Gut microbiota: A new therapeutic target for diabetic cardiomyopathy

Suxin Yuan1†, Zhengyao Cai1†, Xingzhao Luan2†, Haibo Wang3, Yi Zhong1, Li Deng4 and Jian Feng1*

1Department of Cardiology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China, 2Department of Neurosurgery, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China, 3Department of Cardiology, Gulin People’s Hospital, Luzhou, Sichuan, China, 4Department of Rheumatology, The Affiliated, Hospital of Southwest Medical University, Luzhou, Sichuan, China

Diabetic cardiomyopathy seriously affects quality of life and even threatens life safety of patients. The pathogenesis of diabetic cardiomyopathy is complex and multifactorial, and it is widely accepted that its mechanisms include oxidative stress, inflammation, insulin resistance, apoptosis, and autophagy. Some studies have shown that gut microbiota plays an important role in cardiovascular diseases. Gut microbiota and its metabolites can affect the development of diabetic cardiomyopathy by regulating oxidative stress, inflammation, insulin resistance, apoptosis, and autophagy. Here, the mechanisms of gut microbiota and its metabolites resulting in diabetic cardiomyopathy are reviewed. Gut microbiota may be a new therapeutic target for diabetic cardiomyopathy.

KEYWORDS diabetic cardiomyopathy, gut microbiota, oxidative stress, inflammation, apoptosis, autophagy

Introduction

Diabetic cardiomyopathy (DCM) refers to the existence of abnormal myocardial structure and performance in individuals with diabetes mellitus (DM) in the absence of other cardiac risk factors such as hypertension, coronary artery disease and significant valvular disease (Jia et al., 2018a). DCM is a pathophysiological condition that is associated with DM and can lead to heart failure (Dillmann, 2019), which is initially characterized by remodeling, myocardial fibrosis, and associated diastolic dysfunction, which is followed by systolic dysfunction, and ultimately by clinical heart failure (Jia et al., 2018a). The pathophysiological factors in patients with diabetes that drive the development of cardiomyopathy include oxidative stress (Tang et al., 2019), insulin resistance, inflammation (Jia et al., 2018a), autophagy (Dewanjee et al., 2021), cell apoptosis (Zhang et al., 2016), and pyroptosis (Shi et al., 2021). Cardiovascular diseases (CVD) are the leading cause of death with DCM among diabetes mellitus regardless previous risks for coronary disease, and the CVD risk of cardiomyopathy is 2–5 times higher than in non-diabetic patients (Kannel et al., 1974). Therefore, it is highly important to find a new target for the treatment of DCM.
Gut microbiota creates a unique ecosystem. It is considered an endocrine organ (Brown and Hazen, 2015). Recent studies have demonstrated that gut microbiota plays a significant role in human health and in diseases such as CVD, atherosclerosis, hypertension, chronic kidney disease, obesity, and type 2 diabetes mellitus (Tang et al., 2017). Interestingly, recent studies have shown that the gut microbiota is closely linked to mechanisms that influence the development of DCM. In this review, the roles of gut microbiota in DCM are discussed and a theoretical basis for the gut microbiota as a new therapeutic target for DCM is provided.

Gut microbiota and its metabolites

The gut microbiota is a complex microbial community in the gut, consisting of 1,014 species of bacteria, viruses, archaea, fungi, and rotifers (Rajilić-Stojanović et al., 2012; Palm et al., 2015). Most of them belong to Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria, and Microflora verrucose families (Koren et al., 2012; Tremaroli and Bäckhed, 2012; Goodrich et al., 2014). Dysregulation of the gut microbiota has been linked to a variety of diseases, such as the metabolic syndrome, atherosclerosis, hypertension, heart failure, chronic kidney disease, obesity, cancer, and diabetes (Bäckhed et al., 2004; Turnbaugh et al., 2006; Jackson and Theiss, 2020). Changes in the composition of gut microbes and their corresponding products, such as lipopolysaccharide (LPS), trimethylamine N-oxide (TMAO), and lactic acid, are associated with risk of diabetes (Yuan et al., 2019). According to Luedde et al. (2017), the microbiome diversity of 20 patients with heart failure and reduced ejection fraction was lower than that of the control group, especially in those with obesity or type 2 diabetes. Reduced diversity of gut microbiota is associated with insulin resistance, dyslipidemia, and inflammatory phenotypes (Le Chatelier et al., 2013). Close attention has been paid to the relationship between cardiovascular diseases (including coronary heart disease, hypertension, and DCM) and gut microbiota in numerous studies. However, findings were inconsistent, gut microbiota has both protective and negative effects on cardiovascular disease. Some studies have shown that the presence of Enterobacteraceae, Ruminococcus gnavus, and Eggerthella lenta increased significantly in the atherosclerosis group compared with the control group, whereas the presence of butyrate-tensteria nestialis and Faecalibacterium prausnitzii decreased significantly (Jie et al., 2017). In heart failure patients, the level of pathogenic bacteria and Candida species (Pasini et al., 2016), increased, and the level of anti-inflammatory bacteria, such as Faecalibacterium prausnitzii, Lact. Fermentum, Lactobacillus Shirota, and F. Prau snitzii decreased.

Cardiac dysfunction is associated with a variety of changes in microbiota and bacterial metabolite secretion (Bastin and Andreelli, 2020). Some gut bacterial metabolites such as short-chain fatty acids (SCFAs) and trimethylamine (TMA)/TMAO (Brown and Hazen, 2015) also play an important role in cardiovascular disease. However, their role in the heart may
be two-sided. On the one hand, TMA plays a role in increasing cardiometabolic risk and is produced from phosphatidylcholine, choline, carnitine, and food through the enzymatic action of the microbiome. TMAO, which has been shown to increase not only the cardiovascular risk, but also the risk of developing cardiac insufficiency, is formed by oxidation of TMA in the liver (Tang et al., 2019). TMAO can induce myocardial hypertrophy and fibrosis in rats with aortic contraction (Li et al., 2019). In addition, TMAO can induce inflammatory responses through SIRT3-SOD2-mtROS (sirtuin-3-superoxide dismutase 2-mitochondrial reactive oxygen species) pathway and nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway (Seldin et al., 2016; Chen et al., 2017). On the other hand, SCFAs have a protective effect on the heart due to anti-inflammatory properties. This can be explained by different effects of bacteria and metabolites on the host. In case of a maladjusted gut microbiota in an organism, the microbiota may induce a series of changes such as abnormal glucose metabolism, oxidative stress, inflammatory response and apoptosis, all of which are important factors causing DCM. (The roles of these bacteria and their metabolites in oxidative stress, inflammatory response, and other mechanisms is elaborated below) (Table 1).

G protein-coupled bile acid receptor 1 (TGR5) is a bile acid (BA) specific receptor, which is part of the G protein coupled receptors family. TGR5 is highly expressed in immune cells and gut tissues, as well as in organs such as heart, liver and kidney. TGR5 can be activated by decoupled and coupled BAs (Baars et al., 2015) (Figure 1). BA is an important component of bile. Primary BAs are converted to secondary BAs by microbiota, and changes in the composition of BA pools also affect the distribution of gut microbiota (Sayin et al., 2013). Thus, gut microbiota and its metabolites can influence BA metabolism. The exact role of TGR5 in BA metabolism remains to be clarified. However, circulating BA levels were reduced in TGR5 KO mice compared with WT mice, suggesting that TGR5 plays a role in BA homeostasis (Li et al., 2011). Deng et al. (2019) have confirmed that activation of the TGR5 has a cardioprotective effect against mice myocardial cell damage induced by high glucose. Therefore, BA metabolism may play an important role in linking TGR5 closely to gut microbiota.

### Oxidative stress

#### Oxidative stress in DCM

Oxidative stress can induce insulin resistance and β-cell dysfunction, which is a potential culprit in diabetes (Zhang et al., 2020). Oxidative stress has been implicated in the pathogenesis and progression of diabetic vascular complications, including CVD, neuropathy, nephropathy, and retinopathy (Rurali et al., 2013) etc. Studies have shown that DCM increases oxidative stress, and oxidative stress can also accelerate the DCM process (Jia et al., 2018b). In addition, sustained hyperglycemia and the signaling pathway involved in β-oxidation is impaired can lead to reactive oxygen species (ROS) overproduction by disrupting mitochondrial function, increasing mitochondrial oxygen consumption, or activating NOX (an evolutionarily conserved ROS-producing enzyme) (Jia et al., 2016; Zhang and Hu, 2020). Increased ROS levels further induce mitochondrial dysfunction and reduce the oxidative capacity of fatty acids, leading to oxidative stress and inflammation in the heart (Jia et al., 2016). Increased oxidative stress and inflammation in the heart leads to cardiac lipid accumulation, fibrosis, diastolic and systolic dysfunction, and resulting heart failure in patients with diabetes (Jia et al., 2018a).

#### Gut microbiota and oxidative stress

It is well known that increased ROS production can induce cardiac mitochondrial dysfunction, and ultimately lead to clinical heart failure in patients with diabetes. Thus, reducing oxidative

### Table 1: The influence of different gut microbiota and related products associated with diabetic cardiomyopathy.

| Gut Microbiota | Positive | Negative |
|----------------|----------|----------|
| Faecalibacterium prausnitzii | Enterobacteraceae |
| Lact. Fermentum | Ruminococcus gnavus |
| Lactobacillus Shirota | Eggerthella lenta |
| Bifidobacterium (BIF) | canisla |
| Bacteroides fragilis (B. fragilis) | Vibrio proteolyticus (VPRH) |
| Short-chain fatty acid (SCFA) | Trimethylamine (TMA) |
| Bile acids (BAs) | Trimethylamine N-oxide (TMAO) |
| Butyrate | Branched chain amino acids (BCAA) |
| Butyric acid | Lipopolysaccharide (LPS) |

---

Yuan et al. 10.3389/fphar.2022.963672
TABLE 2 Summary of findings in clinical, cell and animal studies.

| Mechanisms and diseases | Animal/Clinical/Cell studies | Summary of findings                                                                 | References |
|-------------------------|------------------------------|------------------------------------------------------------------------------------|------------|
| CVD                     | Clinical                     | the CVD risk of cardiomyopathy is 2-5 times higher than in non-diabetic patients    | Kannel et al. (1974) |
| Heart failure           | Clinical                     | The microbiome diversity in those with obesity or type 2 diabetes was lower         | Ludende et al. (2017) |
| Heart failure           | Clinical                     | the level of pathogenic bacteria and Candida species increased, the level of anti-inflammatory bacteria decreased | Pasini et al. (2016) |
| Atherosclerosis         | Clinical                     | Enterobacteraceae, Ruminococcus gravis, and Eggerthella lenta increased, butyrate-tensteria nestalis and Faecalibacterium prausnitzii decreased | Ji et al. (2017) |
| CVD                     | Animal                       | TMAO can induce myocardial hypertrophy and fibrosis in rats with aortic contraction | Li et al. (2019b) |
| Inflammation            | Animal                       | TMAO can induce inflammatory responses through SIRT3-SOD2-mtROS pathway and NF-kB pathway | Chen et al. (2017) |
|                        | Cell                         | circulating BA levels were reduced in TGR5 KO mice, suggesting that TGR5 plays a role in BA homeostasis | Li et al. (2011) |
| DCM                     | Cell                         | TGR5 has a cardioprotective effect against myocardial cell damage induced by high glucose | Deng et al. (2019) |
| Oxidative stress        | Cell                         | physiological levels of oxidative stress can be generated by the gut epithelial lining | Dumitrescu et al. (2018) |
| Autophagy               | Cell                         | PI3K/Akt/mTOR pathway can be significantly attenuated by the exposure of cells to cell-free supernatant of L. Fermen | Kumar et al. (2020) |
| Insulin resistance      | Animal                       | In diet-induced obese mice, supplementation with SCFAs improved insulin resistance and reduced obesity | Perry et al. (2016) |
| Insulin resistance      | Animal                       | butyric-producing bacteria reduced insulin resistance                              | Tolhurst et al. (2012) |
| Inflammation            | Animal                       | Butyrate inhibits proinflammatory factors in gut macrophages by inhibition of histone deactylase | Chang et al. (2014) |
| Inflammation            | Cell                         | inflammation induced by TMAO can lead to endothelial dysfunction in human umbilical vein endothelial cells | Sun et al. (2016) |
| Autophagy               | Cell                         | TMAO can activate the release of the inflammatory cytokines IL-18 and IL-1β         | Yue et al. (2017) |
| Autophagy               | Animal                       | Cardiac dysfunction and abnormalities can cause autophagy injury in diabetic hearts | Xiao et al., 2018; Wu et al., 2020 |
| Autophagy               | Animal                       | Autophagy damage by AMPK suppression can lead to dyslipidemia in the diabetic environment | Zhang et al. (2014) |
| Autophagy               | Cell                         | RIF improved TNF-α-induced autophagy in Caco-2 cells by inhibiting p62 levels and expression of autophagy-related markers | Nie et al. (2020) |
| Autophagy               | Cell                         | SCFAs can induce autophagy in hepatocytes through the UCP2 | Iannucci et al. (2016) |
| Autophagy               | Cell                         | sodium butyrate promoted the decrease of α-synerulin by regulating the autophagy pathway | Qiao et al. (2020) |
| Cell apoptosis          | Cell                         | A long-term hyperglycemic state induces apoptosis by activating caspase apoptosis, which leads to myocardial injury and dysfunction | Wei et al. (2018) |
| Cell apoptosis          | Animal                       | IncRNA MIAT can modulate myocardial cell apoptosis in DCM through miR-22-3p | Zhou et al. (2017) |
| Pyroptosis              | Animal and Cell              | Abnormal pyroptosis of cardiac fibroblasts can induce cardiac dysfunction and collagen deposition, thus aggravating the development of diabetic myocardial fibrosis | Shi et al. (2021) |
| Cell apoptosis          | Animal and Cell              | Bacteroides fragilis (B. fragilis) had a protective effect on the apoptosis of HT29 cells induced by Shiga toxin | Saito et al. (2019) |
| Pyroptosis              | Animal and Cell              | TMAO promotes the pyroptosis of vascular endothelial cells through the production of ROS, which leads to the development of atherosclerosis | Cohen et al. (2020) |
| Pyroptosis              | Cell                         | sodium butyrate has an antiapoptosis effect on glomerular endothelial cells and protects them from damage caused by high glucose | Gu et al. (2019) |
| Oxidative stress        | Cell                         | gut microbiota can reduce myocardial damage by alleviating oxidative stress | Finamore et al. (2018) |
| Insulin resistance      | Animal                       | FMT prevented weight gain, reduced local TNF-α expression in the ileum and ascending colon, and ameliorated insulin resistance in diabetic mice | Bastos et al. (2022) |
| Insulin resistance      | Cell                         | The improvement in peripheral insulin sensitivity of male metabolic syndrome recipients after receiving heterogeneous gut microbiota from lean donors is attributed to an increased diversity in gut microbiota | Vrieze et al. (2012) |
| FMT                     | Clinical                     | a major disadvantage of FMT is that viruses are also transplanted                    | Chehoud et al. (2016) |

Abbreviations: CVD, cardiovascular diseases; SIRT3-SOD2-mtROS, sirtuin-3-superoxide dismutase 2-mitochondrial reactive oxygen species; TMAO, trimethylamineN-oxide; NF-kB, nuclear factor κ-light-chain-enhancer of activated B cells; DCM, diabetic cardiomyopathy; TGR5, G protein-coupled bile acid receptor 1; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; SCFAs, short-chain fatty acids; IL, interleukin; AMPK, AMP-activated protein kinase; RIF, Rifaxidibacterium; UCP2, uncoupling protein 2; MIAT, myocardial infarction associated transcript; IncRNA, long non-coding RNA; ROS, reactive oxygen species; miR, microRNA; FMT, fecal microbiota transplantation.
stress by regulating gut microbiota will be an important mean to treat DCM. The effect of gut microbiota on oxidative stress remains controversial. Recent research shows that physiological levels of oxidative stress can be generated by the gut epithelial lining (Dumitrescu et al., 2018). Gram-negative bacteria could increase lipopolysaccharide (LPS) levels (Lee and Hüttemann, 2014; Mafra et al., 2019), which could produce a large number of ROS, mainly from macrophages and infiltrating neutrophils (Sah et al., 2011). Moreover, Yang and Zhang (2021) proved that TMAO could promote oxidative stress by mediating inositol-requiring enzyme 1α (IRE1α)/X-box binding protein 1 (XBP-1) pathway. However, some researchers have suggested that the gut microbiota can mitigate oxidative stress. For example, a recent report by Kumar et al. (2020) has shown that Lactobacillus fermentum (Lact. fermentum) significantly attenuated hydrogen peroxide (H₂O₂)-induced ROS production in 3T3-L1 preadipocytes. Meanwhile, another study showed that Lactobacillus Shirota can protect gut cell-like epithelial cells from 2, 2′-azobis (2-amidinopropane) dihydrochloride-induced oxidative and inflammatory stress by regulating the expression of antioxidant enzymes (Finamore et al., 2018). This contradiction may be explained by differences in the richness and composition of the gut microbiota. Therefore, the most critical issue is to maintain the ecological stability of gut microbiota and improve the types of beneficial bacteria for the host in gut microbiota, which will be a major breakthrough in the treatment of DCM.

## Insulin resistance

### Impaired insulin metabolism and cardiac insulin resistance in DCM

Impaired insulin metabolic signaling in the heart plays a key role in the pathogenesis of DCM (Jia et al., 2018b). Cardiac insulin signaling regulates intracellular stability by regulating substrate use, protein synthesis, and cell survival (Jia et al., 2018a). In advanced DCM, the PPARγ coactivator 1α (PGC-1α)/AMP-activated protein kinase (AMPK) signaling pathway involved in β-oxidation is impaired, leading to further mitochondrial dysfunction (Jia et al., 2016). In skeletal muscle, liver, and adipose and heart tissues, glucose transport is mediated by the glucose transporter 4 (GLUT4) (Jia et al., 2016). Under normal physiological conditions, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt; also called Akt) signaling pathway stimulates the translocation of GLUT4 to the membrane in cardiomyocytes, resulting in glucose uptake of cells in the heart (Jia et al., 2016). In addition, cardiac insulin receptor knockout models showed reduced cardiac glucose uptake, induced mitochondrial dysfunction, and increased cardiac ROS production. In case of dual knockout of insulin receptor substrate-1/2 (IRS-1/2), the ATP content in cardiomyocytes was reduced, cardiomyocyte contractility and function were impaired, and the incidence of fibrosis and heart failure was increased (Bugger et al., 2012; Qi et al., 2013). When the PI3K/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway is activated by insulin signaling, not only protein synthesis is stimulated, but autophagy is also inhibited (Figure 2), which could accelerate the DCM process (Mizushima, 2005; Meijer and Codogno, 2006).

## Gut microbiota and cardiac insulin resistance

A healthy gut microbiota can decrease insulin resistance (Saad et al., 2016). It has been suggested that the response of bacterial SCFAs production levels to nutrient-lipid intake plays a key role in the gut microbiota’s ability to regulate energy balance and metabolism (Kimura et al., 2013; Cani, 2014). Moreover, it was shown that an altered intestinal barrier and a dysregulated gut microbiota cause increased levels of branched chain amino acids (BCAA), secondary Bas, and LPS production, all of which can result in insulin resistance (Saad et al., 2016).

In diet-induced obese mice, supplementation with SCFAs improved insulin resistance and reduced obesity (Perry et al., 2016). In other animal studies, butyric-producing bacteria, such as F. Praunzsi, induces colon L cells to secrete glucagon-like peptide 1 (GLP-1) via discrete sampling of the free fatty acid receptor 2 (FFAR2), resulting in reduced insulin resistance (Tolhurst et al., 2012; Christiansen et al., 2018). BAs-induced activation of TGR5 promotes the release of GLP-1 by intestinal cells and indirectly affects the secretion of insulin by pancreatic β-cells, thereby affecting insulin sensitivity (Duboc et al., 2014). Therefore, TGR5 may be an important target to offset insulin resistance and reduce damage caused by diabetes.

## Inflammation

It is generally accepted that an inflammatory response accelerates the development of DCM. The Nucleotide-binding oligomerization domain-like receptor pyrin domains-containing 3 (NLRP3) inflammasome, a new molecular marker of DCM, is activated by impaired insulin metabolic signaling, high FFA levels, and hyperglycemia (Pal et al., 2017). Upon NLRP3 activation, increased migration of monocytes/macrophages through the coronary endothelium occurs, resulting in an increased number of resident cardiac macrophages. When ROS is increased and bioavailable nitric oxide (NO) is reduced, monocytes/macrophages can be polarized into the proinflammatory M1 phenotype (Jia et al., 2016). In a recent study, it was shown that the anti-inflammatory response of M2 macrophages is repressed, whereas the pro-inflammatory polarization of M1 macrophages is upregulated in diabetic heart tissues (Figure 3) (Jia et al., 2015).
Recently, Bartolomaeus et al. (2019) confirmed the anti-inflammatory effects of SCFAs. SCFAs are produced by the fermentation of fibers in the colon and include three main products, namely, propionate, acetate, and butyrate (Chang et al., 2014). Butyrate inhibits proinflammatory factors in gut macrophages, including interleukin-6, interleukin-12, and NO.
by inhibition of histone deacetylase (HDAC) (Chang et al., 2014). Besides, propionate has been shown to significantly reduce cardiovascular damage by reducing the number of T-helper 17 cells and effector memory T cells (Bartolomaeus et al., 2019).

However, gut microbiota and its bacterial products not only have anti-inflammatory effects, but also pro-inflammatory effects. For example, Sun et al. (2016) suggested that inflammation induced by TMAO can lead to endothelial dysfunction in human umbilical vein endothelial cells through activation of the inflammasome ROS- thioredoxin interacting protein (TXNIP)-NLRP3. According to Yue et al. (2017), TMAO can activate the release of the inflammatory cytokines interleukin (IL)-18 and IL-1β in the NLRP3 inflammation. TMAO markedly increased inflammatory markers, such as ICAM1, IL-6, E-selectin, and cyclooxygenase-2 (COX-2), through activation of the mitogen-activated protein kinase (MAPK) and NF-κB signaling pathways, which then led to vascular inflammation (Seldin et al., 2016). This contradiction may be explained by differences in composition of gut microbiota. It is generally accepted that the inflammatory response is an important pathogenic mechanism of DCM. Together, the data indicate that interfering with the composition of the gut microbiota to increase the number of anti-inflammatory bacteria may result in new ways to treat DCM.

**Autophagy**

Autophagy is a highly conserved catabolic process that involves the malfunction of proteins, degradation of long-lived proteins, and injury of organelles through the actions of lysosomes (Li et al., 2016). Autophagy occurs in many cells of the cardiovascular system, including vascular smooth muscle cells, myocytes, macrophages, fibroblasts, and endothelial cells (Lavandero et al., 2015). In preclinical trials, autophagy disorders have been observed in diabetic hearts (Kobayashi and Liang, 2015; Jia et al., 2018a). Interestingly, autophagy has two-sided effects. Several investigators have revealed the pathogenic and protective role of autophagy in patients with DCM in type 1 and type 2 diabetes (Dewanjee et al., 2021). This contradiction may be explained by differences in the degree of autophagy. On the one hand, Autophagy is an adaptive protective response of cardiomyocytes to cellular stresses including hyperglycemia, hyperlipidemia, malnutrition, hypoxia, and redox stress (Mellor et al., 2011; Chen et al., 2020). Autophagy also could help restore plasticity in the heart (Lavandero et al., 2015). Besides, autophagy can enhance the antioxidant capacity of cells by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) (Wible and Bratton, 2018). On the other hand, autophagy damage can lead to heart damage (Orogo and Gustafsson Å, 2015). Cardiac dysfunction and abnormalities can cause autophagy injury in diabetic hearts (Xiao et al., 2018; Wu et al., 2020). Autophagy damage by AMP-activated protein kinase (AMPK) suppression can lead to dyslipidemia in the diabetic environment (Zhang et al., 2014), and dyslipidemia can further inhibit cardiac autophagy by enhancing mechanistic target of rapamycin kinase (mTOR) signaling of cardiomyocytes (Glazer et al., 2009). In addition, the myocardial inflammation in diabetic heart can also occur and establish by damaging cardiac autophagy (Zhang et al., 2016). Lavandero et al. (2015) suggested that autophagy hyperactivation may be a cause of heart failure. Autophagy overactivation in the diabetic heart can lead to self-digestion and enhanced ROS production, which are potential contributors to DCM (Xu et al., 2019). Thus, both inhibition and overactivation of cardiac autophagy can have pathological effects on DCM.

Different scholars have different views on the role of gut microbiota in regulating autophagy. Nie et al. (2020) showed that Bifidobacterium (BIF) ameliorated tumor necrosis factor alpha (TNF-α)-induced autophagy in colorectal adenocarcinoma cell line (Caco-2) cells by inhibiting p62 levels and expression of autophagy-related markers such as microtubule-associated protein 1 light chain 3- II (LC3II) and Beclin1. Lannucci and colleagues have shown that SCFAs can induce autophagy in hepatocytes through the uncoupling protein 2 (UCP2) (Lannucci et al., 2016). Furthermore, sodium butyrate promoted the decrease of α-synuclein both by inhibiting the autophagy pathway of PI3K/Akt/mTOR and enhancing autophagy-mediated by autophagy-related gene 5 (Atg5) (Qiao et al., 2020). Thus, different bacteria in the gut microbiota have different roles in regulating autophagy.

Combining all, with the emergence of new findings, autophagy has been regarded as a crucial player in regulating DCM. It is well known that gut microbiota can regulate the degree of autophagy through PI3K/Akt/mTOR pathway (Qiao et al., 2020). In addition, PI3K/Akt/mTOR pathway plays an important role in the regulation of autophagy in DCM (Zhao et al., 2020). Therefore, the PI3K/Akt/mTOR pathway may be an important bridge between gut microbiota and DCM in autophagy. In addition, different kinds of bacteria in the gut microbiota also have different effects on autophagy, if we can adjust the gut microbiota to maintain autophagy in a favorable state for the body, it will bring benefits to patients with DCM. However, at present, there is no method to detect the autophagy state in the human heart (Dewanjee et al., 2021). Therefore, in order to find more treatments for DCM, it is very urgent for us to find a way to monitor the exact state of autophagy regulated by bacteria.

**Cell apoptosis and pyroptosis**

**Cell apoptosis in DCM**

A long-term hyperglycemic state in diabetic patients induces apoptosis by activating caspase apoptosis, which
leads to myocardial injury and dysfunction (Wei et al., 2018). It has been shown that long non-coding RNA (lncRNA) can modulate functions in DCM (Yang et al., 2018b; Pant et al., 2018). For example, Zhou et al. (2017) have shown that lncRNA myocardial infarction associated transcript (MIAT) can modulate myocardial cell apoptosis in DCM through microRNA (miR)-22-3p. Also, the modulation of the growth arrest-specific 5 (Gas5)/miR-320-3p/transcription factor 3 (Tcf3) pathway in nuclear management coactivator (NMC) and nuclear receptor coactivator (NRC) apoptosis was detected. Moreover, it was demonstrated that Tcf3-activated lncRNA Gas5 modulated the apoptosis of NMC in DCM (Su et al., 2020). However, to date, there is no reported explanation for the low rate of apoptosis in patients with late-stage diabetes and severe cardiac dysfunction (Gu et al., 2018), which needs more experiments to explore it.

**Pyroptosis in DCM**

Pyroptosis is defined as programmed cell death associated with inflammation, and characterized by pore formation, cell swelling and destruction of the plasma membrane (Wan et al., 2020). Pyroptosis plays a role in the process of DCM (Yang et al., 2018a). Abnormal pyroptosis of cardiac fibroblasts can induce cardiac dysfunction and collagen deposition, thus aggravating the development of diabetic myocardial fibrosis (Shi et al., 2021). Shi et al. (2021) demonstrated that miR-21–3p can promote myocardial fibroblasts pyroptosis induced by high glucose (HG) via enhancing NLRP3 and caspase-1 expression. Recently, another data have shown that the regulation of miRs plays an important role in cell pyroptosis and fibrosis (Li et al., 2019), which bearing out Shi et al. (2021)’s research.

**Gut microbiota affects the development of DCM by regulating apoptosis and pyroptosis**

Apoptosis is one of the most studied type of programmed cell death. It is characterized by the formation of unique apoptotic bodies. It is common in patients with heart failure, myocardial infarction and other vascular damage (Zhou et al., 2020). According to the study of Saito et al. (2019), *Bacteroides fragilis* (B. fragilis) had a protective effect on the apoptosis of HT29 cells induced by Shiga toxin. However, gut microbiota also has pro-apoptotic effects. Nie et al. (2020) showed that BIF improved TNF-α-induced apoptosis of Caco-2 cells. Li and Elsasser (2005) suggested that butyric acid induced apoptosis and cell cycle arrest in renal epithelial cells.

Pyrodeath, characterized by cell swelling, the release of cytokines, and damage to subcellular organelles, is a type of pro-inflammatory cell death (Liu et al., 2019). Data have shown that TMAO promotes the pyroptosis of vascular endothelial cells through the production of ROS, which leads to the development of atherosclerosis (Cohen et al., 2020). According to the study of Cohen et al. (2020) the gram-negative bacteria *Vibrio proteolyticus* (VPRH) from the gut tract of borers induced pyroptosis by activating the NLRP3 inflammasome and caspase-1, resulting in the secretion of IL-1β. By contrast, another study demonstrated that sodium butyrate has an antipyroptosis effect on glomerular endothelial cells and protects them from damage caused by high glucose (Gu et al., 2019).

In summary, gut microbiota has apoptosis, anti-apoptosis, pyroptosis, and anti-pyroptosis effects in host cells. The role of bacterial metabolites of gut microbiota in apoptosis and pyroptosis is still controversial. This controversy may be explained by differences in the composition and species of gut microbiota and its metabolites.

**Gut microbiota and the level of calcium ions**

High glucose levels increase Ca²⁺ levels in cardiac myocytes (Cheng et al., 2019). Calcium ions are the key regulator of cardiac hypertrophy; the Ca²⁺-calcineurin-nuclear factor of activated T cells (NFAT) cascade is the main pathway resulting in cardiac hypertrophy (Fiedler and Wollert, 2004). Gut microbiota are the primary source of SCFAs in the plasma (Vinolo et al., 2011). SCFA can regulate the contraction of airway smooth muscle by regulating calcium channels (Mizuta et al., 2020). Gut microbiota and its metabolites can affect the development of pyroptosis, oxidative stress, inflammation, insulin resistance, and autophagy in the host through the regulation TGR5, BA metabolism, and the PI3K/Akt/mTOR, ROS- TXNIP-NLRP3, and MAPK-NF-κB pathways, among others. Therefore, gut microbiota can affect the development of DCM (Figure 4).

**The therapeutic prospect of DCM**

The pathogenesis of DCM is various, and it is generally believed that oxidative stress, inflammation, insulin resistance, cell apoptosis and autophagy are closely related to DCM. In recent years, a large number of scholars have found some new methods to prevent and treat DCM by targeting these mechanisms. For example, Gu et al. (2018) have experimentally confirmed that inhibition of p53 could prevent DCM by preventing early-stage apoptosis. At present, gut microbiota has been applied to some clinical diseases, such as inflammatory bowel disease (IBD), obesity and some other
metabolic diseases (Patterson et al., 2016). The widespread use of probiotics in clinical practice is a good proof. Interestingly, numerous studies have found that the gut microbiota is associated with the pathogenesis of DCM. However, up to now, the role of gut microbiota in DCM is still controversial. Some scholars believe that gut microbiota can reduce myocardial damage in patients with DM by alleviating oxidative stress (Finamore et al., 2018), while others think that gut microbiota can also increase the harmful risk to DCM via increasing inflammatory response and insulin resistance (Sun et al., 2016). The contradiction of the two-sided effects of the gut microbiota can mainly be explained by the difference of the bacterial species present in the gut microbiota. It might be possible to reduce oxidative stress, inflammation response, insulin resistance and maintain appropriate levels of autophagy by intervening with the composition of the gut microbiota to increase the species richness of the bacterias which are beneficial for the host in gut microbiota, thereby reducing diabetic myocardial injury. However, it is very difficult for us to intervene with the composition of gut microbiota due to the limited technology available. If we can solve this thorny problem, it will bring a major breakthrough in the treatment of DCM in the future.

Fortunately, there are possibly three ways to modify the composition of the gut microbiota to treat DCM. First, dietary interventions are a good therapeutic option. Experimental studies have shown that dietary modifications for 5 days (short term) can change the number of bacteria in and species of gut microbiota (David et al., 2014). Second, probiotics may be used for the clinical treatment of DCM in the future. Probiotic bacteria mainly derive from the genera Bifidobacterium and Lactobacillus. Probiotics supplementation has been found to restore the gut microbiota after it had been disrupted. Besides, probiotics supplementation induces changes in the composition of undisrupted gut microbiota. Recent evidence suggests that probiotics affect BA metabolism by altering the microbiota (Baars et al., 2015). Therefore, the probiotics may reduce myocardial injury in DCM by affecting BA metabolism, thereby activating TGR5 expression. Third, fecal microbiota transplantation (FMT) may be a future treatment. FMT is a treatment for patients with gut microecological imbalance. Bacteria or metabolites are introduced from donor feces to the diseased recipient (Cammarota et al., 2014). Bastos et al. (2022) showed that FMT is a safe treatment, they found that FMT prevented weight gain, reduced local TNF-α expression in the ileum and ascending colon, and ameliorated insulin resistance in diabetic mice. The improvement in peripheral insulin sensitivity of male metabolic syndrome recipients after receiving heterogenous gut microbiota from lean donors is attributed to an increased diversity in gut microbiota, including those associated with butyrate production (Vrieze et al., 2012). FMT alone is not sufficient to control glycemic levels effectively. Thus, the regulation of gut microbiota should be combined with other established classical therapies, which can obtain better metabolic parameters (Vallianou et al., 2019; Zhang and Hu, 2020). However, the effectiveness of FMT is challenged by several factors, such as delivery route, number of transplants, fecal volume per sample, disease burden, and target impact (Napolitano and Covasa, 2020). Therefore, FMT is highly difficult to implement and its possibility of success is low. Besides, a major disadvantage of FMT is that viruses are also transplanted (Chehoud et al., 2016) (Table 2). The problem of the...
balance between the advantages and disadvantages of FMT treatment is still unsolved. In the future, there will be more treatments for DCM by regulating the gut microbiota.

Conclusion

DCM has a serious impact on people’s quality of life, and even threatens lives of patients. Therefore, it is very important to find new therapeutic targets to treat DCM. The pathogenesis of DCM is complex and diverse. It is generally accepted that the mechanisms include oxidative stress, inflammation, insulin resistance, and cell apoptosis. In recent years, it has been suggested that the development of DCM is closely related to autophagy and cell pyroptosis.

The gut microbiota has become topic of interest in research. Some studies have shown that gut microbiota plays an important role in cardiovascular disease. However, the role of gut microbiota in DCM may be two-sided. On the one side, some bacteria can reduce myocardial damage by reducing the oxidative stress response. This contradiction can mainly be explained by the difference in the composition of gut microbiota in patients. Therefore, finding an effective way to intervene with the composition of gut microbiota and regulate the metabolism of gut microbes will be a major breakthrough in the clinical treatment of DCM.

Author contributions

SY, ZC, XL, and JF created the contents of this review article. XL, HW, and YZ conducted the initial search of studies and prepared the figures. SY drafted the manuscript. LD and JF revised the manuscript. All authors read and approved the final manuscript.

References

Baars, A., Oosting, A., Kool, J., Garssen, J., and Van Bergenhenegouwen, J. (2015). The gut microbiota as a therapeutic target in IB and metabolic disease: A role for the bile acid receptors FXR and TGR5. Microorganisms 3, 641–666. doi:10.3390/microorganisms3040641

Backhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., et al. (2004). The gut microbiota as an environmental factor that regulates fat storage. Proc. Natl. Acad. Sci. U. S. A. 101, 15718–15723. doi:10.1073/pnas.0407061101

Bartolomaeus, H., Balogh, A., Yakoub, M., Homann, S., Markó, L., Hőges, S., et al. (2019). Short-chain fatty acid propionate protects from hypertensive cardiovascular damage. Circulation 139, 1407–1421. doi:10.1161/circulationa118.0363652

Bastin, M., and Andreadelli, F. (2020). The gut microbiota and diabetic cardiomyopathy in humans. Diabetes Metab. 46, 197–202. doi:10.1016/j.diabet.2019.10.003

Bastos, R. M. C., Simplício-Filho, A., Sávio-Silva, C., Oliveira, L. F. V., Cruz, G. N. F., Sousa, E. H., et al. (2022). Fecal microbiota transplant in a pre-clinical model of type 2 diabetes mellitus, obesity and diabetic kidney disease. Int. J. Mol. Sci. 23, 3842. doi:10.3390/ijms23073842

Brown, J. M., and Hazen, S. L. (2015). The gut microbiota endocrine organ: bacterially derived signals driving cardiometabolic diseases. Annu. Rev. Med. 66, 343–359. doi:10.1146/annurev-med-060513-093205

Bugger, H., Riehle, C., Jaisly, B., Wende, A. R., Tuines, J., Chen, D., et al. (2012). Genetic loss of insulin receptors worsens cardiac efficiency in diabetes. J. Mol. Cell. Cardiol. 52, 1019–1026. doi:10.1016/j.yjmcc.2012.02.001

Cammarota, G., Janiro, G., and Gubarriini, A. (2014). Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. J. Clin. Gastroenterol. 48, 693–702. doi:10.1097/mcg.0000000000000046

Cani, P. D. (2014). Metabolism in 2013: The gut microbiota manages host metabolism. Nat. Rev. Endocrinol. 10, 74–76. doi:10.1038/nrendo.2013.240

Chang, P. V., Hao, L., Offermanns, S., and Medzhitov, R. (2014). The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc. Natl. Acad. Sci. U. S. A. 111, 2247–2252. doi:10.1073/pnas.1322269111

Chehoud, C., Dryga, A., Hwang, Y., Nagy-Szakal, D., Hollister, E. B., Luna, R. A., et al. (2016). Transfer of viral communities between human individuals during fecal microbiota transplantation. mBio 7, e00322. doi:10.1128/mBio.00322-16

Funding

This research was funded by the Key Laboratory of Medical Electrophysiology (KeyME-KeyME-2020-004), the Collaborative Innovation Center for Prevention and Treatment of Cardiovascular Disease of Sichuan Province (xtcx2019-13), the Luzhou Municipal People’s Government - Southwest Medical University Science and Technology Strategic Cooperation (2021LZXNYD-J33), and the Southwest Medical University, Teaching reform project of Southwest Medical University (2020XSJG-C01-19).

Acknowledgments

We thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
TGR5 activation ameliorates hyperglycemia-induced cardiac hypertrophy in female mice. Nutr. Metab. 22, 1751.2020.1720526

NLRP3 in fl/fl mice, and Holst, J. J. (2018). The impact of short-chain fatty acids on GLP-1 and PYY secretion from the isolated perfused rat colon. Am. J. Physiol. Gastrointest. Liver Physiol. 315, G53–g65. doi:10.1152/ajpgi.00346.2017

Cohen, H., Baram, N., Edry-Bozler, L., Munitz, A., Salomon, D., and Gerlic, M. (2020). Vibrio pore-forming leucosin activates pyroptotic cell death via NLRP3 inflammasome. Emeg. Microbes Infect. 9, 279–290. doi:10.1016/j.emiqin.2020.1720526

David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E., Wolfe, B. E., et al. (2014). Diet rapidly and reproducibly alters the human gut microbiome. Nature 505, 559–563. doi:10.1038/nature12820

Deng, L., Chen, X., Zhong, Y., Wen, X., Cai, Y., Li, J., et al. (2019). Activation of TGR5 partially alleviates high glucose-induced cardiomyocyte injury by inhibition of inflammatory responses and oxidative stress. Oxid. Med. Cell Longev. 2019, 4372786. doi:10.1155/2019/4372786

Dewanjee, S., Vallamkondu, J., Kalra, R. S., John, A., Reddy, P. H., and Kandimalla, R. (2021). Autophagy in the diabetic heart: A potential pharmacotherapeutic target in diabetic cardiomyopathy. Aging Res. Rev. 68, 101338. doi:10.1016/j.aging.2021.101338

Dillmann, W. H. (2019). Diabetic cardiomyopathy. Circ. Res. 124, 1160–1162. doi:10.1161/circresaha.118.314665

Duboc, H., Tachié, Y., and Hofmann, A. F. (2014). The bile acid TGR5 membrane receptor: from basic research to clinical application. Dig. Liver Dis. 46, 302–310. doi:10.1016/j.dld.2013.10.021

Dumitrascu, L., Popescu-Olaru, I., Corma, L., Tulb, B., Minec, M. E., Ceafalan, L. C., et al. (2018). Oxidative stress and the microbiota-gut brain axis. Oxid. Med. Cell Longev. 2018, 2406594. doi:10.1155/2018/2406594

Fiedler, B., and Wollert, K. C. (2004). Interference of anthracyclic molecules and signaling pathways with the Ca2+-calcineurin-NFAT cascade in cardiac myocytes. Cardiovasc. Res. 63, 450–457. doi:10.1016/j.cardiores.2004.04.002

Finamore, A., Ambra, R., Nobili, F., Grazugiu, I., Raguzzini, A., and Serapino, M. (2018). Roles of Rickettsia species in the gut microbiota and human health. Front. Immunol. 9, 1313. doi:10.3389/fimmu.2018.01131

Glazer, H. P., Osipov, R. M., Clements, R. T., Sellke, F. W., and Bianchi, C. (2009). Hypercholesterolemia is associated with hyperactive cardiac mTORC1 and mTORC2 signaling. Cell Cycle 8, 1738–1746. doi:10.4161/cc.8.11.8619

Goodrich, J. K., Waters, J. L., Poole, A. C., Sutter, J. L., Koren, O., Blekhman, R., et al. (2015). The robustness of human gut microbiome correlates with metabolic markers. Nature 500, 541–546. doi:10.1038/nature12506

Lee, I., and Hüttemann, M. (2014). Energy crisis: the role of oxidative phosphorylation in acute inflammation and sepsis. Biochim. Biophys. Acta 1842, 1579–1586. doi:10.1016/j.bbadis.2014.05.031

Li, C. J., and Elsasser, T. H. (2005). Butyrate-induced apoptosis and cell cycle arrest in bovine kidney epithelial cells: involvement of caspase and proteasome pathways. J. Anim. Sci. 83, 89–97. doi:10.2527/2005.83189X

Li, J., Xue, J., Wang, D., Dai, X., Sun, Q., Xiao, T., et al. (2019a). Regulation of gasdermin D by miR-379-5p is involved in aseptically induced activation of hepatic stellate cells and in fibrosis via secretion of IL-1β from human hepatic cells. Metallomics. 11, 483–495. doi:10.1039/crt00321a

Li, L., Xu, J., He, L., Peng, L., Zhong, Q., Chen, L., et al. (2016). The role of autophagy in cardiac hypertrophy. Acta Biochim. Biophys. Sin. 48, 491–500. doi:10.1093/abbs/gmw025

Li, T., Holmstrom, S. R., Kir, S., Umetani, M., Schmidt, D. R., Kliewer, S. A., et al. (2011). The G protein-coupled bile acid receptor, TGR5, stimulates gallbladder filling. Mol. Endocrinol. 25, 1066–1071. doi:10.1210/me.2010-0460

Li, Z., Wu, Z., Yan, J., Liu, H., Liu, Q., Deng, Y., et al. (2019b). Gut microbe-derived metabolite trimethylamine N-oxide induces cardiac hypertrophy and fibrosis. Lab. Invest. 99, 346–357. doi:10.1038/s41374-018-0099-y

Liu, J., Wang, Y., Meng, H., Yu, L., Li, H., Li, W., et al. (2019). Butyrate rather than LPS subverts gingival epithelial homeostasis by downregulation of intercellular junctions and triggering pyroptosis. J. Clin. Periodontol. 46, 894–907. doi:10.1111/jcpe.13182

Luedde, M., Winkler, T., Heinzen, F. A., Rühlmann, C. M., Spehlmann, M. E., Bajrovic, A., et al. (2017). Heart failure is associated with depletion of core intestinal microbiota. ESC Heart Fail. 4, 282–290. doi:10.1002/ehf2.12155

Mafra, D., Borges, N. A., Lindholm, B., and Stenvinkel, P. (2019). Mitochondrial dysfunction and gut microbiota imbalance. An intriguing relationship in chronic kidney disease. Mitochondrion 47, 206–209. doi:10.1016/j.mito.2018.11.006

Meijer, A. J., and Codogno, P. (2006). Signalling and autophagy regulation in health, aging and disease. Mol. Asp. Med. 27, 411–425. doi:10.1016/j.mam.2006.08.002

Mellor, K. M., Bell, J. R., Young, M. J., Ritchie, R. H., and Delbridge, L. M. (2011). Myocardial autophagy activation and suppressed survival signaling is associated with insulin resistance in fructose-fed mice. J. Mol. Cell. Cardiol. 50, 1035–1043. doi:10.1016/j.yjmcc.2011.03.002
Su, D., Ju, Y., Han, W., Yang, Y., Wang, F., Wang, T., et al. (2020). TcF3-activated lncRNA Ga5 regulates newborn mouse cardiomyocyte apoptosis in diabetic cardiomyopathy. *J. Cell. Biochem.* 121, 4337–4346. doi:10.1002/jcb.29630

Sun, X., Juo, X., Ma, Y., Liu, Y., Zhang, L., Hu, Y., et al. (2016). Trimethylamine N-oxide induces inflammation and endothelial dysfunction in human umbilical vein endothelial cells via activating ROS-TXNIP-NLRP3 inflammasome. *Biochem. Biophys. Res. Commun.* 481, 63–70. doi:10.1016/j.bbrc.2016.11.017

Tang, S.-G., Liu, X.-Y., Wang, S.-P., Wang, H.-H., Jovanovic, A., and Tan, W. (2018b). Trimethylamine prevents diabetic cardiomyopathy by inhibiting Nrf2/TrPC3-induced oxidative stress. *J. Pharmacol. Sci.* 131, 311–318. doi:10.1016/j.jpfs.2019.01.016

Tang, W. H., Kita, T., and Hazen, S. L. (2017). Gut microbiota in cardiovascular health and disease. *Circ. Res.* 120, 1183–1196. doi:10.1161/circresaha.117.309715

Tang, W. H. W., Li, D. Y., and Hazen, S. L. (2018b). Dietary metabolism, the gut microbiome, and heart failure. *Nat. Rev. Cardiol.* 15, 137–154. doi:10.1038/nrcardio.2018.0108-7

Tollhurst, G., Heffern, H., Lam, Y. S., Parker, H. E., Habib, A. M., Diakogiannaki, E., et al. (2012). Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 61, 364–371. doi:10.2337/db11-1019

Tremeraroli, V., and Baché, F. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature* 489, 242–249. doi:10.1038/nature11552

Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., and Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444, 1027–1031. doi:10.1038/nature05141

Vallianos, N. G., Stratigos, T., and Tzagarakis, S. (2019). Metformin and gut microbiota: their interactions and their impact on diabetes. *Horm. (Athens)* 18, 141–148. doi:10.1414/s42000-019-00093-w

Vinolo, M. A., Rodrigues, H. G., Nachar, R. T., and Curi, R. (2011). Regulation of inflammation by short chain fatty acids. *Nutrients* 3, 858–876. doi:10.3390/nu3308386

Vrieze, A., Van Nood, E., Holleman, F., Salojirvi, J., Koeste, R. S., Battelman, J. F., et al. (2012). Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 143, 913–916. doi:10.1053/j.gastro.2012.06.031

Wan, P., Su, W., Zhang, Y., Li, Z., Deng, C., Li, J., et al. (2020). LncRNA H19 initiates microglial pyroptosis and neuronal death in retinal ischemia/reperfusion injury. *Cell Death Differ.* 27, 176–191. doi:10.1038/s41419-018-0551-4

Wei, X., Yang, X., Jiang, Y. J., Lei, J. M., Guo, W. J., and Xiao, H. (2018). Relaxin ameliorates high glucose-induced cardiomyocyte hypertrophy and apoptosis via the Notch1 pathway. *Exp. Ther. Med.* 15, 691–698. doi:10.3892/etm.2017.5448

Wiblé, D. J., and Bratton, S. B. (2018). Reciprocity in ROS and autophagic signaling. *Curr. Opin. Toxicol.* 7, 28–36. doi:10.1016/j.cotox.2017.10.006

Wu, Q., Liu, C., Cai, Z., Xie, Q., Hu, T., Duan, M., et al. (2020). High-mobility group AT-hook 1 dipeptide promotes cardiac dysfunction in diabetic cardiomyopathy via autophagy inhibition. *Cell Death Dis.* 11, 160. doi:10.1038/s41419-020-2316-4

Xiao, Y., Wu, Q. Q., Duan, M. X., Liu, C., Yuan, Y., Yang, Z., et al. (2018). TAKIP1 overexpression attenuates cardiac dysfunction and remodeling in STZ-induced diabetic cardiomyopathy in mice by regulating autophagy. *Biochim. Biophys. Acta. Mol. Basis Dis.* 1864, 1728–1743. doi:10.1016/j.bbadis.2018.02.012

Xu, T., Ding, W., Li, X., Ao, X., Liu, Y., Yu, W., et al. (2019). Oxidative stress in cell death and cardiovascular diseases. *Oxid. Med. Cell. Longev.* 2019, 9030563. doi:10.1155/2019/9030563

Yang, F., Qin, Y., Lv, J., Wang, Y., Che, H., Chen, X., et al. (2018a). Silencing long non-coding RNA KCNQ1OT1 alleviates pyroptosis and fibrosis in diabetic cardiomyopathy. *Cell Death Dis.* 9, 1000. doi:10.1038/s41419-018-0129-4

Yang, F., Qin, Y., Wang, Y., Li, A., Lv, J., Sun, X., et al. (2018b). LncRNA KCNQ1OT1 mediates pyroptosis in diabetic cardiomyopathy. *Cell Physiol. Biochem.* 50, 1230–1244. doi:10.1155/2019/9030563

Yang, G., and Zhang, X. (2021). TMAO promotes apoptosis and oxidative stress of pancreatic acinar cells by mediating IRE1α-XBP1 pathway. *Saudi J. Gastroenterol.* 27, 361–369. doi:10.4103/sjg.jg.12_21

Yuan, T., Yang, Y., Chen, H., Fu, D., Hu, Y., Wang, J., et al. (2019). New insights into oxidative stress and inflammation during diabetes mellitus–accelerated atherosclerosis. *Redox Biol.* 20, 247–260. doi:10.1016/j.redox.2018.09.025

Yue, C., Yang, X., Li, J., Chen, X., Zhao, X., Chen, Y., et al. (2017). Trimethylamine N-oxide prime NLRP3 inflammasome via inhibiting ATG16L1-induced autophagy
in colonic epithelial cells. *Biochem. Biophys. Res. Commun.* 490, 541–551. doi:10.1016/j.bbrc.2017.06.075

Zhang, J., Cheng, Y., Gu, J., Wang, S., Zhou, S., Wang, Y., et al. (2016). Fenofibrate increases cardiac autophagy via FGF21/SIRT1 and prevents fibrosis and inflammation in the hearts of Type 1 diabetic mice. *Clin. Sci.* 130, 625–641. doi:10.1042/cs20150823

Zhang, L., Ding, W. Y., Wang, Z. H., Tang, M. X., Wang, F., Li, Y., et al. (2016). Early administration of trimetazidine attenuates diabetic cardiomyopathy in rats by alleviating fibrosis, reducing apoptosis and enhancing autophagy. *J. Transl. Med.* 14, 109. doi:10.1186/s12967-016-0849-1

Zhang, P., Li, T., Wu, X., Nice, E. C., Huang, C., and Zhang, Y. (2020). Oxidative stress and diabetes: antioxidative strategies. *Front. Med.* 14, 583–600. doi:10.1007/s11684-019-0729-1

Zhang, Q., and Hu, N. (2020). Effects of metformin on the gut microbiota in obesity and type 2 diabetes mellitus. *Diabetes Metab. Syndr.* 13, 5083–5014. doi:10.2147/dmso.S286430

Zhang, Z., Wang, S., Zhou, S., Yan, X., Wang, Y., Chen, J., et al. (2014). Sulforaphane prevents the development of cardiomyopathy in type 2 diabetic mice probably by reversing oxidative stress-induced inhibition of LKB1/AMPK pathway. *J. Mol. Cell. Cardiol.* 77, 42–52. doi:10.1016/j.yjcc.2014.09.022

Zhao, G., Zhang, X., Wang, H., and Chen, Z. (2020). Beta carotene protects H9c2 cardiomyocytes from advanced glycation end product-induced endoplasmic reticulum stress, apoptosis, and autophagy via the PI3K/Akt/mTOR signaling pathway. *Ann. Transl. Med.* 8, 647. doi:10.21037/atm-20-3768

Zhou, W., Cheng, Y., Zhu, P., Nasser, M. I., Zhang, X., and Zhao, M. (2020). Implication of gut microbiota in cardiovascular diseases. *Oxid. Med. Cell. Longev.* 2020, 5394096. doi:10.1155/2020/5394096

Zhou, X., Zhang, W., Jin, M., Chen, J., Xu, W., and Kong, X. (2017). IncRNA MIAT functions as a competing endogenous RNA to upregulate DAPK2 by sponging miR-22-3p in diabetic cardiomyopathy. *Cell Death Dis.* 8, e2929. doi:10.1038/cddis.2017.321