Biomedicine & Pharmacotherapy 90 (2017) 386–392

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

The role of SIRT1 in diabetic cardiomyopathy

Hedyieh Karbasforooshan[a], Gholamreza Karimi[b,*]

[a] Faculty of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Pharmaceutical Research Center, Pharmacy School, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article history:
Received 21 January 2017
Received in revised form 15 March 2017
Accepted 20 March 2017

Keywords:
Cardiomyopathy
Diabetes
Oxidative stress
SIRT1

ABSTRACT

The prevalence of diabetes mellitus (DM) has been increasing worldwide. Diabetic cardiomyopathy (DCP) is the major risk for diabetes associated morbidity and mortality. Hyperglycemia and hyperinsulinemia play an indispensable role in underlying mechanisms of DCP. They increase advanced glycation end products (AGEs) following a series of events leading to myocardial damage and cardiomyopathy which include oxidative stress, increased inflammation, fibrosis, hypertrophy and apoptosis. SIRT1 is a nicotinamide adenosine dinucleotide (NAD)-dependent deacetylase that removes acetyl groups from proteins which can be implicated in DCP. SIRT1 modulate different proteins related to hyperglycemia. SIRT1 inhibits transcriptional factors, such as p300, NF-κB, P38MAPK, Histone 3, MMP-9, FOXO3a and p53. On the other hand, it increases SERCA2a, ERK1/2/Homer1, eNOS, PGC-1α and AMPK. Therefore, SIRT1 attenuate cardiac dysfunction and improve DCP. This review focus on the role of SIRT1 in diabetic cardiomyopathy.

Contents

Abbreviations: SIR2, Silent Information Regulator2; HDACs, histone deacetylases; NAD +, nicotinamide adenine dinucleotide; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; DCP, diabetic cardiomyopathy; MRI, magnetic resonance imaging; MAPK, mitogen-activated protein kinases; JNK, C-JUN terminal kinases; ERK, extracellular signal-regulated kinase; AGEs, advanced glycation end products; AMPK, adenosine monophosphate-activated protein kinas; UPR, unfolded protein response; ER, endoplasmic reticulum; SERKA2a, sarcoplasmic reticulum calcium ATPase; LVH, left ventricular hypertrophy; TGFB1, transforming growth factor B1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated of B cells; MMP-9, matrix metalloproteinase9; CHM, hypertrophic cardiomyopathy; IGF-1, insulin-like growth factor; PARP1, poly ADP-ribose polymerase; NO, nitric oxide; I/R, ischemia-reperfusion; FOXO, fork head box o; PI3K, phosphatidylinositol-3-kinase; PGC-1α, Peroxisome proliferator-activated receptor gamma-coactivator alpha.

* Corresponding author.
E-mail address: KarimiG@mums.ac.ir (G. Karimi).

http://dx.doi.org/10.1016/j.biopha.2017.03.056
0753-3322/

1. Introduction

1.1. Sirtuins

Silent Information Regulator 2 (SIR2) proteins-Sirtuins-are a family of histone deacetylases (HDACs) that catalyse deacetylation of both histone and none-histone lysine residues [1]. Sirtuins regulate important metabolic pathways in prokaryotes and eukaryotes and are involved in many biological process such as cell survival, senescence, proliferation, apoptosis, DNA repair, cell metabolism and calorie restriction [2]. In mammals, there are 7 homologues of SIR2 termed sirtuins (SIRT1-SIRT7). SIRT1 was the first SIRT family member to be discovered and is still the most studied. It needs cellular nicotinamide adenine dinucleotide (NAD $^{+}$) as a cofactor for deacetylation reactivity. Nicotinamide is liberated from NAD $^{+}$, generating the novel metabolite o – acetyl – ADP – ribose. Sirt1 is found in the nucleus and cytoplasm and is considered as a potential target for the treatment of human pathologies such as cardiovascular diseases especially diabetic cardiomyopathy [3] (Fig. 1).

1.2. Diabetes

Diabetes mellitus (DM) is one of the major health threats in the modern societies [4]. The incidence and prevalence of diabetes mellitus have significantly increased worldwide in recent decades [5]. It is also the most common lifestyle disorder in the developed and developing countries [6]. DM is a metabolic disease characterized by hyperglycemia resulting from defects of insulin secretion or insulin action or both [7]. There are two main from of diabetes, type I and type II. Cardiovascular disease are responsible from the three quarter of the deaths among this population. Although coronary artery disease (CAD) is very common, heart failure (HF) is also a major cause of mortality and morbidity in diabetic patients [8].

Some studies demonstrated the increased incidence of HF in diabetic males (2.4:1) and female (5:1). Female patients seem to be particularly susceptible to the development of this complications of metabolic disease [9].

T type 2 diabetes is a polygenic disease. Various genetic factors increase the risk of T2DM and its complications, such as cardiomyopathy. Single nucleotide polymorphism in different candidate genes, such as Guanine nucleotide-binding protein subunit beta3 (GNB3), Norepinephrine transporter (NET), Potassium channel gen (KCNJ11), Transcription factor 7-like2 (TCF7L2) and Glucocorticoid receptor (GRL) are involved in the pathway leading to T2DM. Thus, a susceptible gene in one population might not show the same phenotypic effect in other population. Identification of these genes help in prevention of diabetes and also the risk of secondary complication, such as cardiomyopathy [10].

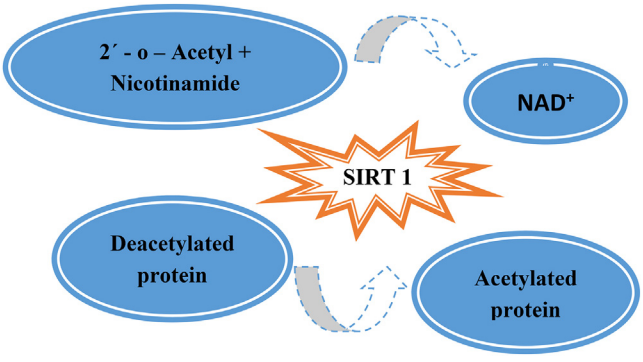

Fig. 1. Cellular nicotinamide adenine dinucleotide (NAD^{+}) needed as a cofactor for deacetylation reaction catalyzed by sirt1: sirt1 act by removing acetyl groups from proteins in the presence of NAD+. It add the acetyl group from the protein to the ADP-ribose part of NAD+ to form o-acetyl-ADP-ribose and nicotinamide.

Under physiological conditions, insulin stimulate the uptake of glucose into cardiac muscle, skeletal muscle, liver, adipose tissue and other metabolic tissue to maintain glucose homeostasis. Reduced insulin signaling and/or insulin resistance together with the associated diminution in glucose transport, promotes an increase in pancreatic production of insulin that results in hyperinsulinaemia. Insulin resistance and hyperinsulinaemia are associated with the cardiac metabolic syndrome, contributing to the early stage of cardiovascular disease [11].

1.3. Diabetic cardiomyopathy

Diabetic cardiomyopathy (DCP) was first defined by Rubler in 1972 [8]. It is characterized by ventricular systolic and (or) diastolic dysfunction that occurs in patients with diabetes independent of coronary artery disease (CAD), hypertension and other cardiovascular diseases [12]. DCP occurs in both type 1 and type 2 diabetes and contributes to increase the incidence of heart failure in diabetic population [13]. The most frequently used diagnostic methods are electrocardiography and cardiac magnetic resonance imaging (MRI). Although strict glycemic control seems to play the central role for prevention and treatment of DCP, we need novel therapeutic agent, specific to diabetic cardiomyopathy. On these findings, it is necessary to understand pathogenesis of DCP [8]. The metabolic dysfunction associated with diabetes, such as hyperglycemia, increased circulating fatty acids, hyperinsulinemia and increased inflammatory cytokines, alter multiple molecular pathways within the cardiomyocytes which impair cardiac contractility and promote myocyte dysfunction, injury and cell death. The exact mechanism of DCP pathogenesis is still unclear, but some mechanisms have been shown to play an important role in the development of DCP, such as; altered signal transduction (insulin signaling), altered metabolism and mitochondrial dysfunction, post-translational modifications of structural and signaling proteins and altered cell homeostatic processes such as autophagy and ER stress. These ways result in oxidative stress and apoptosis [14]. All together lead to common changes of diabetic heart like myocyte hypertrophy, interstitial fibrosis and increase in contractile protein glycosylation [8]. This review summarizes the role of sirt1 in the diabetic cardiomyopathy. Understanding the mechanisms of sirt1 will increase the prospects for controlling and preventing cardiovascular complication in diabetes mellitus [15].

1.3.1. ERK1/2/Homer1a/SIRT1

Hyperglycemia is an important risk factor for cardiovascular diseases no matter if it is resulted from type I or type II DM [16]. Hyperglycemia leads to an increase in oxidative stress and activate the calcium channels of cardiomyocytes that cause an acute rise of intracellular calcium concentration.

Intracellular calcium overload results in mitochondrial calcium accumulation which leads to the generation of reactive oxygen