Metabolic and Contractile Remodelling in the Diabetic Heart: An Evolutionary Perspective

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Abstract The application of evolutionary biology to the study of human disease has given rise to the idea that disease can result from inappropriate adaptations to a change in environment. This concept can also be applied to the function of organs and responding to their local environments within the human body. The heart is an omnivorous organ which can use any substrate it is supplied with. The metabolic machinery of the heart is exquisitely attuned both to its metabolic needs and to the available energy substrates in its local environment. Diabetic cardiomyopathy is a disease process which arises as a result of the inability of the heart to adapt to a diabetic metabolic milieu. The heart becomes locked into a progressively maladaptive state from which it cannot escape by its own devices; due to the phenomenon of hyperglycemic memory, even restoration of a normal milieu may not be sufficient to completely reverse the remodeling. The pathways which initiate, progress and perpetuate this downward spiral are the same pathways which normally allow the heart to sense and respond to its local metabolic environment. These include metabolite-sensitive transcriptional regulatory pathways and, most probably, epigenetic and miRNA regulatory pathways. Overall, the application of evolutionary concepts provides a valuable framework for understanding the origins and importance of metabolic and contractile disturbances in the diabetic heart, and a strong rationale for the use of metabolic therapy as a treatment.

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1 Introduction

Nothing in biology makes sense except in the light of evolution. Theodosus Dobzhansky, 1973

The application of evolutionary biology to the study of human disease has given rise to the idea that disease can result from adaptations which, although appropriate for the environment in which humans originally evolved, are inappropriate for the environment in which humans live today. This concept can also be applied to the function of cells, tissues, organs and systems responding to their local environments within the human body. In this context, disease results from a maladaptive response of the organ to a change in its local environment. The concept of the reaction norm describes the pattern of phenotypes that a single genotype can produce across a range of environments (Fig. 1). This pattern provides what can be regarded as a map of all possible adaptations, or "a map of plasticity". In the heart, reaction norms include the heart's ability to undergo metabolic and contractile remodeling, which it will do in response to a wide range of stressors. These include metabolic dysregulation (most notably diabetes), pressure overload, unloading, ischemia, hypobaric hypoxia and hypothyroidism. These stressors change the phenotype of the heart, and when

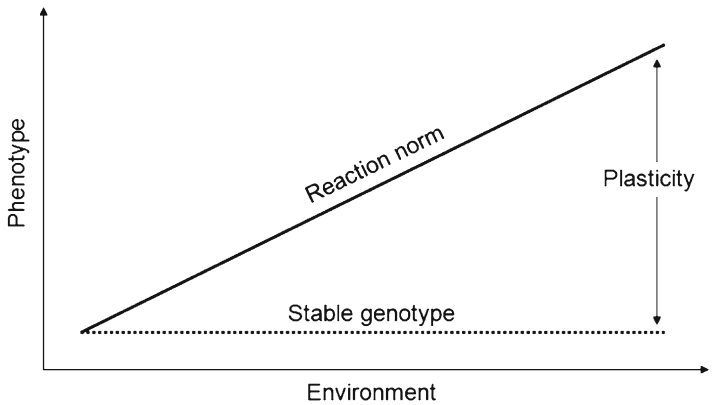

Fig. 1 A simplified representation of a reaction norm. Genotypes which produce the same phenotype over a range of environments are stable, whereas those which produce a range of phenotypes in different environments produce plasticity. Plasticity refers to the range of phenotypes which a genotype can produce. The reaction norm is the relationship between the environment and the phenotype

the phenotype moves from a point on the reaction norm which is adaptive to one which is maladaptive, function is impaired. Diabetic cardiomyopathy can be understood, from an evolutionary perspective, by understanding how and to what extent the phenotype of the heart becomes maladaptive in response to the metabolic milieu it is exposed to following the onset of diabetes. To put it simply, the heart has not evolved to be able to cope with a diabetic metabolic milieu. Before exploring this concept further, it is worthwhile to consider how the heart, and its metabolic machinery, first evolved.

2 An Overview of the Evolution of the Heart

The heart probably first emerged in the Bilateria, a group of organisms whose root is the flatworm and who lived 600–700 million years ago. The Bilateria, in turn, were ancestors of three main groups:

1. The Ecdysoa, which gave rise to the insects
2. The Lophotrochozoa, which gave rise to annelids and mollusks
3. The Deuterosomes, or "two-ended animals", which gave rise to the Echinodermata, whose members include sea urchins and starfish, the hemichordates, also known as acorn worms, and the Chordates [1].

The first heart is believed to have been a tubular pulsatile structure, devoid of chambers, septae and valves, which pumped fluid through a peri-cellular interstitium [1]. The features of the myocytes of which this tube was comprised probably varied, with features of striated muscle, vertebrate cardiomyocytes and myoepithelium all emerging in different organisms. This basic structure then underwent subsequent morphological and genetic modifications.

With the development of Deuterostomes, genes encoding the contractile proteins began to increase in number and diversify in their function. The Deuterostomes, in turn, gave rise to the Chordates, defined by the presence of a dorsal nerve cord and its supporting notochord. Two of the current branches of this group, namely the Urochordates (tunicates) and the Cephalocordates, retained a simple tubular heart. It is in the third branch, the vertebrates that the heart continued to evolve. Hagfish are at the base of the Vertebrates, and are followed, in order, by the Elasmobranchs, Teleost fish, Amphibians, Reptiles, Birds and Mammals. Hagfish possess a closed vascular system which has contractile elements at several points. The systemic heart of the hagfish is equivalent to the left-sided heart chambers in birds and mammals, whereas the portal vein heart, which pumps blood to the gill vasculature, is equivalent to the right-sided chambers. As we move upwards through the taxa, the Elasmobranchs are the first vertebrates to show vagal innervation of the heart. In the Teleost fish, the heart is a two-chambered organ, separated by an atrioventricular valve, which pumps blood to both the gill and the systemic vasculatures. Between the development of the teleost fish, and their separation into the amphibians during

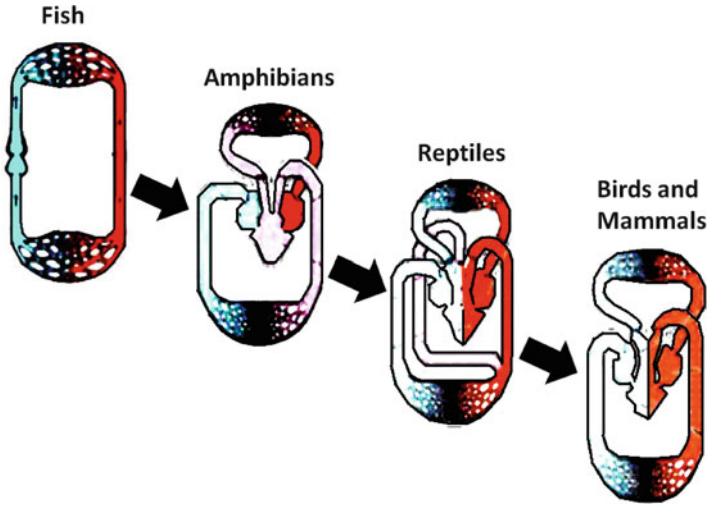

Fig. 2 The heart and vasculature of fish, amphibians, reptiles, birds and mammals, illustrating the key developments

the transition to terrestrial life, separation of the systemic and pulmonary vasculatures began. The amphibian heart has two atria and a single ventricle. In reptiles, a muscular ridge running from the base to the apex of the heart creates a partial division of the ventricular chamber, allowing oxygenated and deoxygenated blood to be separately directed. The degree of mixing which occurs depends on the size of the ridge; in turtles, the ridge is small, but in lizards and snakes, it is larger. Birds and mammals have a complete interventricular septum, enabling complete separation of the pulmonary and systemic circulations (Fig. 2).

The evolution of the heart from a tubular to a four-chambered structure was associated with a myriad of adaptations. In this brief treatise, a few key adaptations are worthy of mention. The first is the specialization of the contractile elements. The initial radiation occurred, as mentioned above, with the evolution of the Deuterostomes during the Cambrian explosion. Separation and specialization of striated and smooth muscle isoforms appeared at this time. Separation between skeletal and cardiac isoforms occurred later, initially with the separation of cardiac actin and troponin C before the frog-mammal divergence, followed by the separation of the cardiac, slow skeletal and fast skeletal isoforms before the bird-mammal divergence [1]. The second is the ability to replace myocytes, which was mostly lost during the development of endothermy, although a small pool of undifferentiated precursor cells does exist in human myocardium [1]. The third is the development of connexin-based gap junctions and a specialized conduction system. Gap junctions allowed rapid communication and enabled the transition from the peristaltic contractions of the early tubular heart to the rapid contractions of the vertebrate heart.

The development of a specialized conduction system further promoted synchronous contraction.

In terms of energy metabolism, the fundamental biochemical machinery of the cell has been conserved by evolution. Basic problems of transport created by an increase in vertebrates' size have been addressed by reducing the metabolic rate in larger organisms. Likewise, many of the adaptations seen during the evolution of the vertebrate heart are adaptations to optimize energy consumption and storage on the background of conserved biochemical machinery. These include the development of an efficient vasculature, sophisticated neural and endocrine regulatory systems, and plasticity of the heart itself.

It has been observed that ontogeny can recapitulate phylogeny. In other words, evolutionary stages in the development of an organism can be observed during the stages of embryonic and fetal development of that organism. During fetal development of the mammalian heart, the heart begins as a tubular heart, develops into a trabeculated heart and thence into the fully septated heart. Full separation of the pulmonary and systemic circulations does not occur until after birth. The tubular heart is mainly dependent on anaerobic glycolysis. Once this develops into the trabeculated heart, metabolism transitions to oxidative metabolism, but oxidative glucose metabolism predominates, with only very low rates of fatty acid oxidation (see [2] for review). In the newborn period, fatty acid oxidation rates increase dramatically, and the preference of the adult mammalian heart for fatty acids becomes established.

To a certain extent, this ontogenic pattern recapitulates the phylogeny of cardiac energy metabolism. Examination of enzyme activities and high-energy phosphate concentrations show that, across the taxa, carbohydrate metabolism plateaus at low levels of cardiac demand, and the increased requirement for ATP production necessitated by the increased need for power development by the heart is met by increasing the capacity for fatty acid oxidation [3]. This pattern is also supported by studies looking directly at substrate utilisation; fatty acid use tends to increase in higher taxa [4–7] whereas glycolysis decreases [8]. However, superimposed on this broad trend is a considerable degree of interspecies variation, particularly in fish, which exhibit marked differences in their substrate preferences [9]. The evolutionary advantage of fatty acids is that they generate more ATP per gram of fuel than carbohydrates. Despite the fact that fatty acid oxidation is less efficient in terms of oxygen consumption, expansion of fatty acid oxidation to meet increased energy demands is the adaptation which seems to have been preferred by evolution.

The mammalian heart is an omnivorous organ which can use any substrate it is supplied with. To cope with transient changes in substrate supply, this is clearly an advantageous adaptation. However, the ability of the heart to cope with sustained shifts in substrate preference, away from its normal balance, is limited. The balance of substrate utilization by the heart has been slowly established through its evolution, and the pathways which deliver substrates to their myriad cellular fates have evolved with this balance 'in mind'. Although short term shifts in preference are easily handled, sustained shifts lead to the cytoplasmic accumulation of metabolic

intermediates, some of which are toxic, and to an increase in flux of substrates through alternate, potentially maladaptive, pathways. The main exception is the adaptation to hypoxia and hypobaria; the hearts of peoples who live at high altitude, such as the Sherpas, Tibetans and Andean natives, use 60 % glucose and 40 % fatty acids [10–13]. This appears to be a beneficial adaptation because glucose oxidation is more efficient in a hypobaric environment. However, most instances of a sustained shift in cardiac substrate preference, either towards glucose oxidation or towards fatty acid oxidation, are associated with disease. This phenomenon has a clear evolutionary origin.

3 The Pathogenesis of Diabetic Cardiomyopathy

The diabetic state immediately changes the delivery and utilization of metabolic substrates by the heart. Myocardial glucose transport is all but lost as a result of decreased Glut-4 translocation to the membrane, and decreased total Glut-4 protein and mRNA levels [14]; this is a direct result of the loss of insulin signalling. In contrast, fatty acid delivery to the heart from the coronary lumen by the enzyme lipoprotein lipase (LPL), and its subsequent uptake by fatty acid transporters, is increased to such an extent that it swamps the capacity of the heart to utilize fatty acids, even though cardiac fatty acid oxidation is increased [15]. Cytoplasmic lipids therefore accumulate, mainly in the form of long-chain acyl-CoA's [15]. These are converted into the toxic substance ceramide, which induces reactive oxygen species (ROS) and cardiomyocyte apoptosis [16]. This process has been named 'lipotoxicity' [15, 17]. Fatty acids bind and activate peroxisome proliferator-activated receptors (PPAR's) of which PPAR-α is the key isoform in the heart. It acts as a 'lipostat' which induces genes involved in fatty acid metabolism [18, 19]. PPAR-α-overexpression induces a phenotype similar to that seen in diabetic cardiomyopathy, and worsens the diabetic phenotype [15]. Conversely, deletion of PPAR-α protects against diabetic cardiomyopathy [15]. The phenotype of PPAR-α overexpression is rescued by knocking out cardiac lipoprotein lipase [20]. PPAR-α is therefore essential to the pathogenesis of diabetic cardiomyopathy, and seemingly requires the cytoplasmic accumulation of fatty acid intermediates.

High rates of fatty acid oxidation increase the ratios of $NADH/NAD^+$ and acetyl CoA/free CoA, both of which feed back into and inhibit glucose oxidation by decreasing flux through pyruvate dehydrogenase (PDH) [15]. High rates of fatty acid oxidation also increase citrate production, which in turn nhibits glycolysis by inhibiting the key glycolytic enzyme phosphofructokinase (PFK). This is referred to as the Randle Cycle, and it results in an intracellular accumulation of intermediate products of glucose metabolism [2].

As mentioned above, inhibition of the main pathways of glucose metabolism increases the flux of glucose through alternate, potentially maladaptive, pathways. The first of these is the polyol pathway. Aldose reductase is an enzyme which catalyses the conversion of glucose to sorbitol, which is subsequently converted into

fructose by sorbitol dehydrogenase (SDH) using NAD^{+}[29] [21]. Excess glucose enters the polyol pathway and selectively stimulates aldose reductase without affecting sorbitol dehydrogenase; leading to an accumulation of sorbitol [21]. This has several consequences: the NADH/NAD^{+} ratio is increased, leading to inhibition of glycolysis, and the consumption of NADPH increases. Reduction in the availability of NADPH compromises the ability of myocytes to regenerate reduced glutathione [22], potentially interfering with the heart's ability to cope with oxidative stress. Effects on myocardial gene expression have been postulated but not extensively studied [23]. The second pathway is the hexosamine biosynthetic pathway, which converts glucose-6-phosphate to hexosamine-6-phosphate which, in turn, is converted into uridine-5′-diphosphate-N-acetylglucosamine (UDP-GlcNAc). Approximately 5 % of the glucose which enters cardiac myocytes is metabolized by this route. UDP-GlcNAc serves as an important substrate for protein glycosylation which is thought to play a role in decreased expression of several key components of the mitochondrial oxidative phosphorylation complexes as well as increased expression of pro-inflammatory proteins [22]. An important mechanism of this effect is the glycosylation of key transciption factors such as sp-1, leading to an increase in their binding affinity for DNA [24]. One of the consequences of this may be activation of the fetal gene program [25].

The shift toward exclusive use of fatty acid oxidation may be energetically detrimental, partly because fatty acid oxidation requires more oxygen per mole of ATP produced, and partly because it is associated with increased mitochondrial uncoupling. It also, at a global level, restricts the reaction norm; the heart is unable to use the range of substrates it can normally use (glucose being the key example). The heart is therefore effectively locked into a maladaptive state from which it cannot escape by its own devices.

In parallel with this metabolic remodeling, contractile remodeling also occurs. It is possible that contractile remodeling is a consequence of metabolic remodeling. Induction of the so called 'fetal gene program' results in a shift from the fast V_1 isomyosin pattern seen in the normal heart to a predominantly V_3 pattern in the diabetic heart [26]. The fetal gene program involves the re-expression within the heart of genes that are expressed during fetal development (e.g. skeletal muscle actin, beta myosin heavy chain, atrial natriuretic peptide within the ventricle) along with blunting of the expression of genes expressed in the adult heart (e.g. alpha-myosin heavy chain, cardiac actin, sarcoplasmic reticulum calcium ATPase-2 (SERCA-2)). The decrease in SERCA-2 is one of the changes which causes disturbances in calcium handling. The debate continues as to whether activation of this program is adaptive or maladaptive. In the setting of mechanical overload and pathological hypertrophy, re-expression of the fetal gene program allows the stretched fibres to contract at their usual energy cost, because Vmax is slowed. The adaptation is therefore helpful for individual fibres. Likewise, the fetal gene program may also be beneficial at the level of the cell, because it supports pro-survival signalling pathways, including the Akt pathway [27, 28]. However, at the level of the heart itself, the resulting slowing of Vmax is the initial deleterious change that eventually leads to heart failure.

Changes to the ultrastructure are also observed, including alterations in myofibrillar arrangements, disrupted mitochondria and an increased cytoplasmic area [29]. It is unclear whether these are causes or consequences of metabolic remodeling. The metabolic pathways within the cardiomyocyte are spatially organized, and although the majority of the cell's energy is derived from fatty acid oxidation, there are particular ATPases which rely more heavily on glycolytic ATP production (see [30] for review); these include the ATPases involved in sarcoplasmic reticulum function, and it therefore makes sense that sarcoplasmic reticulum function, and therefore calcium handling, would be susceptible to both the ultrastructural and the metabolic changes which occur in the diabetic heart.

When myocardium starts to fail in the non-diabetic heart, the reaction norms aim to restore normal economy (calories/g of tension). Two of the adaptations which permit this are reexpression of the fetal phenotype (with the consequent slowing of Vmax), and a decrease in the heat produced per gram of tension, achieved through shifts in metabolism towards glucose oxidation [31]. The former adaptation occurs in the diabetic heart, but the latter adaptation is clearly not available to the diabetic heart. One intriguing question, very difficult to answer in practice, is whether a switch towards glucose oxidation, is more cardioprotective, or at least less maladaptive, than a switch to fatty acid oxidation, because of a need to limit the heat produced per gram of tension. A third mechanism for restoring cardiac economy is provided by cardiac hypertrophy, which increases muscle mass to restore wall stress. These processes are beneficial at the level of the cardiomyocyte, because they improve economy, but they become maladaptive at the level of the heart because a slowing of Vmax contributes to decreased contractile function and remodelling of the heart impairs its mechanical function. The basic problem is that the adaptive responses seem to favour restoration of economy over restoration of inotopy. In other words, they have evolved to serve the needs of the cells but not of the organ they form.

The changes discussed so far induce a mild diastolic dysfunction which is too subtle to be detected by routine echocardiography and is only appreciable on Doppler echocardiography. The superimposition of ventricular hypertrophy, cardiomyocyte apoptosis and necrosis, and fibrosis causes progression of the diastolic dysfunction and induces a mild systolic dysfunction sufficient to activate the renin-angiotensin system. Autonomic neuropathy also occurs and exacerbates the dysfunction. As the disease reaches its most advanced stage, microangiopathy develops, and the superimposition of hypertension and ischemic heart disease leads to combined systolic and diastolic function, severe enough to activate the sympathetic nervous system. Within these responses, a range of other maladaptive responses can be observed. Activation of the renin-angiotensin and sympathetic nervous systems are maladaptive responses of systems which have not evolved to discern and respond differentially to cardiogenic causes of low blood pressure. The superimposition of pressure overload may trigger mechanosensor-mediated contractile remodeling. It is impossible to dissect the relative importance of metabolic, hormonal and mechanical stimuli to a particular reaction norm. However, the fact that metabolic and contractile remodeling predates any appreciable pressure overload in the pathogenesis of diabetic cardiomyopathy strongly suggests that the early triggers are biochemical and hormonal rather than mechanical.

4 The Mechanisms of the Reaction Norms

There are two major mechanisms by which the metabolic milieu could change the cardiac phenotype, thereby creating the reaction norms. The first involves molecular transcriptional regulators such as PPAR-α or the effectors of the hexosamine biosynthetic pathway which have already been discussed. However, an additional feature of this response is worthy of brief consideration. One of the most crucial adaptations a cell, tissue, organ system or organism requires is the ability to anticipate and prepare for predictable cyclical changes in the environment. If the appearance of a stimulus follows a circadian pattern, then the reaction norm would be well served by linking the phenotype not just to the environmental signal, but to an internal clock which can anticipate the appearance of that signal. Such a molecular clock exists, and it is intricately interwoven with a range of metabolic loops [32]. Intriguingly, diabetes induces a phase advance in the clock, which could exacerbate an already maladaptive state. There is a difference in the disposition of glucose and fatty acids between the awake and sleep phases [33, 34]. During the awake phase, glucosyl units are channelled towards complete oxidation, whereas during the sleep phase, exogenous fatty acids are channelled into synthetic pathways for phospholipids, DAG and TAG and oxidation of fatty acids is reduced. The susceptibility of the heart to cytoplasmic accumulation of fatty acids and depression of cardiac function is normally greatest during the sleep phase. This has implications for the pathogenesis of the metabolic syndrome and type 2 diabetes which are beyond the scope of the present discussion. What is relevant is that the phase shift would be expected to alter the periods during which the diabetic heart is susceptible to depression of cardiac function so that they occur during the awake phase (see [35] for review).

The second potential mechanism is epigenetic regulation. Epigenetics refers to heritable information other than the DNA sequence. Two of the most common and best characterized mechanisms are DNA methylation and acetylation. In general, genes are inactivated by the attachment of methyl groups to cytosines or the detachment of acetyl groups from lysines on histones. Methylation of histones can either activate or deactivate a gene. Epigenetic regulation is known to be intricately linked to calorie availability through mitochondrial energetics (see Fig. 3). This nuclear-mitochondrial interaction has an evolutionarily ancient origin [36]. The original proto-nucleus-cytosol had a limited metabolic capacity which was relieved when a symbiotic relationship developed between the proto-nucleus-cytosol and an oxidative protobacterion, which became the proto-mitochondrion, giving rise to the first eukaryotic cells. The limiting factor for the growth and replication of these cells was the amount of energy the proto-mitochondria could produce, which in turn was limited by the calorie availability. It was therefore necessary for growth and replication to be regulated so that it could respond to calorie availability. Epigenetic mitochondrial-nuclear interactions therefore evolved. Given the fact that diabetes is associated with fundamental alterations in metabolic fluxes, it is highly likely that there are associated alterations in the mitochondrial-nuclear interactions which lead to altered gene expression. However, this is a virtually untapped area of research.

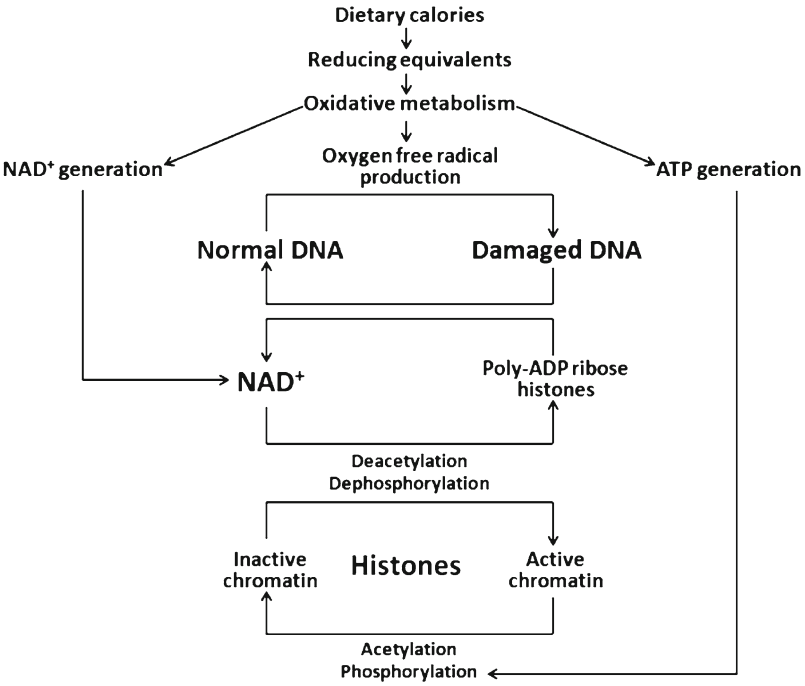

Fig. 3 Simplified schematic providing an overview of the regulation of the epigenome by energetics. Oxidative metabolism of reducing equivalents leads to the production of NAD^+, ATP and oxygen free radicals. Oxygen free radicals produce DNA damage, the repair of which is coupled via NAD^+ to epigenetic regulation. NAD^+ itself drives deacetylation reactions, while ATP fuels phosphorylation reactions, including chromatin phosphorylation

There is emerging evidence that vascular complications of diabetes can develop even with intensive glycemic control. One possible explanation for this is the phenomenon of hyperglycemic memory, in which a transient exposure to hyperglycemia produces permanent cellular effects which persist long after the restoration of normoglycemia. There is evidence which suggests that DNA methylation induced by transient hyperglycemia could be the underlying mechanism of this effect [37]. Furthermore, a wide range of genes involved in the pathogenesis of diabetic cardiomyopathy have been shown to be subject to epigenetic regulation. These include the fetal gene program, endothelin-1, glut-4, the angiotensin-1 receptor, transforming growth factor-β, matrix metalloproteinases, PPAR-γ and a range of pro-inflammatory genes (see [38, 39] for review). A few such genes have also been shown to be epigenetically regulated in the heart itself, either by hyperglycemia or chronic diabetes [40–49] (Table 1).

The final stage in the development of diabetic cardiomyopathy is associated with the superimposition of ischemic heart disease, and epigenetic regulation, in addition to mediating the primary pathogenesis of the disease, could conceivably increase

Table 1 A summary of currently described examples of pathologically-relevant epigenetic regulation in the diabetic heart

Gene	Cell type or organ	Effect	Reference
NF-Kb p65 subunit	Vascular cells	Activation by hyperglycemia	[41, 42]
Interleukin-6 and monocyte chemotactic protein-1	H9C2 cells	Activation by hyperglycemia	[43]
IGF-1 receptor	Cardiomyocytes	Repressed by hyperglycemia	[48]
Hypertrophic genes	Mouse heart	Activation in type 2 diabetes, increased by renal failure	[40]
Angiogenic factors	Human cardiac tissue	Differential expression in cardiomyopathy	[44]
SERCA-2	Cardiomyocytes	Repression in diabetes, mediated by tumour necrosis factor-α	[45]
p21 (cell cycle control protein)	Cardiomyocytes	Up-regulation in streptozotocin-diabetes	[47]
Cyclin D1	Cardiomyocytes	Repression in streptozotocin-diabetes	[46]
Liver X receptor-α	Rat heart	Activation in streptozotocin-diabetes	[49]

the susceptibility of the diabetic heart to ischemic damage. The Reperfusion Injury Salvage Kinase (RISK) pathway (which includes Akt and Erk 1/2), the Survivor Activating Factor Enhancement pathway (which includes STAT-3) and the Sirtuin-1 (Sirt-1)-p53 pathway are activated in the setting of myocardial infarction and are believed to be cardioprotective in the short-term, and to be involved in cardiac remodelling in the long-term [50, 51]. There is some evidence that the expression and activity of the proteins in these pathways is inhibited in the diabetic heart; the mechanism appears to partly involve decreased acetylation of a transcription factor involved in regulating Sirtuin-1 expression, which hints at a possible link to epigenetic regulation [52].

An additional form of gene regulation exists in the form of micro-RNAs (miRNAs), which are endogenous short non-coding RNAs that inhibit gene expression either by repressing translation or by enhancing degradation of their target mRNAs. Micro-RNAs are evolutionarily conserved, and their evolution and development has been linked to the emergence of organismal complexity (see [53] for review). In the context of heart disease, miRNA-mediated mechanisms have, to date, mostly been identified in the pathways of cardiac hypertrophy, fibrosis and apoptosis. Intriguingly, there is preliminary evidence of bi-directional modulation between miRNAs and epigenetic regulatory pathways. A subgroup of miRNAs called epi-miRNAs target the proteins involved in the epigenetic machinery. Conversely, the first evidence for epigenetic regulation of miRNA expression is beginning to emerge (see [39] for review).

5 Conclusion

The heart is an omnivorous organ which can use any substrate it is supplied with. The metabolic machinery of the heart is exquisitely attuned both to its metabolic needs and to the available energy substrates in its local environment. Diabetic cardiomyopathy is a disease process which arises as a result of the inability of the heart to adapt to a diabetic metabolic milieu. The heart becomes locked into a progressively maladaptive state from which it cannot escape by its own devices; due to the phenomenon of hyperglycemic memory, even restoration of a normal milieu may not be sufficient to completely reverse the remodeling. The pathways which initiate, progress and perpetuate this downward spiral are the same pathways which normally allow the heart to sense and respond to its local metabolic environment. These include metabolite-sensitive transcriptional regulatory pathways and, most probably, epigenetic and miRNA regulatory pathways. Overall, the application of evolutionary concepts provides a valuable framework for understanding the origins and importance of metabolic and contractile disturbances in the diabetic heart, and a strong rationale for the use of metabolic therapy as a treatment.

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