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Minireview

Diabetic cardiomyopathy and metabolic remodeling of the heart

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ABSTRACT

The incidence and prevalence of diabetes mellitus are both increasing rapidly in societies around the globe. The majority of patients with diabetes succumb ultimately to heart disease, much of which stems from atherosclerotic disease and hypertension. However, the diabetic milieu is itself intrinsically noxious to the heart, and cardiomyopathy can develop independent of elevated blood pressure or coronary artery disease. This process, termed diabetic cardiomyopathy, is characterized by significant changes in the physiology, structure, and mechanical function of the heart. Presently, therapy for patients with diabetes focuses largely on glucose control, and attention to the heart commences with the onset of symptoms. When the latter develops, standard therapy for heart failure is applied. However, recent studies highlight that specific elements of the pathogenesis of diabetic heart disease are unique, raising the prospect of diabetes-specific therapeutic intervention. Here, we review recently unveiled insights into the pathogenesis of diabetic cardiomyopathy and associated metabolic remodeling with an eye toward identifying novel targets with therapeutic potential.

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Introduction

The incidence and prevalence of diabetes mellitus (DM) are both rising rapidly (Roger et al., 2012). DM affects 350 million people around the world, and the WHO has projected that diabetes deaths will double between 2005 and 2030 (http://www.who.int/diabetes/en/). Within this rapidly expanding public health epidemic of worldwide proportions, type 2 DM (T2DM) accounts for 90–95% of all diagnosed diabetes in adults (Roger et al., 2012). Patients with diabetes are at increased risk for developing coronary artery disease (CAD), hypertension, and heart failure (HF), and the majority of these patients succumb ultimately to heart disease. However, despite the importance of heart disease-promoting comorbidities, ventricular

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dysfunction and a clinical syndrome of HF can develop independent of underlying CAD, a condition termed "diabetic cardiomyopathy" (Rubler et al., 1972). Indeed, epidemiological studies demonstrate that obesity and diabetes are critical risk factors for cardiovascular disease, independent of blood pressure and coronary atherosclerosis (Grundy, 2012). Diabetic cardiomyopathy and the other diabetes-associated cardiovascular risks are the leading cause of morbidity and mortality in these individuals.

T2DM is typified by hyperglycemia, hyperinsulinemia and obesity, and insulin resistance is a cardinal feature (Witteles and Fowler, 2008). At later stages of disease, some patients manifest insufficient insulin action. Together, these events, acting through a variety of mediators such as altered intracellular calcium, increased reactive oxygen species (ROS), ceramides, hexosamines, advanced glycation end products, and more, contribute to the pathogenesis of the disorder (Battiprolu et al., 2010). Additionally, the interplay between dysregulated function of endothelial cells and fibroblasts contributes, highlighting the multifactorial etiology of diabetic cardiomyopathy. Now, metabolic derangements within the cardiomyocyte itself are emerging as important elements in the pathogenesis of the disorder.

Cardiomyocytes are capable of metabolizing a spectrum of substrates. These "metabolic omnivores" normally rely on fatty acids and glucose, and to a lesser extent lactate and ketone bodies, to produce ATP (Hue and Taegtmeyer, 2009). These substrates, however, are unable to enter the cardiomyocyte by simple diffusion and must be taken up by facilitated transport. Fatty acid uptake is mediated by FAT (fatty acid translocase, also known as cluster of differentiation 36, CD36), and glucose intake is accomplished by GLUT4 (glucose transporter type 4). In response to availability of nutrients or increased cardiac work, plasma insulin concentrations rise (Schwenk et al., 2008). This, in turn, provokes GLUT4 as well as FAT/CD36 translocation to the myocyte sarcolemma. To date, many studies have implicated signaling pathways that regulate GLUT4 translocation with those involved in transport of FAT/CD36 to the sarcolemma (Schwenk et al., 2008; Steinbusch et al., 2011). However, during the development of insulin resistance and T2DM, FAT/CD36 becomes preferentially sarcolemma-localized, whereas GLUT4 is internalized. This reciprocal positioning of GLUT4 and FAT/CD36 is central to aberrant substrate uptake in the diabetic heart, where fatty acid metabolism is chronically increased at the expense of glucose (Schwenk et al., 2008; Steinbusch et al., 2011). In addition, the interplay of preferential substrate utilization is impacted by a variety of other mediators, as previously reviewed (Battiprolu et al., 2010).

Dissection of the pathophysiology of diabetic cardiomyopathy and disease-related metabolic remodeling in the heart has progressed considerably in recent years. As a result, several novel mechanisms have emerged. Here, we highlight several of these molecular targets (graphical abstract, Fig. 1), acknowledging that space limitations and the scope of this review do not allow us to discuss them all.

Forkhead 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 (Ferdous et al., 2010; Ronnebaum and Patterson, 2010). Abundant evidence demonstrates that three members of the FoxO subfamily (FoxO1, -3, -4) are critical to maintenance of cardiac function and stress responsiveness (Ferdous et al., 2010; Ronnebaum and Patterson, 2010). FoxO transcription factors regulate cardiac growth and govern insulin signaling and glucose metabolism in heart (Ni et al., 2006; Ni et al., 2007). Further, recent work has implicated chronic activation of FoxOs in the pathogenesis of diabetic cardiomyopathy (Battiprolu et al., 2012). Specifically, cardiomyocyte-specific inactivation of FoxO1 (FoxO1 KO) rescued high fat diet (HFD)-induced myocyte hypertrophy and associated declines in cardiac function while preserving cardiomyocyte insulin responsiveness (Battiprolu et al., 2012). FoxO1-depleted cardiomyocytes displayed a shift in their metabolic substrate usage from free fatty acids to glucose, and accumulation of myocardial lipids was reduced (Battiprolu et al., 2012). Furthermore, a direct causal link was demonstrated, where FoxO1-dependent down-regulation of insulin receptor substrate 1 (IRS1) resulted in blunted Akt signaling and insulin resistance. While these findings suggest that activation of FoxO1 is a significant mechanism underlying diabetic cardiomyopathy, in-depth understanding of specific molecular targets and the transcriptional interplay between FoxO1 and IRS1 will be required in order to move this biology toward the clinic.

On the other hand, excessive cardiac insulin signaling can also be detrimental to heart function. Shimizu et al. (2010) studied cardiac insulin signaling in mice subjected to pressure overload. Both streptozotocin treatment and cardiac-specific IRS-1 knockdown were beneficial, suggesting that over-activation of cardiac insulin signaling can convey maladaptive actions (Shimizu et al., 2010).

FoxO has emerged recently as a major mechanism governing insulin signaling and glucose metabolism in a variety of tissues, including the liver (Cheng and White, 2012; Lu et al., 2012). Chronic activation of hepatic FoxO1 triggers dysregulated expression of a wide array of gluconeogenic genes, a process which contributes to systemic insulin resistance (Cheng and White, 2012; Lu et al., 2012). Interestingly, concomitant liver-specific deletion of both Akt1/2 and FoxO1 in mice restored appropriate adaptation to the fed and fasted states, as well as normal insulin action to suppress hepatic glucose production (Cheng and White, 2012; Lu et al., 2012). Accordingly, a major role of Akt is to inhibit FoxO1 activity which appears to be dispensable for other insulin actions. Moreover, silencing of hepatic FoxO1 largely normalized gluconeogenesis gene expression, lowered the concentration of circulating glucose, and diminished the basal rate of glucose production in insulin resistant, diabetic mice (Cheng and White, 2012; Dong et al., 2008; Lu et al., 2012). Thus, inhibition of FoxO1 activity might emerge as a promising strategy to ameliorate features of the metabolic syndrome, such as hyperglycemia, hyperinsulinemia, and insulin resistance (Cheng and White, 2012). However, the role of FoxO1 in hypertriglyceridemia and hepatic steatosis, which typically accompany insulin resistance and hyperglycemia, warrants further investigation (Cheng and White, 2012; Lu et al., 2012). It has also been reported that Notch1 signaling can act in a coordinated manner with FoxO1 to regulate hepatic glucose production, and pharmacological inhibition of the Notch1 cascade enhanced insulin sensitivity in diet-induced obese mice (Pajvani et al., 2011).

Mammalian target of rapamycin

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that regulates cell growth and metabolism and is dysregulated in cancer and DM (Laplante and Sabatini, 2009; Zoncu et al., 2011). mTOR comprises two multiprotein complexes: mTORC1, which regulates pathways involved in mRNA translation and autophagy, and mTORC2, which regulates insulin signaling and other cellular processes. Insulin and insulin-like growth factors (IGFs) are major mTOR activators that signal through phosphoinositide-3-kinase (PI3K) and Akt (Hay and Sonenberg, 2004). Also, AMPK (adenosine monophosphate-activated protein kinase), which is activated upon energy depletion, calorie restriction, or genotoxic damage has been implicated in stress-responsive inhibition of mTOR (Hay and Sonenberg, 2004; Towler and Hardie, 2007). mTOR stimulates cell growth and anabolism by increasing protein and lipid synthesis through activation of S6K (p70 ribosomal protein S6 kinase), 4E-BP (eukaryotic translation initiation factor 4E-binding protein), and SREBP (sterol response element binding protein) (Hay and Sonenberg, 2004; Porstmann et al., 2008; Wullschleger et al., 2006) and by decreasing autophagic catabolism through inhibition of ATG1 (Wullschleger et al., 2006). Persistent activation of mTOR has been implicated in diverse disorders, including cancer and obesity-related metabolic

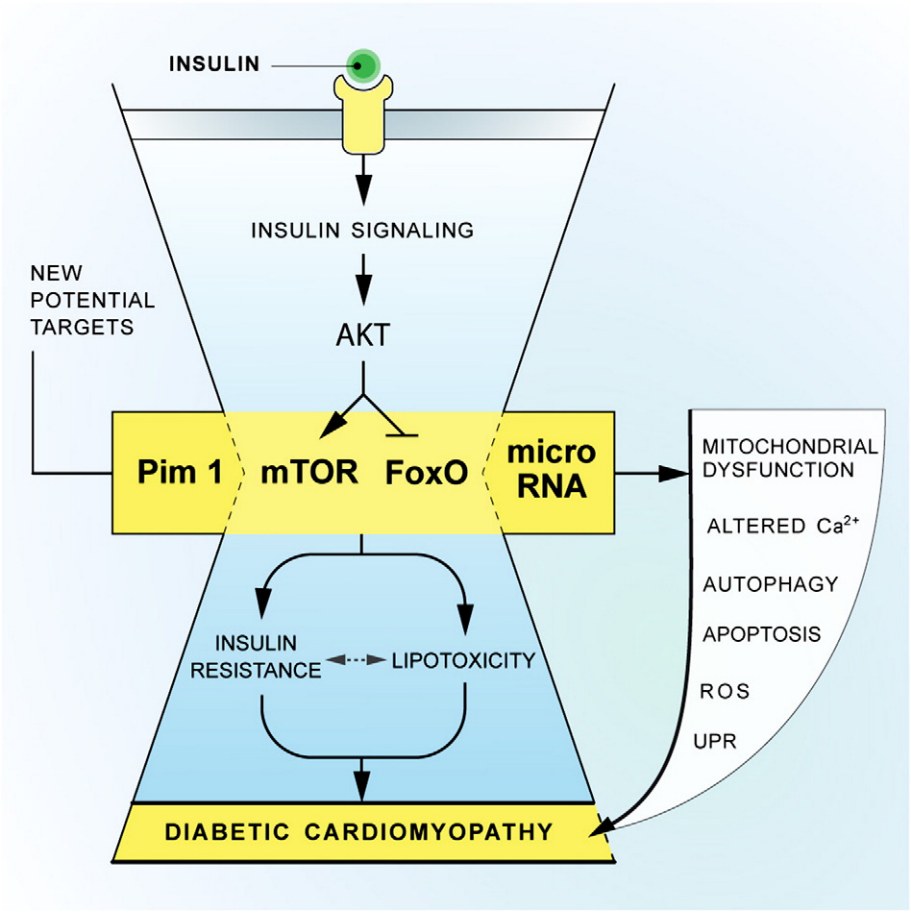

Fig. 1. New molecular targets and their role in diabetic cardiomyopathy. Schematic depiction of important elements of disease pathogenesis in diabetic cardiomyopathy, highlighting recently discovered molecular pathways.

pathologies (Wullschleger et al., 2006). Sestrins, another group of conserved stress-responsive proteins are increased by ROS accumulation, leading to activation of JNKs (c-Jun N-terminal kinase) and FoxOs (Lee et al., 2010). In contrast, loss of sestrins resulted in triglyceride accumulation, mitochondrial dysfunction, muscle degeneration and cardiac dysfunction, suggesting that these proteins function as negative feedback regulators of mTOR (Lee et al., 2010).

mTOR, along with other kinases such as JNK, phosphorylate IRS-1 on serine residues, leading ultimately to IRS-1 degradation (Hiratani et al., 2005). Indeed, deletion of mTOR substrates such as S6K1 is sufficient to improve insulin sensitivity and to extend lifespan in mice (Selman et al., 2009). This suggests that rapamycin, an established inhibitor of mTORC1, might act in a similar manner. Conversely, recent work suggests that chronic treatment with rapamycin impaired, rather than improved, glucose homeostasis (Lamming et al., 2012). This effect was shown to be mediated by mTORC2 inhibition, provoking insulin resistance and impaired glucose homeostasis potentially by blocking insulin-responsive Akt (Hughes and Kennedy, 2012; Lamming et al., 2012). Thus, modulators of either mTOR (e.g. rapamycin) or the distinct branches of the mTOR signaling cascade and their downstream molecular targets (e.g. GRB10, growth factor receptor-bound protein 10) (Hsu et al., 2011; Yu et al., 2011), are of interest as potential points of therapeutic attack in diabetic heart disease.

MicroRNAs

MicroRNAs (miRNAs or miRs) are naturally occurring, small non-coding single-strand RNAs that regulate gene expression usually by targeting mRNAs for degradation or by repressing protein translation. In some cases, miRNAs up-regulate translation of some mRNAs, especially during cell cycle arrest or in terminally differentiated cells (Vasudevan et al., 2007). miRNAs have been identified as important molecular regulators participating in many biological functions. However, their actions are complex and nuanced, as they target a wide range of transcripts, often in a cluster of processes involved in given biological event (e.g. fibrosis, cell death). Further, miRNAs merely fine-tune, as opposed to frankly suppress, the actions of their target mRNAs.

Numerous miRNAs are altered in diabetes (Greco et al., 2012; Lu et al., 2010; Shantikumar et al., 2012; Shen et al., 2011). For example, miRNAs 103 and 107 (miR-103/107) are negative regulators of hepatic insulin sensitivity (Trajkovski et al., 2011), and both are up-regulated in obesity. Silencing miR-103/107 rescues insulin sensitivity in *ob*/*ob* and diet-induced obese mice by affecting adipocyte differentiation (Trajkovski et al., 2011). One of targets for miR-103/107 is the gene encoding caveolin-1, the major protein of caveolae, the distinctive lipid- and cholesterol-enriched invaginations of the plasma membrane. Caveolin-1 stabilizes caveolae and their associated insulin receptors, promoting insulin signaling. By reducing caveolin-1 levels, miR-103/107 alters insulin receptor stability and activation (Trajkovski et al., 2011). However, whereas both miRNAs are strongly expressed in cardiac and skeletal muscles (Finnerty et al., 2010), their potential role in insulin resistance in the heart remains unknown.

miR-223 is another miRNA which is consistently up-regulated in diabetes, including in cardiac tissue (Lu et al., 2010). miR-223 expression increases basal glucose uptake in cardiomyocytes, and exposure to insulin does not lead to further increases (Lu et al., 2010). This enhanced glucose uptake is caused by elevated expression and preferential

plasma membrane translocation of GLUT4 (Lu et al., 2010). Because plasma membrane-localized GLUT4 is markedly down-regulated in diabetic hearts (Cook et al., 2010), the increase in miR-223 expression in diabetic patients could be an adaptive response to restore glucose uptake.

A recent report demonstrated that the cardiac-specific miR-208a regulates systemic energy homeostasis by targeting MED13, a subunit of the mediator complex which controls transcription by nuclear hormone receptors, including the thyroid hormone receptor (Grueter et al., 2012). Pharmacological inhibition of miR-208a or cardiac over-expression of MED13 enhances metabolic rate, confers resistance to obesity, improves glucose homeostasis and lowers plasma lipid levels in mice (Grueter et al., 2012). Further research remains to be done to elucidate mechanisms whereby MED13 alters systemic metabolic rate.

Alterations in intracellular calcium handling and impaired SERCA2a (sarcoendoplasmic reticulum Ca^{2+}-ATPase 2) activity are cardinal features of the failing heart. Indeed, SERCA2a gene therapy in failing hearts improves cardiac function and reduces arrhythmias *in vivo* (Lyon et al., 2011; Miyamoto et al., 2000). Interestingly, elevated cytoplasmic calcium concentrations in failing cardiomyocytes promote CaMKK (calcium/calmodulin-dependent protein kinase kinase)-dependent activation of Akt, which in turn inhibits FoxO3a activity, leading to down-regulation of miR-1, a FoxO3a target (Kumarswamy et al., 2012). NCX-1 (sodium-calcium exchanger 1) mRNA is one of the main targets of miR-1, and increases in NCX-1 levels may contribute to calcium mishandling in HF. SERCA2a gene therapy restored calcium levels in cardiomyocytes from failing hearts, normalizing Akt and FoxO3a activity and miR-1 and NCX-1 levels (Kumarswamy et al., 2012).

Pim-1

In addition to altered calcium homeostasis, down-regulation of prosurvival signaling factors has also been implicated in diabetic cardiomyopathy (Katare et al., 2011). Pim-1 (proviral integration site for Moloney murine leukemia virus-1) is a serine/threonine protein kinase that modulates SERCA and promotes cardiomyocyte survival and function (Katare et al., 2011; Muraski et al., 2007). Pim-1 is upregulated in failing hearts, potentially as an inefficient, last-ditch attempt to preserve cardiac function (Muraski et al., 2008). Interestingly, Pim-1 is down-regulated in the initial phase of diabetic cardiomyopathy and continues to decline as contractile dysfunction and HF progress (Katare et al., 2011). Furthermore, Pim-1 is positively regulated by STAT3 (signal transducer and activator of transcritption 3) and Akt (Muraski et al., 2007), both of which are down-regulated in diabetic cardiomyopathy (Katare et al., 2010). Both STAT3 and Akt act as modulators of insulin and nutritional status in the heart (Shiojima et al., 2002). On the other hand, Pim-1 is inactivated by PP2A (protein phosphatase 2A) (Ma et al., 2007) and is a target of miR-1 (Nasser et al., 2008). It has been proposed that the increased levels of intracellular ceramide in diabteic myocardium may in part explain the upregulation of PP2A (Ma et al., 2007) and hence its fate over Pim-1. Pim-1 is also implicated in promotion of cardiomyocyte survival via activation of Bcl2 (B-cell lymphoma-2), BAD (phosphorylation/inhibition of BCL-2-associated death promoter), and in the maintenance of mitochondrial integrity (Borillo et al., 2010; Muraski et al., 2007). Furthermore, Pim-1 increases the proliferative activity of cardiac progenitor cells by inducing c-Myc, nucleostemin, cyclin E expression and p21 phosphorylation (Cottage et al., 2010; Tjwa and Dimmeler, 2008). Therefore, it is tempting to speculate that the accrual of alterations in upstream Pim-1 activators (Katare et al., 2010) and the confounding up-regulation of Pim-1 inhibitors, such as PP2A and miR-1, contributes to the unique features observed in hearts of diabetic mice compared with other ischemic and pressure-overload models. Additionally, as noted above, some work suggests that cardiac-specific Pim1 gene therapy attenuates the progression of diabetic cardiomyopathy (Katare et al., 2011), raising yet further the prospects of targeting this interesting molecule.

It is important to point out that studies of Pim-1 have been performed in streptozotocin-treated animals, a model used to mimic the later stage of T2DM characterized by insufficient insulin action. Studies to investigate the relevance of Pim-1 in earlier stages of T2DM pathogenesis, as well as metabolic syndrome, are warranted.

Mitochondrial dysfunction

Mitochondrial dysfunction contributes to progression of diabetes and diabetic cardiomyopathy (Duncan, 2011). The transcription factor p53 is induced by ischemia, chronic pressure overload, or metabolic disturbances. A recent report suggests that p53 contributes to cardiac dysfunction in diabetes by promoting mitochondrial oxygen consumption, ROS production, and lipid accumulation (Nakamura et al., 2012). The SCO2 (synthesis of cytochrome c oxidase 2) gene is a transcriptional target of p53, and its protein product plays a key role in the assembly of mitochondrial respiration complex IV, the center of oxygen consumption. Nakamura et al. (2012) reported a marked increase in cardiac SCO2 expression in diabetic mice that contributed to increases in mitochondrial respiration rate. This elevated mitochondrial activity triggers enhanced lipid uptake which exceeds mitochondrial oxidation capacity, leading to lipid accumulation and increased mitochondrial ROS production, together culminating in cardiac dysfunction.

Unfolded protein response

Accumulating evidence points to disruption of endoplasmic reticulum (ER) homeostasis in diabetic cardiomyopathy (Ceylan-Isik et al., 2011; Li et al., 2010; Miki et al., 2009; Wu et al., 2011). The ER is the central organelle for secretory/transmembrane protein folding, calcium storage, and lipid synthesis. Elevated demand for synthesis of new proteins and lipids poses a special burden on the ER. When the throughput of proteins being processed in the ER exceeds folding capacity, “ER stress” ensues and the so-called unfolded protein response (UPR) is activated (Back and Kaufman, 2012; Walter and Ron, 2011). To ameliorate ER stress, the UPR activates three pathways that antagonize the cellular stress (Harding et al., 2002). PERK, a transmembrane protein kinase in the ER phosphorylates eIF2α, which in turn promotes chaperone synthesis and transiently suppresses other protein synthesis. ATF6 undergoes proteolytic cleavage triggered by the UPR. The processed ATF6 functions as a transcription factor for a host of ER chaperone proteins to enhance ER protein folding capacity. IRE1 manifests nuclease activity when phosphorylated during ER stress, and splices a downstream target mRNA, Xbp1. The resulting Xbp1s drives expression of ER chaperones and molecules involved in the ER-associated protein degradation pathway. Thus, all three branches of the UPR (PERK, ATF6, IRE1-Xbp1) act coordinately to relieve ER stress and restore protein processing homeostasis. When ER stress is persistent, however, excessive and unremitting activation of the UPR becomes maladaptive and may activate apoptotic pathways for cell destruction (Tabas and Ron, 2011).

Mounting evidence suggests that the UPR plays critical roles in the heart during diabetic cardiomyopathy. Using a genetic model of T2DM, Miki et al. (2009) found markers of ER stress were induced in OLETF rats compared to control LETO rats. Similarly, it has been reported that the UPR is triggered in hearts of *ob*/*ob* mice, including up-regulation of BIP (binding immunoglobulin protein, also known as GRP-78, 78 kDa glucose-regulated protein), and eIF2α and PERK phosphorylation (Ceylan-Isik et al., 2011). Moreover, induction of the UPR is evident in the myocardium in streptozotocin-induced type 1 DM (Li et al., 2010). Consistently, ER stress is seen in

cardiomyocytes maintained in culture medium containing high glucose (28 mM) (Younce et al., 2010).

Whereas induction of the UPR has been observed both *in vitro* and *in vivo*, the association between ER stress and diabetic cardiomyopathy remains correlative, and clear mechanistic links are lacking. Moreover, although the three branches of the UPR share similar targets, their temporal induction patterns differ and their specific functions are distinct, conferring additional complexity to the putative role(s) of ER stress in diabetic cardiomyopathy (Lin et al., 2007). During ER stress, PERK is activated to terminate protein synthesis and reduce the burden of ER cargo, providing a window for rejuvenated protein folding. Subsequently, IRE1-Xbp1 and ATF6 are stimulated to increase ER chaperone production and enhance folding capacity. Some evidence points to the IRE1-Xbp1 and ATF6 pathways as pro-survival and adaptive in diabetes, cancer, and cardiomyopathy (Doroudgar et al., 2009; Lin et al., 2007; Thuerauf et al., 2006).

Several groups have tested drugs and chemical chaperones to manipulate ER stress in diabetic cardiomyopathy. Studies using valsartan (Wu et al., 2011), tauroursodeoxycholic acid (Ceylan-Isik et al., 2011; Miki et al., 2009), and apocynin (Li et al., 2010) all reported improved heart function in the setting of diabetic stress. Consistently, activation of ER stress markers was decreased, assessed mainly as GRP78 levels and PERK phosphorylation. These studies, although well designed and carefully conducted, only demonstrate correlation between ER stress and diabetic cardiomyopathy and fall short of providing a clear picture of the degree and extent of cellular ER stress activation. To address these questions, gain- and loss-of function of individual ER stress elements, ideally at selected temporal windows of disease progression, are required.

Adipokines

Adipose tissue expansion is, of course, a hallmark of obesity. Over the past 20 years, our view of adipose tissue has been revolutionized from previously being viewed as an inert energy storage tissue now to clear recognition of its role as the largest endocrine organ in the body (Scherer, 2006). Beside fatty acids, adipocytes synthesize and secrete a host of proteins, including adiponectin, leptin, resistin, tumor necrosis factor alpha (TNFα) interleukin-6 (IL-6), and many more, collectively named adipokines (Deng and Scherer, 2010). In a wide array of circumstances, adipose tissue communicates with multiple organs and tissues throughout the body through these adipokines.

Adiponectin, the only adipokine manifesting reverse correlation with adipose tissue mass, has attracted tremendous attention during the past two decades. Adiponectin is specifically synthesized in adipocytes, folded in the ER, and secreted as a range of complexes, including a trimer, hexamer, and high molecular weight form (18-mer). Circulating levels of adiponectin as well as the distribution of its various protein complexes, are altered in obesity and diabetes (Wang and Scherer, 2008). Low levels of adiponectin are a marker of cardiovascular disease, and some evidence suggests that genetic and pharmacological approaches to increase adiponectin levels may have efficacy in modulating obesity-associated cardiac disease (Hui et al., 2012).

Adiponectin antagonizes diabetic cardiomyopathy by various mechanisms. For one, adiponectin manifests potent anti-hypertrophic activity in cardiomyocytes. For example, Shibata et al. (2004) found that adiponectin inhibits hypertrophic growth of the heart in the setting of pressure overload, events which are mediated by AMPK activation (Shibata et al., 2004). Adiponectin can reverse endothelial dysfunction by increasing endothelial nitric oxide synthase and nitric oxide production, leading to improved blood pressure control (Wang and Scherer, 2008). Moreover, adiponectin blunts cardiac cell death via apoptosis by inhibiting ceramide production and inflammation (Holland et al., 2011). Administration of adiponectin to adult cardiomyocytes isolated from *db*/*db* animals rescues over-activation of IRS1 and c-Jun in association with increased intracellular calcium and enhanced calcium decay (Dong and Ren, 2009). In summary, circulating adiponectin manifests cardioprotective effects by blunting cardiac and endothelial cell death, inhibiting inflammation, and suppressing hypertrophy.

In contrast, resistin, another adipokine synthesized by and secreted from adipose tissue (Rajala et al., 2002), may participate in declines in cardiac function in diabetic cardiomyopathy. Similar to adiponectin, resistin circulates as multiple protein complexes. Clinical studies have shown that serum levels of resistin are positively correlated with insulin resistance, obesity, T2DM and cardiovascular disease (DeClercq et al., 2008; Nogueiras et al., 2010).

Recent studies suggest resistin directly affects heart function in rodents. Resistin is expressed in heart at both mRNA and protein levels. Cardiomyocyte resistin levels are higher in the setting of diabetes (Kim et al., 2008). Cardiomyocyte over-expression of resistin by means of adeno-associated virus serotype 9-mediated gene delivery is associated with pronounced cardiac remodeling, including increased fibrosis and hypertrophy, reduced cardiac performance, and elevated markers of inflammation (Chemaly et al., 2011). The same group reported that resistin over-expression in cultured cardiomyocytes *in vitro* significantly increased cellular hypertrophy, activated JNK, and provoked serine phosphorylation (and desensitization) of IRS1, which together correlated with insulin resistance under high resistin conditions (Kang et al., 2011; Kim et al., 2008).

Metabolic role of autophagy

Autophagy is an evolutionarily ancient process of intracellular protein and organelle recycling (Yang and Klionsky, 2010). Faced with nutrient deprivation, most cells manifest a complex autophagic response that initiates with the formation of an intracellular membrane organelle that engulfs cytoplasmic material forming an autophagosome. After fusion with a lysosome, the intra-autophagosomal cargo is digested and the resulting degradation products are released to provide nutrients and cellular building blocks for sustenance of energy, cellular integrity and function. Autophagy is also critical for clearing defective organelles and degrading long-lived proteins. Autophagy has been implicated in numerous biological processes and diseases, including development, starvation, obesity, diabetes, infectious disease, cancer and cardiovascular disease (Mizushima et al., 2008; Wang et al., 2010). Some evidence suggests that autophagy is altered in diabetic cardiomyopathy. H9c2 cells maintained in high glucose-containing culture medium (28 mM) manifest increases in autophagy (Younce et al., 2010). Mice fed a high fructose diet manifest insulin resistance, cardiac remodeling, and elevated levels of cardiomyocyte autophagy (Mellor et al., 2011). However, another report noted reduced autophagy in diabetic heart of OVE26 mice (Xie et al., 2011). Importantly, in all these studies, autophagy was assessed as steady state levels of LC3 measured by immunoblot. Autophagy, however, is a highly dynamic process of flux, with constant generation and processing of autophagosomes (Wang et al., 2010), and a snapshot in time of LC3 abundance is insufficient to distinguish between enhanced autophagy initiation versus defective processing downstream in the autophagic cascade. This important point may explain some of the discrepancies reported in the literature.

Due to the complexity of autophagy, its role in diabetic cardiomyopathy has yet to be elucidated. It has been reported that metformin-induced AMPK activation in diabetic mice is associated with increased autophagy and preservation of cardiac function (Xie et al., 2011). Without more detailed analysis, however, this correlation cannot be used to attribute the apparent cardioprotective effects of metformin solely to autophagic changes. Likewise, correlations between autophagic activation and cardiac impairment with fructose feeding in rodents fall short of demonstrating a compelling mechanistic link (Mellor et al., 2011). In conclusion, cardiomyocyte autophagic responses are altered in diabetic cardiomyopathy, yet further work is required to ferret out potential causal roles.

Conclusions and perspective

HF has remained the leading cause of death in industrialized nations for some years. Numerous events contribute to the rise in HF, but the increasing prevalence of DM is an important contributor. Derangements in insulin signaling have widespread and devastating effects in numerous tissues, including the cardiovascular system. 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. Despite these recent efforts, our understanding of diabetic cardiomyopathy – a disease which is at once intricate and clinically significant – remains rudimentary.

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 (Gerstein et al., 2011). 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. Continued efforts to identify effective preventive strategies and treatments are essential. At the same time, there remains a growing need to identify therapies that slow, arrest, or even reverse disease progression, and ongoing research efforts suggest that such may emerge with time.

Conflict of interest statement

The authors have declared that no conflicts of interest exist.

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