosis (miR-125b, miR-150, miR-199a, miR-29b, and miR30a), hypertrophic growth (miR-1, miR-150, miR-199a, miR-133a, miR-214, miR-29a, miR-125b, miR-221, and miR-212), autophagy (miR-133a, miR-221, miR-212, and miR-30a), oxidative stress (miR-221, miR-146a, miR-34a, miR-210, miR-19b, miR-125b, miR27a, and miR-155), and heart failure (miR-423, miR-499, and miR-199a) [51]. These results indicated that glycemic control is insufficient to completely revert the alteration of miRNAs in diabetes, providing a new mechanistic insight into the HGM phenomenon in diabetic cardiomyopathy. Costantino *et al*. [52] recently confirmed the protective role of JunD, a member of the activated protein-1 family of transcription factors that act as a major gatekeeper against oxidative stress in the pathogenesis of hyperglycemia- or ROS-induced myocardial dysfunction. Furthermore, they revealed that the expression of JunD is epigenetically regulated by hypermethylation in the gene promoter region, as well as by translational repression via miRNA-673, suggesting a complex regulatory mechanism involving microRNAs and epigenetic modifications of critical genes in diabetic cardiomyopathy.

Our previous study revealed that miR-320 expression is elevated in the heart of diabetic mice compared with that in the controls, and this elevation promotes CD36 transcription by facilitating the association of argonaute 2 (Ago2) with RNA polymerase II (Fig. 2). Given that CD36 is known to contribute to fatty acid (FA) uptake, upregulated CD36 results in myocardial lipid deposition and cell apoptosis, subsequently triggering cardiac dysfunction and diabetic myocardiopathy [43]. Sadoshima [53] commented that "the selective upregulation of CD36 transcription by miR-320 shown by Li *et al* represents a novel mechanism by which lipid uptake is enhanced in the absence of increases in FA oxidation." Sadoshima added that "interestingly, miR-320 forms an RNA-induced silencing complex with Ago2 to promote RNA interference in the cytosol but miR-320 and Ago2 also form a distinct complex, called a RITA complex, in the nucleus, thereby activating transcription" [53]. Moreover, miR-320 is one of those microRNAs that persistently dysregulate in transient hyperglycemia. The lipotoxicity mediated by miRNAs might be one of the underlying mechanisms of the HGM phenomenon in diabetic cardiomyopathy. The issue of whether other miRNA-mediated factors are involved in lipotoxicity and "hyperglycemic memory" is largely unknown and remains to be addressed.

Persistent mitochondrial oxidation stress

Overproduction of superoxide by the mitochondrial electron-transport chain, which is then converted to other more reactive oxygen free radical species, is another important mechanism in diabetic cardiovascular complications [54–56]. In fact, myocardial glucose-derived pyruvate oxidation is markedly decreased in diabetes because of impaired glucose uptake and cardiomyocyte oxidation [57]. Therefore, the energy fuel in myocytes is mainly derived from FA oxidation. This energy substrate alteration leads to increased β-oxidation of fatty acyl-coenzyme A (CoA) within the mitochondria and subsequent overproduction of acyl-CoA [58]. However, owing to the uncoupling of mitochondrial enzymes, the tricarboxylic

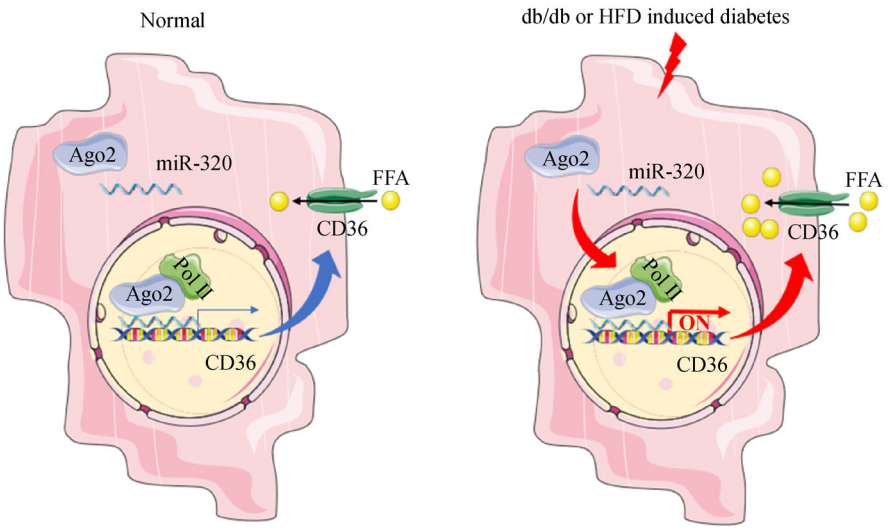

Fig. 2 Elevated miR-320 in the heart of diabetic mice acts in the nucleus to promote CD36 transcription by facilitating the association of argonaute 2 (Ago2) with RNA polymerase II, which increases the FFA uptake of cardiomyocytes and results in myocardial lipid deposition, causing cell apoptosis and cardiac dysfunction. Adapted from reference [37] with permission (OA related license).

acid (TCA) cycle is insufficient to oxidize excessive acyl-CoA, leading to the production of toxic intermediates, including ROS [59,60].

By comparison, an increase in acyl-CoA oxidation in the TCA cycle increases the flux of electron donors (NADH and FADH2) into the electron transport chain and consequently elevates the voltage gradient across the mitochondrial membrane. As the voltage gradient reaches a critical threshold, the electron transfer within complex III is blocked, and the electrons would return to coenzyme Q, which donates the electrons to molecular oxygen, thus forming superoxide [61]. Previous studies have determined superoxide as the initial oxygen free radical formed by the mitochondria, which is then converted to other types of ROS [62]. Most importantly, the mitochondria have been demonstrated to be required for the initiation of hyperglycemia-induced superoxide production, which in turn could activate other superoxide production pathways and amplify the original detrimental effects of hyperglycemia, including redox changes, NADPH oxidases, and uncoupled eNOS [63]. In fact, some researchers have even considered enhanced mitochondrial superoxide overproduction as the common step of various mechanisms that underlie hyperglycemia-induced injuries, such as elevated aldose reductase activity, PKC activation, hexosamine pathway flux, AGE formation, and RAGE ligand binding [63,64].

With regard to the HGM phenomenon, the adverse impact of mitochondrial oxidation stress on targeted organs in diabetes displays an enormous potential to persist even after normoglycemia. Ihnat *et al.* [65] found that multiple markers of oxidative stress, such as BCL-2-associated X protein, NAD(P)H oxidase subunit p47phox, and 3-nitrotyrosine, which are induced by high glucose treatment, can remain elevated for 1 week after glucose level is normalized in human endothelial cells and ARPE-19 retinal cells, which can be interrupted by the blockade of reactive species [65]. Furthermore, the mammalian Shc (Src homology 2 domain containing) gene encodes three different adaptor protein isoforms ($p46^{Shc}$, $p52^{Shc}$, and $p66^{Shc}$), but only $p66^{Shc}$ is involved in mitochondrial ROS generation [66]. Targeted mutation of $p66^{Shc}$ reduces the production of intracellular oxidants and increases the resistance to oxidative stress [66], whereas $p66^{Shc-/-}$ mice are protected against vascular and cardiac injuries induced by diabetes by reducing ROS generation and ameliorating hyperglycemia-induced endothelial impairment [67]. Cosentino *et al.* [68] indicated that in the aortas of diabetic mice and high glucose-treated HAECs, the activation of $p66^{Shc}$ would persist even after reverting to normoglycemia. Specifically, PKC enhances $p66^{Shc}$ expression, whereas $p66^{Shc}$ upregulates PKC in response to high glucose levels, leading to a detrimental cycle despite the restoration of normoglycemia [68]. Moreover, persistent activation of $p66^{Shc}$ results in ROS overproduction, reduced NO bioavailability, and subsequent cell apoptosis, all of which drives HGM-related cardiovascular complications [68]. Accordingly, gene silencing of $p66^{Shc}$ can inhibit ROS production, restore endothelium-dependent vasorelaxation, and prevent cell apoptosis both *in vivo* and *in vitro*, thereby attenuating endothelial dysfunction in diabetes [69]. These studies indicated that persistently activated $p66^{Shc}$ has a critical role in the HGM phenomenon.

Lee *et al*. [70] recently revealed a vicious cycle involving transglutaminase 2 activation and ROS generation in the aortic endothelium of mice exposed to transient hyperglycemia, and this cycle can be disrupted by oral administration of either Cys (a type of TGase inhibitor) or N-acetylcysteine, an ROS scavenger.

NADPH oxidase is remarkably activated in the cardiomyocytes of diabetic Wistar rats, leading to ROS overproduction and myocardial apoptosis [71]. Our recent study also found that the excessive ROS generated in the mitochondria is regulated by miR-92a-2-5p and let-7b-5p in the heart of diabetic mice. Specifically, a decrease in miR-92a-2-5p and let-7b-5p in the mitochondria down-regulates the expression of mitochondrial gene cytochrome-b (mt-Cytb), a critical protein in the process of ROS generation, and consequently increases mitochondrion-derived ROS under diabetes conditions, which can be rescued by the re-expression of miR-92a-2-5p and let-7b-5p in cardiomyocytes [72]. Interestingly, the let-7 family has also been demonstrated to be involved in the HGM phenomenon [51]. In fact, ROS overproduction and disrupted redox balance have been extensively reported to mediate the expression of various microRNAs [73]. Kim *et al*. [74] indicated that miR-210 is upregulated by various sources of ROS in adipose-derived stem cells, whereas He *et al*. [75] revealed that miR-199a and miR-125b are inhibited by ROS via hypermethylation in their promoter regions. Therefore, mitochondrion-derived ROS along with microRNAs might possibly constitute a vicious cycle that can persist even after restoration of normoglycemia, thereby contributing to the pathogenesis of HGM in diabetic cardiomyopathy.

Importantly, mitochondrial DNA (mtDNA) is prone to enhanced oxidative damage because it lacks a DNA repair mechanism and owing to its special subcellular location wherein it is too close to the electron transport chain [76]. Given that mtDNA encodes several essential protein subunits of the oxidative phosphorylation system, persistently impaired mtDNA as induced by hyperglycemia-derived superoxide would result in further ROS production, which might be the potential mechanisms underlying sustained diabetic cardiomyopathy.

DNA methylation and histone protein modification

DNA methylation and histone protein modification also play an important role in the HGM phenomenon in diabetic cardiomyopathy [77,78]. Cytosine–phosphate–guanine (CpG) hypomethylation in the promoter region of protein-coding genes generally results in transcriptional activation. By contrast, methylation of CpG sites by DNA methyl transferase (DNMT) promotes the binding of promoter regions with methyl-CpG binding domain proteins instead of transcription factors, and the former in turn recruits histone deacetylases, leading to transcriptional repression [77]. Metabolism plays a central role in DNA methylation. Demethylation is regulated by ten-eleven translocation (TET) family enzymes, which utilize the TCA cycle intermediate α-ketoglutarate to remove methyl groups [79]. Succinate acts as a competitor of α-ketoglutarate to inhibit TET activity [80]. Succinate levels are increased in type 2 diabetes [81]. Therefore, metabolic perturbations regulate the activity of enzymes involved in the balance between DNA methylation and demethylation [82].

Histones are subject to diverse post-translational modifications, which include acetylation and methylation of lysines and arginines, phosphorylation of serines and threonines, and ubiquitylation and sumoylation of lysines [83]. Foremost among them are acetylation and methylation. In general, acetylation of histones (H2A, H2B, H3, and H4) in different lysine sites is usually associated with transcriptional activation [84]. Numerous studies have revealed that in diabetes, the expression levels of various genes are regulated by acetylation, but these can be reversed by the application of histone acetyltransferases (HATs) or histone deacetylases (HDACs), thus attenuating cardiac dysfunction [85–87]. Hyperglycemia decreases the activity of glucose-6-phophate dehydrogenase [88], which results in increased global levels of H3 and H4 acetylation [89]. An altered metabolic environment and an abnormal accumulation of intermediates (such as CoA derivatives, free CoA, NAD^+, and NADH) would stimulate or inhibit the activity of HATs or HDACs, thereby changing the states of histone acetylation. The enzymes that regulate histone acetylation are HATs and HDACs, and these enzymes can also directly acetylate or deacetylate various transcription factors and regulatory proteins aside from histones [90]. Yu *et al*. [91] recently found that STZ-induced diabetes in mice and high glucose environment for neonatal mouse cardiomyocytes can suppress Sirt3 (a member of HDACs), thereby reducing Foxo3A deacetylation and subsequent Parkin expression. Suppressed Sirt3-Foxo3A-Parkin expression leads to impaired mitophagy and cardiac contractile dysfunction [91].

A global analysis of histone code modifications in cardiac mesenchymal cells (CMSCs) derived from patients with diabetes revealed a greater reduction in histone 3 lysine 9 acetylation (H3K9Ac) and histone 3 lysine 14 acetylation—compared with the CMSCs derived from patients without diabetes [92]. Given that the CMSCs used in this study were cultured in the presence of normal glucose levels, sustained alteration of histone acetylation state might be involved in the HGM phenomenon [92].

Moreover, an increase in β-oxidation of FAs leads to upregulated acetyl-CoA levels within the mitochondria.

Although acetyl-CoA is the only known substrate for acetylation in most eukaryotes, abundant acetyl-CoA and high pH (which has been shown to enhance the ratio of neutral and nucleophilic forms of lysine residues) lead to substantial spontaneous mitochondrial protein acetylation via both enzymatic and nonenzymatic mechanisms [93]. Irregular hyperacetylation reportedly inhibits many catalytic activities of mitochondrial enzymes [94]. Hyperacetylation of some cytoplasmic proteins, such as $p66^{Shc}$, has been demonstrated to promote its phosphorylation at Ser36 and its translocation to the mitochondria, which then increase ROS production through the generation of hydrogen peroxide [95]. However, the question of whether nonnuclear proteins are acetylated requires further study.

Methylation in the lysine residue of histone is a considerably more complex process as it involves diverse conserved lysine loci, such as lysine 4 of H3 (H3K4), lysine 9 of H3 (H3K9), and lysine 20 of H4 (H4K20), as well as different methylation patterns, including mono-, di-, or tri-methylation, all of which usually cluster within specific regions and lead to the reorganization of chromosomes into different structural and functional domains [77]. Moreover, histone methylation processes are regulated by multiple enzymes, including histone methyltransferases (HMTs) and histone demethylases (HDMs or HDMTs). Recent studies have found that high glucose levels decrease lysine methyltransferase 5A (KMT5A) and cAMP response element binding protein. Thus, high glucose levels reduce histone H4 lysine 20 methylation (H4K20me1, a downstream target of KMT5A) in protein tyrosine phosphatase 1B promoter, which then augments expressional activity in human umbilical vein endothelial cells (HUVECs) [96]. Wang *et al*. [97] also revealed that high glucose levels inhibit SET8 (a methyltransferase) expression and H4K20me1 in the microtubule affinity regulating kinase 4 (MARK4) promoter region, resulting in induced MARK4 expression and NLRP3 inflammasome activation. Of note, SET8, along with LSD1 (one of the HDMs), controls the protein stability of DNMT1 via methylation-mediated, ubiquitin-dependent degradation, consequently influencing DNA methylation [98]. In conclusion, a high glucose level itself can alter the expression and activity of multiple histone modification enzymes and accordingly influence DNA and histone methylation states.

Miao *et al*. [99] utilized the samples from The Diabetes Control and Complications Trial (DCCT) to profile H3K9Ac-, H3K4Me3-, and H3K9Me2-linked gene promoter regions in blood monocytes obtained from 30 DCCT conventional treatment group subjects (case subjects) and 30 DCCT intensive treatment group subjects (control subjects). They found that the case subjects had a substantially higher average number of regions enriched with H3K9Ac than the control subjects. Of note, the genes universally hyperacetylated in promoter regions were found to be enriched to diabetes-related pathways, including ROS, apoptosis, and macrophage and dendritic cell functions [99]. Chen *et al*. [100] compared the DNA-me profiles in genomic DNA of whole blood isolated at EDIC Study baseline from 32 cases (previous DCCT conventional therapy group subjects) with those of 31 controls (previous DCCT intensive therapy group). They found a set of differentially methylated loci despite the lack of notable difference in HbA1c levels between cases and controls [100]. Olsen *et al*. [101] used zebrafish, which can spontaneously recover from diabetes via pancreatic β-cell regeneration, to perform CpG island methylation and genome-wide microarray expression analysis with daughter tissues that were never exposed to hyperglycemia. Interestingly, they discovered the persistence of hyperglycemia-induced global DNA hypomethylation in a subset of loci associated with abnormally expressed genes in these daughter tissues, and this hypomethylation might explain the impaired caudal fin regeneration to the same extent as that of diabetic zebrafish [101], implicating DNA methylation as a potential contributor to the HGM phenomenon.

El-Osta *et al*. [102] found that in aortic endothelial cells, exposure to transient and prior hyperglycemia causes sustained epigenetic changes in the NF-κB subunit p65 (NF-κB-p65) promoter, resulting in persistent NF-κB-p65 gene expression. Specifically, transient hyperglycemia results in ROS overproduction by the mitochondrial electron transport chain, thereby increasing H3K4 monomethylation (H3K4me) in the NF-κB-p65 promoter via recruitment of histone methyltransferase Set7 [103]. Another important epigenetic mechanism that underlies sustained NF-κB-p65 activation is the distinct and persistent H3K9 demethylation (including dimethylation and trimethylation) in proximal p65 promoter, which is mediated by hyperglycemia-induced recruitment of the methyl-lysine eraser LSD1 [102]. H3K4me appears to be a crucial post-translational modification that triggers gene expression. Hyperglycemic stress increases H3K4 monomethylation in NF-κB-p65 promoter, driving proinflammatory gene expression (such as monocyte chemoattractant protein-1 and VCAM-1, both of which play a major role in the pathogenesis of atherosclerosis), and these alterations cannot be restored by removing from hyperglycemic environment [104–106].

Histone 3 lysine-9 trimethylation (H3K9me3) also appears to be involved in the inflammation process induced by hyperglycemia and the HGM phenomenon [107]. In cardiomyocytes incubated with high glucose levels, the protein levels of the H3K9me3 methyltransferase Suv39h1 are considerably reduced in accordance with the decreased association of Suv39h1 with IL-6 promoter. As a result, a reduction in H3K9me3 in the IL-6 promoter region leads to the transcriptional activation of IL-6 [107]. Interestingly, in

contrast to sustained inflammatory phenotype and epigenetic histone modification, high glucose level-induced myocardial apoptosis and mitochondrial dysfunction are reversible [107]. In high glucose level-treated human THP-1 monocytic cells, the transcription factor NF-κB, along with its transcriptional coactivators, including HATs, such as CBP/p300 and p/CAF, are recruited to TNF-α and COX-2 promoters, which increase the concomitant acetylation of histone H3 and histone H4 in the promoter regions, leading to chromosome remodeling and the expression of these proinflammatory genes [108]. Via chromatin immunoprecipitation linked to microarray, Miao *et al*. [109] unveiled genome-wide H3K9me2 patterns in the blood lymphocytes and monocytes from patients with diabetes versus healthy control subjects. They found substantially increased expression of the promoter H3K9me2 in autoimmune- and inflammation-related genes, such as p38 mitogen-activated protein kinase, Toll-like receptor, and IL-6 [109].

An aspect that should not be ignored is that the expression levels of epigenetic modification enzymes also reportedly persistently change in response to transient high glucose stimulus. Zheng *et al*. [110] uncovered that hyperglycemia downregulates NAD-dependent deacetylase sirtuin-1 levels in bovine retinal capillary endothelial cells and returning to normoglycemia fails to rescue SIRT1 reduction. Moreover, elevated glucose levels reduce lysine methyltransferase SET8 proteins in HUVECs, which remain at a low level after switching to normoglycemia [111].

Methylation of histone lysine residues is a class of reasonably stable epigenetic modifications despite a certain degree of reversibility, and it might partly explain the persistent epigenetic changes in the promoter of critical genes after intensive blood glucose control in diabetes. In fact, methylation at different lysine residues in histones has been extensively demonstrated to display differential turnover rates, some of which (such as H3K27me3, H4K20me3, and others) are considerably slower than many other post-translational modifications [112,113]. Previous studies have also shown that histone modification enzymes (such as HATs, HDACs, and HMTs) are associated with histones of the type that they can produce, suggesting a positive feedback where modified nucleosomes recruit enzymes that similarly modify nearby nucleosomes, which make it possible for a cluster of nucleosomes to maintain a specific stable modification state, thus causing an "epigenetic memory" [114–116]. Dodd *et al*. [117] adopted a simplified stochastic model of dynamic nucleosome modification to confirm this mechanism. They found that this mechanism endows a strong bistability to the modification state of a cluster of nucleosomes despite multiple changes in the modification status for each nucleosome. These characteristics of histone modifications suggested that they have a critical role in the mechanisms that underlie the HGM phenomenon.

Other mechanisms

Patients with diabetes mellitus are often accompanied by multiple metabolic disorders, including abnormal lipid metabolism, obesity, and insulin resistance, all of which cannot be rescued by simple hypoglycemic therapy. For instance, our previous studies have revealed that hyperglycemia increases the myocardial uptake of free FAs by miR-320 by elevating the expression of the FA transporter protein CD36. Lipid deposition results in lipotoxicity in myocytes and consequently induces cell apoptosis, which in turn accelerates the pathogenic progress of diabetic cardiomyopathy [43,53]. Interestingly, miR-320 has been demonstrated to be one of the microRNAs that are persistently altered despite normoglycemia [51]. Therefore, the lipotoxicity mediated by miR-320 might provide novel insights into the HGM phenomenon in diabetic cardiomyopathy. Other factors that contribute to cardiac lipotoxicity in diabetes, such as FA transporting proteins other than CD36, elevated glycerol-3-phosphate acyltransferase (GPAT) activity, increased diglyceride acyltransferase, and other cellular pathways that participate in lipotoxic mechanisms, are indeed involved in diabetic cardiomyopathy, but their functions in the HGM phenomenon are yet to be studied.

Low-grade inflammation is commonly observed in various tissues in response to lipid overload, and this condition appears to promote diabetes development via insulin resistance [118,119]. Adipose tissues, especially enlarged or dysfunctional adipocytes, are considered the main source of inflammatory factors in obesity, and they attract immune cells and subsequently induce their polarization into a proinflammatory phenotype [118].

The HGM phenomenon has also been observed in clinical settings. Intensive glucose control has been found to have a little effect on reducing the overall risk of cardiovascular complications in individuals with diabetes, and it might be associated with the side effects of hypoglycemic drugs that are extensively used in diabetes therapy [25]. All antihyperglycemic drug therapies can potentially mechanically exert detrimental effects on cardiac dysfunction, thereby precipitating heart failure in patients with diabetes. Moreover, drug-induced hypoglycemia has been shown to cause the activation of sympathetic nervous system and increase the heart rate, both of which contribute to thrombus formation and arrhythmia, thereby further aggravating ventricular remodeling and cardiac dysfunction. For example, insulin can reportedly stimulate the activity of a wide range of sodium transporters, including NHE3, sodium–potassium (Na/K)

ATPase, and the sodium bicarbonate cotransporter (NBCe1) in proximal tubules; sodium–potassium–chloride (NKCC2) cotransporter and Na/K ATPase in the loop of Henle; and amiloride-sensitive sodium channel (ENaC) in distal tubules, all of which increases sodium reabsorption in the kidneys, causing water–sodium retention and subsequent cardiac dysfunction [25]. Therefore, aside from the cellular memory properties induced by high glucose stimulation, the side effects of hypoglycemic drugs may also play a role in the HGM phenomenon in diabetic cardiomyopathy.

Conclusions and perspectives

The mechanisms that underlie the HGM phenomenon has not been fully understood thus far. Numerous studies have suggested that multiple molecular pathways, such as AGEs, oxidative stress, and epigenetic modification, might be involved in this process. However, these mechanisms do not seem to exist in isolation but form a complex network in which these components exert mutual regulatory effects, forming various vicious cycles (Fig. 3). The abnormal metabolism caused by high glucose levels causes mitochondrial oxidative stress. For example, ROS overproduction inhibits the activity of glyceraldehyde-3-phosphate dehydrogenase and leads to the accumulation of glycolytic intermediates, which then activate the polyol and hexosamine pathways, causing the activation of the protein kinase C-β (PKC-β) pathway and the formation of AGEs [120,121]. AGEs promote ROS production in myocytes, thus forming a vicious cycle between ROS and AGEs. In addition, ROS can induce various post-translational modifications of histones, such as acetylation, methylation, phosphorylation, and ubiquitination. Even if hypoglycemic treatment is able to restore the glucose metabolism pathway to its normal state and leads to ROS production, most epigenetic modifications are irreversible, causing persistent abnormal expression patterns of multiple genes (including ROS-related genes), and ultimately contributing to the progressive worsening of myocardial function [103,122]. The abnormal expression of miRNAs can also further lead to mitochondrial dysfunction and ROS overproduction [72].

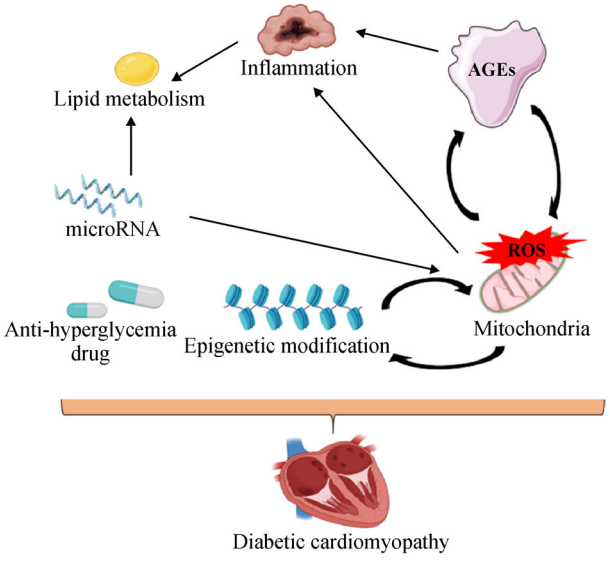

Fig. 3 Various pathogenic mechanisms by which diabetic cardiomyopathy (DCM) forms a complex network.

The pathogenic molecules mentioned above form a complex interlocking network. However, which molecules in these pathogenetic processes are the most critical and initiating factors remain unclear. Therefore, further time point studies are warranted to unveil the earliest signal molecule and the key abnormal pathways in diabetic cardiomyopathy. Other important pathways are also involved in diabetic cardiomyopathy. For instance, although the glucose within diabetic cardiomyocytes shows reduced flux through glycolysis, it actually participates in more than one carbon cycling pathways, as well as in multiple glycolytic side branch pathways, such as the polyol pathway, the hexosamine biosynthetic pathway, and the pentose phosphate pathway [58]. These pathways are crucial to the O-17 GlcNAc modification of proteins and alteration of relative protein function or stability [123–126]. However, compared with the well-studied irreversible AGE modifications, the role of dynamic and enzymatic O-GlcNAcylation in hyperglycemic memory remains unclear and requires further study.

Sustained high glucose stress despite subsequent normoglycemia is not limited to diabetic cardiomyopathy. The HGM phenomenon is a common phenomenon in various diabetic complications, such as nephropathy and retinopathy [127,128], which were not included in this review because our focus was on cardiovascular complications. Diabetic damages in various target organs and cell types have been indicated to be quite different. For instance, in diabetic nephropathy and retinopathy, persistent hyperglycemic stress on endothelial cells plays a pivotal role. By comparison, in diabetic cardiomyopathy, various cells, such as cardiomyocytes, myocardial microvascular endothelial cells, fibroblasts, and immune cells, may jointly participate in the pathogenesis of the HGM phenomenon. Previous studies have also revealed that intensive glucose control effectively lowers the risk of myocardial infarction/coronary artery disease, further supporting different pathogenesis in different target organs/cells suffering from the HGM phenomenon.

Although the HGM phenomenon has been confirmed by substantial clinical and experimental studies, intensive glucose control at the early stage can indeed be able to

bring benefits for diabetic complications. For instance, the incidence of cardiovascular diseases in type 1 diabetes patients is reduced if intensive glycemic control is provided soon after diagnosis [129]. Preclinical experiments have also suggested that good control of blood glucose soon after the induction of diabetes offers protective effects against retinopathy, neuropathy, or oxidative and nitrative stress [130–132]. These findings highlighted the concept of "point of no return," which occurs during the process of diabetes mellitus and related complications, beyond which the onset of good glycemic control would be no longer sufficient to revert pathological changes in target cells and organs, leading to failure in preventing some of the diabetic end point events.

Future studies should focus on exploring the unique mechanism of the HGM phenomenon in different organs/cells, as well as in cell–cell interactions. A profound elucidation of the temporal and spatial changes in this process would assist in providing novel insights into the prevention and treatment of diabetes complications.

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Compliance with ethics guidelines

Jiabing Zhan, Chen Chen, Dao Wen Wang, and Huaping Li declare no conflicts of interest. This manuscript is a review and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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