The incidence and prevalence of diabetes mellitus are each increasing rapidly in our society. The majority of patients with diabetes succumb ultimately to heart disease, much of which stems from atherosclerotic disease and hypertension. However, cardiomyopathy can develop independent of elevated blood pressure or coronary artery disease, a process termed diabetic cardiomyopathy. This disorder is a complex diabetes-associated process characterized by significant changes in the physiology, structure, and mechanical function of the heart. Here, we review recently derived insights into mechanisms and molecular events involved in the pathogenesis of diabetic cardiomyopathy.

Introduction
Heart disease is rampant in the developed world, and the epidemic is spreading rapidly around the globe [1]. Numerous events contribute to the rise in heart disease, but the increasing prevalence of diabetes is an important contributor. Diabetes mellitus currently affects more than 180 million people around the world, a statistic which has doubled since 2000; the number of affected individuals is anticipated to rise to 300 million by 2025 [2]. In the US, one in three children over the age of 2 years is overweight, and one in six adolescents is obese. Diabetes and insulin resistance are powerful predictors of cardiovascular morbidity and mortality and are independent risk factors for death in patients with established heart failure (HF) [3].

Patients with diabetes often develop atherosclerosis and hypertension, both of which are major contributors to the development of heart disease. However, cardiomyopathy can also develop in the absence of established risk factors [4]. Indeed, over 4 decades ago Rubler et al. coined the phrase ‘diabetic cardiomyopathy’ to describe this form of disease [5]. Since then, this term has not emerged in the mainstream of clinical jargon, as it is often difficult to exclude contributions beyond diabetes alone in patients presenting with heart failure. Nevertheless, it is clear that this process, which sometimes emerges in isolation, is widespread and synergizes with the numerous diabetic co-morbidities. Characteristic structural, morphological, and functional abnormalities seen in diabetic cardiomyopathy are summarized in Box 1.

Several molecular mechanisms have been proposed to contribute to the pathogenesis of diabetic cardiomyopathy [7–11]. However, evidence for a direct, causal link between insulin resistance, a hallmark of diabetes, and ventricular dysfunction has not been established. Here, we discuss evidence implicating a variety of molecular targets in the pathogenesis of this disorder.

The natural history of diabetic cardiomyopathy has been divided into two phases (Table 1) [10]. The first phase has
been suggested to represent short-term, physiological adaptation to the metabolic alterations of diabetes; the second phase involves degenerative changes which the myocardium is unable to repair and that ultimately culminate in irreversible pathological remodeling.

Molecular mechanisms

Diabetes mellitus is a complex disease characterized by hyperglycemia stemming from absolute or relative insulin deficiency. In many instances, it is associated with insulin resistance. The disease itself arises from a variety of causes [12], including dysregulated glucose sensing or insulin secretion (maturity-onset diabetes of the young), autoimmune-mediated β-cell destruction (type 1 diabetes, T1DM), or insufficient compensatory insulin secretion in the setting of peripheral insulin resistance (type 2 diabetes, T2DM, which accounts for 90% of diabetes).

The concept of diabetic cardiomyopathy is based on the notion that the disease, diabetes mellitus, itself is the key factor eliciting changes at the molecular and cellular levels of the myocyte, culminating in structural and functional abnormalities in the heart [5]. The etiology of diabetic cardiomyopathy is multifactorial and incompletely characterized (Fig. 1).

The hormone insulin is central to the control of intermediary metabolism, orchestrating substrate utilization for storage or oxidation in all cells [13]. As a result, insulin has profound effects on both carbohydrate and lipid metabolism throughout the body, as well as significant influences on protein metabolism. Consequently, derangements in insulin signaling have widespread and devastating effects in numerous tissues, including the cardiovascular system. Insulin is the main hormone for the regulation of blood glucose and, generally, normoglycemia is maintained by a precisely tuned balance between insulin action and insulin secretion. Importantly, the normal pancreatic β-cell can adapt to changes in requirements for circulating insulin; when the downstream actions of insulin are hampered (e.g. insulin resistance), the pancreas compensates by up-regulating β-cell function (hyperinsulinemia). Relative insulin resistance occurs when the biological actions of insulin are inadequate for both glucose disposal in peripheral tissues and for suppression of hepatic glucose production [14].

Hyperglycemia and glucotoxicity

Hyperglycemia, a consequence of decreased glucose clearance and augmented hepatic gluconeogenesis, plays a central role in the pathogenesis of diabetic cardiomyopathy. In patients with T2DM, endogenous glucose production is accelerated [15]. As this increase occurs in the presence of hyperinsulinemia, at least in the early and intermediate stages of disease, it is apparent that hepatic insulin resistance is a driving force of hyperglycemia.

Chronic hyperglycemia leads to glucotoxicity, which contributes to cardiac injury through multiple mechanisms, including direct and indirect effects of glucose on cardiomyocytes, cardiac fibroblasts, and endothelial cells. Chronic hyperglycemia promotes the over-production of reactive oxygen species (ROS) through the electron transport chain which can induce apoptosis [16] and activate poly (ADP-ribose) polymerase-1 (PARP). This enzyme mediates the direct

<table>
<thead>
<tr>
<th>Phase</th>
<th>Molecular and cellular events</th>
<th>Alterations in structure and morphology</th>
<th>Myocardial performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Metabolic disturbances: hyperglycemia, increased circulating free fatty acids, insulin resistanceAltered Ca2+ homeostasisEndothelial dysfunction</td>
<td>Insignificant changes in myocardial structure: normal LV dimensions, wall thickness, and mass</td>
<td>Impaired diastolic compliance with normal systolic function, or no obvious functional changes</td>
</tr>
<tr>
<td>Middle</td>
<td>Cardiomyocyte injury, apoptosis, necrosisActivation of cardiac fibroblasts leading to myocardial fibrosis</td>
<td>Minor changes in structure: slightly increased heart mass, wall thickness or sizeCardiomyocyte hypertrophyInsufficient myocardial vascular changes</td>
<td>Significant changes in diastolic and systolic function</td>
</tr>
<tr>
<td>Late</td>
<td>Hypertension Coronary artery diseaseMicroangiopathy Cardiac autonomic neuropathy</td>
<td>Significant changes in structure: increased heart size, wall thickness and mass Myocardial microvascular disease</td>
<td>Abnormal diastolic and systolic function</td>
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ribosylation and inhibition of glyceraldehyde phosphate dehydrogenase (GAPDH), diverting glucose from the glycolytic pathway toward alternative biochemical cascades that participate in hyperglycemia-induced cellular injury. These include increases in advanced glycation end products (AGEs) and the activation of the hexosamine pathway, the polyol pathway, and protein kinase C [16,17]. Hyperglycemia-induced apoptosis is stimulated by ROS [18], PARP [19], AGEs [20] and aldose reductase [21]. Hyperglycemia also contributes to altered cardiac structure and function through posttranslational modification of extracellular matrix components (e.g. collagens) and altered expression and function of both the ryanodine receptor (RyR) and sarco(endo)plasmic reticulum Ca²⁺-ATPase (SERCA), which in aggregate contribute to decreased systolic and diastolic function [16].

**Hyperlipidemia and lipotoxicity**
Enhanced lipid synthesis in hepatocytes and increased lipolysis in adipocytes together lead to increases in circulating FAs and triglycerides (TGs) in patients with diabetes. Also, insulin stimulates FA transport into cardiomyocytes [22]. Thus, elevated circulating lipids and hyperinsulinemia together increase FA delivery to cardiac cells which rapidly adapt by promoting FA utilization. However, if FA delivery overcomes the oxidative capacity of the cell, FAs accumulate intracellularly with lipotoxicity the result [23]. Several major mechanisms contribute to cardiac lipotoxicity:

- **ROS generation**: High rates of FA oxidation increase mitochondrial membrane potential, leading to the production of ROS, which under normal, physiological conditions are removed by molecular antioxidants and antioxidant enzymes. However cardiomyocyte damage and death by apoptosis ensue if ROS generation exceeding degradation leads to ROS accumulation (oxidative stress) [24].
- **Ceramide production**: Accumulation of intracellular lipids can contribute directly to cell death under conditions in which FAs are not metabolized [25,26]. Reaction of palmitoyl-CoA with serine leads to the generation of ceramide, a sphingolipid which can trigger apoptosis through inhibition of the mitochondrial respiratory chain [27].
- **Insulin resistance**: Diacylglycerol, ceramide, and fatty acyl CoA can each activate a negative regulatory signaling pathway involving the atypical protein kinase C-δ and IκB kinase (IKK). Both kinases, in turn, stimulate serine phosphorylation of the IRS (insulin receptor substrate), impairing insulin signaling [28].
- **Impaired contractility**: Intracellular FA accumulation can trigger opening of the K-ATP channel leading to action potential shortening. This, in turn, diminishes the duty

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**Figure 1.** Triggers, mediators, and consequences involved in the pathogenesis of diabetic cardiomyopathy. RAAS, renin–angiotensin–aldosterone system; PKC, protein kinase C; ROS, reactive oxygen species; AGE, advanced glycation end products; PPARα, peroxisome proliferator-activated receptor-α; FoxO, Forkhead box O group transcription factors; NO, nitric oxide.
cycle of the L-type Ca2+ channel, leading to reduced sarcoplasmic reticular Ca2+ stores and depressed contractility [29].

Thus, high FA uptake and metabolism not only stimulate accumulation of FA intermediates but also increases oxygen demand, provoke mitochondrial uncoupling and ROS generation, decrease ATP synthesis, induce mitochondrial dysfunction, and trigger apoptosis. Together, these events participate importantly in the pathogenesis of diabetic cardiomyopathy.

**Hyperinsulinemia, insulin resistance, and altered substrate metabolism**

Early clinical studies reported an association between systemic hyperinsulinemia and development of cardiac hypertrophy [30,31]. Potential mechanistic explanations include cross-talk between insulin-dependent signaling and pro-growth pathways in the heart. For example, the signaling cascade activated by insulin shares common elements with the neurohormonal growth agonists IGF-1 and angiotensin II (Ang II) [32]. These pathways, in turn, activate both the ERK and PI3K/PKB/Akt/mTOR cascades, each of which is involved in regulating cell growth and protein synthesis. Activation of the latter pathway (PI3K/PKB/Akt/mTOR) is associated with the development of physiological hypertrophy, whereas ERK signaling, along with the PKC and calcineurin/NFAT pathways, mediates pathological hypertrophy [32]. Also, activation of the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS) have each been reported in diabetes, leading to enhanced stimulation of both adrenergic and AT1 receptors [10,33]. Chronic hyperinsulinemia may augment myocardial Akt-1 indirectly through increased SNS activation [34] or by triggering the Ang II pathway [35].

In a normal heart, approximately two-thirds of the energy required for cardiac contractility is derived from FA oxidation, with the remainder being derived from glucose and lactate metabolism. By contrast, in conditions of insulin resistance or diabetes, myocardial glucose use is significantly reduced, and a greater proportion of substrate utilization shifts to β-oxidation of FA [36]. Associated with the reduction in glucose use by diabetic myocardium is depletion of the glucose transporter proteins, GLUT-1 and -4. Indeed, altered myocardial substrate metabolism favoring FAs over glucose as energy source has been identified as a metabolic target of relevance. The diabetic heart relies on FA oxidation and is unable to switch to glucose, despite its lower oxygen consumption requirement. As a consequence, cardiac efficiency, the ratio of cardiac work to myocardial oxygen consumption, decreases; diminished cardiac efficiency has been reported in humans and experimental animals with diabetes [7–9,11].

Insulin resistance is defined as diminished insulin-dependent stimulation of myocardial glucose uptake [7–9,11]. Underlying mechanisms include accumulation of FAs which impairs insulin-mediated glucose uptake through inhibition of IRS and Akt. As noted above, the serine protein kinases PKC-θ and IKK, which elicit serine phosphorylation of IRS, are activated [37]. Phosphorylation and activation of PI3K and Akt are reduced with significant consequences on the metabolic effects of insulin in the heart [38].

**Abnormalities in intracellular Ca2+ homeostasis**

Precise control of intracellular Ca2+ homeostasis is central to the regulation of myocardial function and growth [39]. During each heartbeat, Ca2+ enters the cardiomyocyte through L-type channels. The resulting increase in intracellular Ca2+ triggers further Ca2+ release from the SR through the RyR, raising Ca2+ levels around the sarcomere. Binding of Ca2+ to troponin C in the contractile apparatus, in turn, initiates actin-myosin cross-bridging and myocardial contraction. Ca2+ reuptake into the SR by SERCA and consequent decline in cytoplasmic Ca2+ allow for cardiac relaxation [39]. Oxidative stress, accumulation of long-chain acylcarnitines, and abnormal membrane lipid content also contribute to abnormalities of Ca2+ handling in diabetic cardiomyopathy [9]. Alterations in the function or expression of SERCA, Na+–K+ ATPase Na+/Ca2+ exchanger, and RyR have each been observed in diabetic animals [40–43], and cardiac over-expression of SERCA improves Ca2+ homeostasis and contraction in diabetic mice [44].

**Mitochondrial dysfunction and oxidative stress**

Mechanisms whereby mitochondrial dysfunction contributes to diabetic cardiomyopathy are poorly understood. However, existing evidence suggests that hyperglycemia-induced mitochondrial ROS is a significant contributor [7–9,11]. Mitochondrial oxidative metabolism is the major source of ATP production in the heart. Acetyl-CoA generated from either FA oxidation or glycolysis is metabolized in the tricarboxylic acid cycle for the production of NADH and FADH2. These electron carriers transfer electrons to the mitochondrial electron transport chain, where ATP and ROS are generated. Increased ROS generation in the setting of high FA oxidation induces pathological accumulation of ROS and consequent oxidative stress and cell damage [7–9,11]. In addition, some studies suggest that hyperglycemia promotes the production of mitochondria-derived ROS and Rac1-mediated increases in NADPH [45], each promoting accelerated apoptosis. The activation of NADPH oxidase by Rac1 can induce myocardial remodeling and dysfunction in diabetic mice [46], suggesting that these two molecules are relevant therapeutic targets. Inhibition of ROS by over-expression of antioxidant enzymes protects against mitochondrial dysfunction and cardiomyopathy [47].

**Dysregulation of renin–angiotensin system**

Involvement of the renin–angiotensin system (RAS) in the pathogenesis of diabetes-associated HF is becoming increas-
ingly recognized. For example, angiotensin II (Ang II) has diverse and widespread actions that affect cardiac function [48]. Ang II also exerts actions on other insulin-sensitive tissues, such as liver, skeletal muscle, and adipose tissue, where it has effects on the insulin receptor (IR), IRS proteins, and the downstream effectors PI3K, Akt, and GLUT4 [49]. Underlying molecular mechanisms have not been elucidated definitively, but phosphorylation of both the IR and IRS-1 proteins contributing to desensitization of insulin action is well established [49]. Ang II also has direct effects on cardiomyocytes and cardiac fibroblasts through AT1 receptors, promoting cardiac hypertrophy and fibrosis [50]. Both hyperglycemia and diabetes induce cardiac dysfunction which can be prevented by pharmacological inhibition of the RAS [33]. Up-regulation of the RAS has also been described in diabetes and is associated with the development of cardiac hypertrophy and fibrosis [51,52]. In addition, cardiomyocytes and endothelial cells in the hearts of individuals with diabetes and end-stage HF manifest evidence of oxidative stress, apoptosis, and necrosis that correlate with RAS activation [53,54].

Adipokines
Historically, adipose tissue has been viewed largely as a repository for surplus lipid, available for mobilization in times of metabolic need. It is now known that adipocytes synthesize and secrete several cytokines (adipokines) that play significant roles in type II diabetes and insulin resistance and interact with most organs in the body. Studies to date have focused on the effects of adipokines in promoting or retarding progression from metabolic syndrome to overt T2DM. However, the effects of long-term exposure to circulating adipokines in diabetes warrant further exploration.

- **Leptin:** The hormone leptin is largely involved in regulating food intake, via actions in the central nervous system, and energy metabolism in peripheral tissues. However, despite extensive investigation into the role of leptin in diabetic cardiomyopathy, controversy persists [55]. For one, leptin has been thought to exert largely detrimental effects on the heart, including negative inotropy (mediated by endogenously produced nitric oxide), pro-hypertrophy (via an autocrine response to endothelin-1 and Ang II stimulation), and decreased cardiac efficiency (mediated by increased FA oxidation and TG hydrolysis) [9]. Now, there is growing evidence to suggest that leptin protects the heart from lipotoxicity and the relatively hypoxic milieu associated with diabetic cardiomyopathy. Administration of exogenous leptin reverses both LV dysfunction and hypertrophy and is associated with improved mortality in leptin-deficient ob/ob mice following 4 weeks of coronary ligation [56]. Although elevated plasma leptin levels are generally predictors of poor outcome in patients with coronary artery disease and HF, leptin may protect against ischemia/reper-

- **Resistin:** This 12 kDa hormone circulates as a high order complex in plasma [65]. Ample evidence from animal studies points to a significant proinflammatory action of resistin to promote insulin resistance in various tissues [66]. Epidemiological studies have revealed a positive correlation between circulating resistin levels and risk of developing HF [67]. Recent studies suggest that resistin can modulate glucose metabolism, insulin signaling, and contractile performance in the diabetic heart. Resistin has been reported to impair glucose transport in isolated murine cardiomyocytes and to be up-regulated by cyclic stretch and aorta-caval shunting in rodent models, suggesting that resistin impacts cardiac function [9]. Adenoviral transduction of resistin in neonatal rat cardiomyocytes triggers
robust hypertrophy with increased expression of hypertrophic genes [68]. Resistin is also associated with activation of the ERK1/2-p38 MAPK pathways and with increased serine-636 phosphorylation of IRS-1 [68]. Adenoviral induction of resistin in adult myocytes reduces contractility, possibly via a reduction in \( \text{Ca}^{2+} \) transients [68]. It is likely, therefore, that high levels of resistin as observed in diabetes contribute to the impairment of cardiac function, possibly through alterations in cardiac metabolism and the induction of myocardial insulin resistance.

**FoxO transcription factors**

FoxO (Forkhead box-containing protein, \( O \) subfamily) proteins are emerging as important targets of insulin and other growth factor action in the myocardium [69,70]. Originally identified by their involvement in chromosomal translocations associated with leukemias and rhabdomyosarcomas [69,70], abundant evidence now suggests that three members of the FoxO subfamily, FoxO1, FoxO3, and FoxO4, are crucial to maintain of cardiac function and cardiac stress-responsiveness. The direct metabolic effects of FoxO signaling are not yet entirely clear, and actions of FoxO in non-myoocyte cellular elements of the heart are largely unknown.

With respect to cardiac function, FoxO factors participate in remodeling [71,72], autophagy [73], apoptosis [74], responses to oxidative stress [75], regulation of metabolism [76], and cell cycle control [77] (Fig. 2). Through a variety of transcriptional targets, FoxO factors facilitate the response to changes in the environment via regulation of metabolic enzymes and energy-dependent proteins. Work in *Caenor-
hambdix elegans has demonstrated a link between hormonal inputs, Akt signaling, and FoxO [75,78]. Whereas the traditional notion is that FoxO-dependent transcriptional activity is inhibited by PI3K-Akt signaling, a more complex feedback regulatory network has been reported by our group, positioning FoxO proteins as central elements in the control of insulin signaling [79]. Forced expression of FoxO in primary cardiomyocytes triggers Akt phosphorylation via a calcineurin/PP2A-dependent mechanism, culminating in reduced insulin sensitivity and impaired glucose metabolism (Fig. 2). At present, we are testing the physiological relevance of this novel pathway as a potential avenue for the treatment of metabolic syndrome and insulin-resistance-induced diabetic cardiomyopathy.

**Potential therapeutic options**

Therapy specific for diabetic cardiomyopathy does not exist, but there is reason to believe that such may emerge in the future. The central role of myocyte insulin resistance in the pathogenesis of cardiomyopathy suggests that this signaling cascade is a logical starting point for targeted treatment. For one, lifestyle changes, including diet and exercise, can reduce the incidence of T2DM and improve cardiovascular health [80]. Additionally, drugs that enhance glycemic control, like the anti-diabetic drug metformin, which activates AMPK, may confer cardiovascular benefit. AMPK plays a central role in the heart regulating metabolism and energy homeostasis [81]. By contrast, AMPK activation can be cardioprotective during conditions of ischemic stress. Incretin pathway modulators, such as GLP-1 agonists, have been suggested to be cardioprotective [82], but whether these effects extend to treatment of diabetic cardiomyopathy is not known. Modulators of free fatty acid metabolism (e.g. perhexiline, trimetazidine, ranolazine, and amiodarone), some originally identified as anti-anginal drugs, have also been suggested to be of potential benefit and may reduce lipotoxicity [83]. Resveratrol, an activator of the NAD-dependent protein deacetylase Sirt1, lowers blood glucose and increases insulin sensitivity [84], and Sirt1 regulates the activity of FoxO transcription factors [85]. Additionally, Sirt1 modulates the activity of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1 alpha) which is involved in, among other things, mitochondrial biogenesis and function [85]. More potent activators of Sirt1 are currently being developed. Finally, cell-based therapy and genetic correction (vector-based gene transfer) of abnormalities in cardiac excitation-contraction coupling and insulin signaling are emerging as potential strategies in the treatment of HF [9].

**Conclusions**

The pathogenesis of diabetic cardiomyopathy is at once intricate, multifactorial, and clinically important. The multiple, interlacing events occurring in patients with diabetes culminate in an environment which, coupled with insulin resistance, leads to diabetic cardiomyopathy. In recent years, novel insights into mechanisms that increase vulnerability of the diabetic heart to failure have emerged. Functional consequences, including diastolic dysfunction, systolic dysfunction, fibrosis, and ultimately clinical heart failure, correlate with glycemic control. These organ-level functional alterations are preceded by a complex array of molecular and cellular changes, many of which are present in asymptomatic diabetic individuals and experimental models of diabetes.

Constant and unremitting metabolic stress on the heart leads over time to progressive deterioration of myocardial structure and function. This suggests that therapeutic interventions early in the disease, targeting specific metabolic and structural derangements, may be required. This is especially relevant as rigid control of hyperglycemia, however central to treatment, has not fulfilled hopes of meaningful morbidity and mortality benefit. Recent and ongoing research into mechanisms of metabolic control, insulin resistance, and diabetes-associated derangements portend novel therapies designed to benefit the rapidly expanding cohort of patients with diabetes.

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