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Review

An overview of the crosstalk between inflammatory processes and metabolic dysregulation during diabetic cardiomyopathy

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ABSTRACT

Metabolic disorders such as obesity, insulin resistance and type 2 diabetes mellitus are all linked to cardiovascular diseases such as cardiac hypertrophy and heart failure. Diabetic cardiomyopathy in particular, is characterized by structural and functional alterations in the heart muscle of people with diabetes that finally lead to heart failure, and which is not directly attributable to coronary artery disease or hypertension. Several mechanisms have been involved in the pathogenesis of diabetic cardiomyopathy, such as alterations in myocardial energy metabolism and calcium signaling. Metabolic disturbances during diabetic cardiomyopathy are characterized by increased lipid oxidation, intramyocardial triglyceride accumulation, and reduced glucose utilization. Overall changes result in enhanced oxidative stress, mitochondrial dysfunction and apoptosis of the cardiomyocytes. On the other hand, the progression of heart failure and cardiac hypertrophy usually entails a local rise in cytokines in cardiac cells and the activation of the proinflammatory transcription factor nuclear factor (NF)-κB. Interestingly, increasing evidences are arising in the recent years that point to a potential link between chronic low-grade inflammation in the heart and metabolic dysregulation. Therefore, in this review we summarize recent new insights into the crosstalk between inflammatory processes and metabolic dysregulation in the failing heart during diabetes, paying special attention to the role of NF-κB and peroxisome proliferator activated receptors (PPARs). In addition, we briefly describe the role of the AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1) and other pathways regulating cardiac energy metabolism, as well as their relationship with diabetic cardiomyopathy.

1. Introduction

If uncorrected, metabolic diseases such as obesity and type 2 diabetes mellitus may lead to cardiac hypertrophy and compromised myocardial function. Insulin resistance, which is a hallmark of type 2 diabetes, is a risk factor of heart failure, the leading cause of death in type 2 diabetic patients [1]. However, despite this epidemiological evidence, the mechanisms by which type 2 diabetes impairs the heart function have not been completely unveiled. Diabetic cardiomyopathy, which refers to structural and functional alterations in the heart of these patients, is related to disturbances in myocardial energy metabolism that lead to the pathogenesis of cardiac diseases. The diabetic heart is characterized by concentric left ventricular hypertrophy, dilated cardiomyopathy and extracellular fibrosis, all affecting cardiac output [2]. This is accompanied by increased lipid oxidation, intramyocardial triglyceride accumulation and reduced glucose utilization, resulting in enhanced oxidative stress, mitochondrial dysfunction and apoptosis.

An increasing body of evidence suggests a potential link between chronic low-grade inflammation and metabolic disorders such as insulin resistance, overt obesity and type 2 diabetes, which are associated with abnormal cytokine production. Dietary fat affects gene expression, structure, metabolism and contractile function in the heart. Indeed, a high-fat diet in mice results in myocardial insulin resistance and is related to a range of direct cardiac effects, including inflammation, hypertrophy, fibrosis and contractile dysfunction [3]. Cardiac glucose metabolism is reduced in obese mice fed a high-fat diet, in a process which is associated with increased levels of pro-inflammatory cytokines [4]. On the other hand, the progression of heart failure and cardiac hypertrophy usually entails a local rise in cytokines such as interleukin

Abbreviations: ACO, acyl-CoA oxidase; ACS, acyl-CoA synthase; AMPK, AMP-activated protein kinase; CPT, carnitine palmitoyl transferase; ERK1/2, extracellular signal-regulated protein kinase 1/2; ERR, estrogen-related receptor; FABP, fatty acid binding protein; FAT/CD36, fatty acid translocase/CD36; FATP, fatty acid transport protein; FOXO1, forkhead transcription factor; IKK, IκB kinase; IL-6, interleukin 6; JNK, c-Jun N-terminal kinase; LDL, low density lipoprotein; LPL, lipoprotein lipase; MAPK, mitogen-activated protein kinase; MCAD, medium-chain acyl-CoA dehydrogenase; MCP-1, monocyte chemoattractant protein-1; NADH, nicotinamide adenine dinucleotide; NFAT, calcineurin-nuclear factor of activated T cells; NF-κB, nuclear factor-κB; PDC, pyruvate dehydrogenase complex; PDK, pyruvate dehydrogenase kinase; PI3K, phosphatidylinositol 3 kinase; PKB/Akt, protein kinase B; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; PPAR, peroxisome proliferator-activated receptor; PPRE, peroxisome proliferator response element; ROS, reactive oxygen species; RXR, retinoid X receptor; SAFE, survival activating factor enhancement; SIRT1, sirtuin 1; STAT, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; TCA, tricarboxylic acid cycle; TNF-α, tumor necrosis factor-α.

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(IL)-6, monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) [5]. These molecules exert several autocrine effects in cardiac cells via downstream activation of the transcription factor nuclear factor (NF)-κB, which may contribute to states that are associated with myocardial inflammation, such as ischemic myocardial injury, heart failure and dilated cardiomyopathy [6,7]. Therefore, in this review we summarize recent insights into the crosstalk between inflammatory processes and metabolic dysregulation in the failing heart during diabetes, paying special attention to the role of NF-κB and peroxisome proliferator activated receptors (PPARs). The importance of the potential cardioprotective action of PPARs is also discussed. In addition, we briefly discuss the role of the AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1), and other pathways regulating cardiac energy metabolism and their relationship with inflammation during diabetic cardiomyopathy.

2. Metabolic regulation in the normal heart

The human heart consumes 10 to 15 times its own weight every day, but ATP cardiac reserves are barely sufficient for 10 s of cardiac function [8]; thus, a constant supply of fuel is required. Mitochondria are responsible for meeting the energy demands of the postnatal mammalian heart through oxidative phosphorylation, and consistent with this, cardiac myocytes contain numerous mitochondria. Free fatty acids, predominantly long-chain fatty acids bound to albumin and fatty acid esters present in chylomicrons and lipoproteins, are the preferred energy substrate in the adult heart, supplying about 70% of total ATP [2]. Nevertheless, other substrates such as glucose (20%) or lactate (10%) may provide additional fuel sources in diverse physiological and nutritional circumstances [9].

Glucose uptake by cardiac cells is mostly regulated by the amount and activity of the glucose transporters GLUT1 and GLUT4, of which GLUT4 is the most abundant [10]. Once inside the cardiomyocytes, glucose is phosphorylated by hexokinase into glucose-6-phosphate, which can either be stored as glycogen or converted into pyruvate, the end product of glycolysis, through anaerobic metabolism in the cytosol of the cardiomyocyte (Fig. 1). Pyruvate derived from glucose or lactate enters the mitochondria where it undergoes oxidative decarboxylation by the pyruvate–dehydrogenase complex (PDC), localized within the inner mitochondrial membrane. With regard to the fatty acids, besides a significant amount of fatty acids that may enter the cardiomyocyte cell membrane by passive diffusion, several proteins have been identified as being involved in their transport and uptake, such as fatty acid translocase (FAT/CD36), fatty acid binding protein (FABP) and fatty acid transport protein 1 (FATP1) [10]. In the cytoplasm, long-chain fatty acids are activated into acyl-CoAs by the acyl-CoA synthetase (ACS), and either enter the mitochondria by the action of carnitine palmitoyl transferase 1 (CPT-1) or are incorporated into the intracellular lipid pools. CPT-1 catalyzes the transfer of long-chain fatty acids from acyl-CoA to carnitine to form acyl-carnitine, which is the rate-controlling step in the mitochondrial fatty acid oxidation pathway. Next, acylcarnitine translocates to the inner mitochondrial membrane

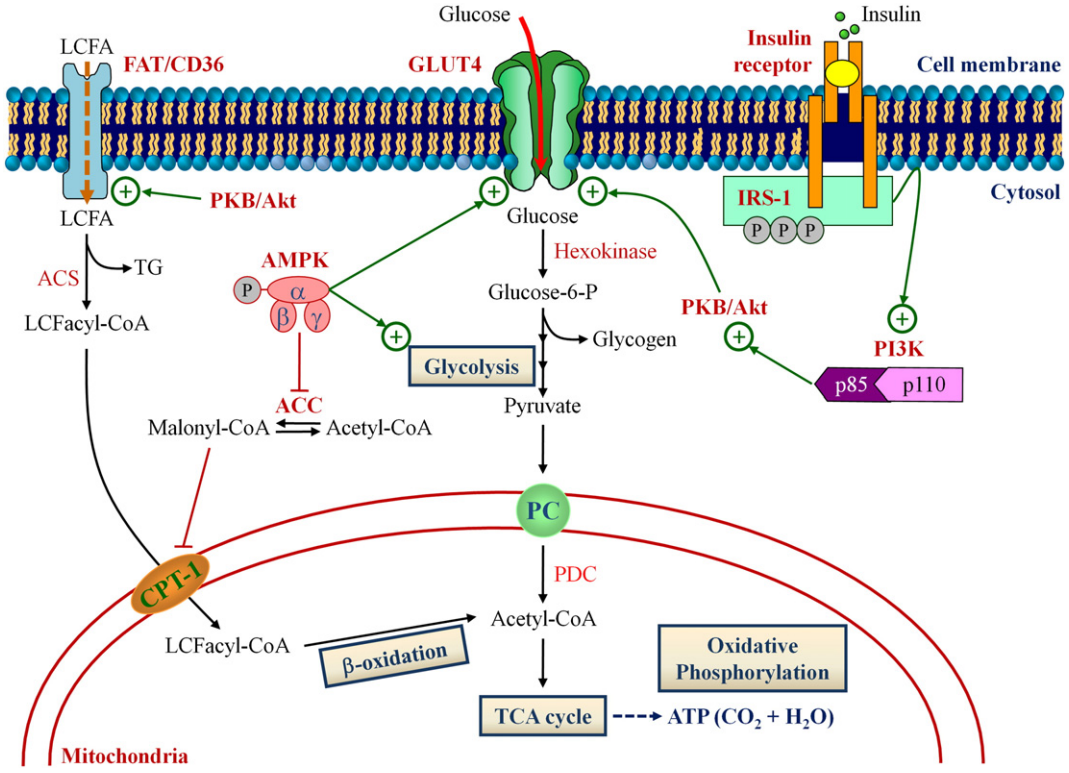

Fig. 1. Metabolic regulation in the normal heart. Upon uptake by GLUT4, glucose is phosphorylated by hexokinase into glucose-6-phosphate, which can either be stored as glycogen or converted into pyruvate, the end product of glycolysis. Pyruvate enters the mitochondria through a specific and as yet unidentified carrier (pyruvate carrier, PC), where it undergoes oxidative decarboxylation by the pyruvate–dehydrogenase complex (PDC). Long-chain fatty acids (LCFA) enter by passive diffusion or specific transporters (fatty acid translocase, FAT/CD36). In the cytoplasm, LCFA are activated into acyl-CoAs (LCFacyl-CoA) by the acyl-CoA synthetase (ACS), and either enter the mitochondria by the action of carnitine palmitoyl transferase 1 (CPT-1), or are incorporated into the intracellular lipid pool (as triglycerides, TG). In the mitochondrial matrix, fatty acids are oxidized by the fatty acid β-oxidation pathway to form acetyl-CoA. The acetyl-CoA formed during glucose or fatty acid oxidation enters the tricarboxylic acid (TCA) cycle and finally generates ATP through oxidative phosphorylation. The binding of insulin to its receptor on the cell surface activates the phosphorylation of tyrosine residues at the insulin receptor substrate 1 (IRS-1). IRS-1 activates the phosphatidylinositol 3 kinase (PI3K), which initiates a kinase cascade that activates the protein kinase B (PKB)/Akt. PKB/Akt induces the translocation of GLUT4 to the cell membrane of cardiac cells, thereby increasing the glucose uptake rate. PI3K is also capable of promoting FAT/CD36 translocation to the sarcolemma in adult cardiomyocytes. AMPK activation through phosphorylation at its Thr172 residue induces the acetyl-CoA carboxylase (ACC) phosphorylation-mediated inhibition, resulting in the down-regulation of malonyl-CoA levels, an inhibitor of CPT-1. Furthermore, AMPK promotes myocardial GLUT4 expression and translocation to the plasma membrane, and also stimulates glycolytic enzymes.