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Review

SIRT3-mediated cardiac remodeling/repair following myocardial infarction

Aynaz Mihanfar[a,b,1], Hamid Reza Nejabati[b,d,e,1], Amir Fattahi[f], Zeinab latifi[b,d], Yousef Faridvand[b], Masoud Pezeshkian[c], Ahmad Reza Jodati[c], Naser Safaie[c], Abbas Afrasiabi[c,**], Mohammad Nouri[b,f,*]

[a] Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[b] Stem Cell and Regenerative Medicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Department of Biochemistry and Clinical Laboratories, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Department of Reproductive Biology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences Tabriz, Iran

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ABSTRACT

The recent investigations have extensively focused on the importance of sirtuins, as a highly conserved family of gene products, particularly SIRT3 in various biological and pathological processes. SIRT3, the mitochondrial NAD + -dependent deacetylase has been demonstrated to target a broad range of proteins involved in the oxidative stress, ischemia–reperfusion injury, mitochondrial metabolism homeostasis and cellular death. The critical function of SIRT3 in myocardial infarction (MI), which is one of the complex phenotype of coronary artery disease and a result of interaction between various genetic and environmental factors, as well as in cardiac repair and remodeling post-MI have attracted more attention in the recent years. Therefore, in this review, we will summarize important literature about the involvement of SIRT3 in cardiac remodeling/repair following MI and its potential underlying mechanisms.

1. Introduction

Myocardial infarction (MI), as one of the complex phenotype of coronary artery disease, is a result of interaction between various genetic and environmental factors [1,2]. MI is followed by the some important structural remodeling in cardiac muscle including an increased inflammatory response and generation of fibrous scar at the site of infarction. More importantly, in the non-infarcted sites of affected myocardium, vascular remodeling and interstitial fibrosis are also observed [3]. At the site of cardiomyocyte loss, fibrous scar plays critical role in the preserving structural integrity, hence cardiac recovery, which finally results in the impairment of myocardial tissue behavior. Also, in this process, various substances and proteins have been reported to act crucial functions in cardiac repair/remodeling, therefore, attracted substantial interest as pharmacological intervention [4]. Recently, sirtuins, as a plausible novel highly conserved family of gene products, have been attracted a considerable attention, through their moonlighting role in the various biological processes including oxidative-stress resistance, cell-cycle regulation, insulin secretion, mitochondrial energetics and inflammatory cardiomyopathy [5]. This family has seven members named SIRT1–7, and SIRT1 is the most well-known member of this family. In addition to high degree of structural similarity in all sirtuin proteins, some significant differences are reported in their C and N termini, which have increasing importance in the diverse biological behavior of proteins including, enzymatic activities, specific substrates, expression pattern and subcellular localization [6]. Among this gene family, loss of function of SIRT3 has been reported to be involved in the pathogenesis of cardiac hypertrophy and the transition into heart failure. Additionally, accumulating studies investigating gain of function of SIRT3, as well as activation of SIRT3 through treatment approaches, have demonstrated that signaling through this member of sirtuin family can ameliorate cardiac pathologies through various

Abbreviations: MI, myocardial infarction; HIF, hypoxia inducible factor-1α; SOD2, superoxide dismutase; FOXO3A, forkhead box O3a; OPA1, optic atrophy 1; MMPs, matrix metalloproteinases; TGF-β, transforming growth factor-β; PARP-1, poly (ADP ribose)- polymerase 1; VEGF, vascular endothelial growth factor; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; EPCs, endothelial progenitor cells

* Corresponding author at: Stem Cell and Regenerative Medicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran.
** Corresponding author at: Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail addresses: aaaafrasa@gmail.com (A. Afrasiabi), nourimd@yahoo.com (M. Nouri).
[1] These authors considered equally as co-first authors.

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mechanisms, therefore represent a promising therapeutic strategy for cardiac pathologies, particularly cardiac repair following MI [7]. In the present review, we will focus on the underlying mechanism of SIRT3 signaling, by which cardiac repair/ remodeling can be increased.

2. SIRT3: structure and molecular signaling

SIRT3, as an important member of sitruins family with recently discovered plenty of biological functions, is a soluble protein located at mitochondria and has considerably high expression levels in tissues enriched with mitochondria [7]. In addition, recent studies investigating the precise physiological and pathophysiological function of this protein, have been reported the crucial role of SIRT3 in cellular stress, oxidative stress response, fatty acids metabolism, energy metabolism, tumor suppression, and age-associated hearing loss [7]. In the normal myocardium, it is estimated that oxidative phosphorylation in mitochondria is responsible for the providing approximately 90% of ATP required for cardiac normal function. The key material source for this type of energy production is fatty acid beta oxidation [4]. The main enzymes with critical function in oxidative phosphorylation, hence mitochondrial energy metabolism are under direct regulation of SIRT3, which can modulate the enzymatic activity of various enzymes through deacetylation [8]. Reduction in SIRT3 levels is one of the main promoters of glycolysis pathway through two different mechanisms. First, when SIRT3 is absent, hexokinase II is activated because of highly acetylated state of peptidylprolyl isomerase D, and through phosphorylation of glucose, produced glucose-6-phosphate (G6P) [9]. Second mechanism is consisted of stabilization of transcription factor, hypoxia inducible factor-(HIF) 1α, through inducing enhancement in the reactive oxygen (ROS) production. The results of this pathway are regulation of glycolytic gene expression [10]. Deacetylation activity of SIRT3 also plays critical function in stimulation of β oxidation through modification and activation long-chain acyl-CoA dehydrogenase [11]. Acylglycerol kinase, medium chain-specific acyl-CoA dehydrogenase, and acyl-CoA synthetase short-chain family member 2 are also reported to be directly regulated by SIRT3 [12–14]. The later one is involved in the conversion of acetate to acetyl-CoA and its entrance to tricarboxylic acid cycle [13,14]. 3-hydroxy-3-methylglutaryl-CoA synthase 2 (ketone-body biosynthesis) [15], glutamate dehydrogenase 1 (amino acid metabolism) [16], ornithine transcarbamylase (urea cycle) [17], the ribosomal protein MRPL10 [18], electron transport chain complex I and II including [16], ATP synthase activity [19], are all deacetylated and hence activated by SIRT3. Another important function of SIRT3 is enhancing the ability of the mitochondria to deal effectively with ROS, and subsequent increased oxidative stress, cellular damage and death, which are closely associated with various cardiac pathologies such as coronary atherosclerosis [20–24], cardiac hypertrophy [25–27], hyperlipidemia [17,28], diabetes [29,30]. SIRT3 is also demonstrated to deacetylate and activate Mn superoxide dismutase (SOD2), the main superoxide radicals scavenger [31–33], hence decrease ROS production and protective response against oxidative stress-induced cellular damage. SIRT3- mediated decrease in the translocation of Forkhead box O3a (FOXO3A) from the nucleus into cytosol results in the robust transcription of SOD2 and other antioxidation [34]. In addition to these well-defined functions of SIRT3, some studies have focused on the effects of SIRT3 expression on the apoptosis and reported controversial results. However, what is evident is that SIRT3 is a potent inhibitor of cardiomyocyte apoptosis in various studies. This function of SIRT3 is indicated to be mediated by interesting pathways, such as deacetylation and activation of optic atrophy 1 (OPA1) [35,36], Ku70 [34], and cyclophilin D [26], as well as inhibition of the mitochondrial permeability [37].

3. Cardiac repair/remodeling following MI

Following MI and necrotic death of cardiomyocytes, cardiac repair/remodeling, which recruits some inflammatory responses make some important structural changes in both infarct and remote site [38]. Immediately after an infarction event in myocardium, matrix metalloproteinases (MMPs) are activated and begin to degradation of extracellular matrix (ECM) and coronary vasculature [39,40]. After one week, significant upregulation occurs in the expression levels of tissue inhibitors of MMPs (TIMPs), which results in the decrease in proteolytic activity of MMPs [41]. Following MI, inflammatory cells including neutrophils, which involved in the proteolytic digestion, and monocytes/macrophages, which are contributed in phagocytosis of the affected tissues, are recruited to MI site, and enter to infarcted tissue by signaling through chemoattractant cytokines and adhesion molecules, as well as MMP proteolytic activity, event that occur in different sites of body like ovulation, embryo implantation, tissue repair, and cancer [40,42–49]. Endothelial cells of the various kind of tissues and coronary vasculature are responsible for the expression of these factors [45,50]. The peak of this inflammatory reaction occurs approximately 1 and 2 weeks after a MI event, and is abolished by disappearance of inflammatory cells from MI site, which is a result of apoptosis of these cells within 3–4 weeks. Lost parachymal cells are replaced by fibrogenic component, which is triggered by the activation of transforming growth factor (TGF)-β1, as a main component of fibrogenesis [50]. After one week, collagen fibers are appeared in infarcted site and begin to assembly in the form of scar tissue at week 2, by transformed fibroblast-like cells, with exclusive morphological and phenotypic properties [51]. Myofibroblasts are fibroblast-like cells, which express α-smooth muscle actin [52] microfilaments and earn contraction ability, through signaling by macrophages-released TGF-β1 [53]. Rapidly proliferation and expression of type I and III fibrillar collagens by myofibroblasts are responsible for the generation of the contractile scar tissue in infarct site [54]. These cells are also involved in the production of renin, angiotensin-converting enzyme, angiotensin receptors, endothelin-1, and vasopressin, which play key functional role in the promotion of scar tissue contraction [55–57]. In addition to infarct site, interstitial fibroblasts develop fibrosis non-infarcted myocardium at week 3. However, myofibroblasts do not appear at unaffected sites [50].

4. SIRT3 in cardiac diseases

Accumulating number of previous studies has been reported that SIRT3 paly pivotal role in the pathogenesis of various cardiovascular diseases, including ischemic heart disease, cardiac hypertrophy and heart failure, diabetic cardiomyopathy and cardiac lipotoxicity, drug-induced cardiotoxicity, and particularly MI, which is the main discussing of present review [8,58,59]. From the developmental point of view, SIRT3 has reported to not be an important player, since SIRT deficient mice do not present significant abnormality in phenotype. However, after birth, SIRT3-/- mice are very sensitive to stress stimuli [27,60]. The most important reason for this finding is the critical function of this sitruin in the regulation of the activity of mitochondrial substrates such as several enzymes involved in the oxidative stress, electron transport and ATP production. In addition, downregulation of SIRT3 results in the significant enhancement in the risk of ischemia-reperfusion injury in adult hearts, as well as cardiac-derived cells [61,62]. It is also increasingly reported that SIRT3 play substantial roles in the vascular inflammation, the fact which potentiates the importance of SIRT3 in atherosclerosis. In chemical- induced model of vascular inflammation, it was reported that downregulation of SIRT3 resulted in the ROS production and hence increase in inflammation in endothelial cells [63]. However, the precise mechanism underlying the function of SIRT3 in atherosclerosis is not clearly understood, particularly the results of a recent study, which showed that SIRT3 deficiency did not exert any significant impact on the atherosclerotic plaque stability, and lesions progression, is an indicative of this fact [64]. In addition, an accumulating body of recent studies have been showed that cardiac hypertrophy, which causes myocardial cell death and fibrosis, and