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Invited critical review

SIRT1: Role in cardiovascular biology

Lina Ma, Yun Li *

Department of Geriatrics, Xuan Wu Hospital, Capital Medical University, Beijing 100053, China

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ABSTRACT

SIRT1 (silent information regulator two protein) is a type III protein deacetylase that regulates a variety of important metabolic and physiologic processes including stress resistance, metabolism, apoptosis and energy balance. It reverses cholesterol transport and reduces risk for development of atherosclerosis and cardiovascular disease. The following review highlights the potential role of SIRT1 on cardiovascular biology and function.

Contents

1. Introduction

Cardiovascular disease (CVD), the leading cause of death worldwide, is a progressive disorder dependent on complex interactions between cholesterol biosynthesis, the immune system and vascular endothelial cell function [1,2]. Silent information regulator factor 2 related enzyme 1 (SIRT1) is a class III histone deacetylase and the most important

* Corresponding author at: Department of Geriatrics, Xuan Wu Hospital, Capital Medical University, #45 Changchun Street, Xicheng District, Beijing 100053, China. Tel./fax: +86 10 83198707.
E-mail address: liy_xw@sina.com (Y. Li).

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protein among the sirtuin family members. The highly conserved, nicotinamide adenine dinucleotide (NAD^+)-dependent SIRT1 is involved in many physiologic processes such as gene silencing, genomic stability, cell longevity, and metabolic regulation through deacetylation of histones and a variety of non-histone substrates. Studies have recently found that SIRT1 is involved with cardiovascular disease. In fact, SIRT1 and its downstream pathways appear critical for both normal homeostasis and protection from CVD-induced defects [1]. SIRT1 regulates important metabolic and physiologic processes including stress resistance, metabolism, apoptosis and energy balance [3–5]. It also reverses cholesterol transport and reduces the risk for development of atherosclerosis and cardiovascular disease [6]. In this paper, the role of SIRT1 in cardiovascular biology is reviewed.

2. Molecular biology of SIRT1

Silencing information regulator complex (Sir complex) regulates gene transcription and plays an important role in controlling the life span of yeast [7]. In yeast, there are four Sir protein complexes (Sir1–Sir4) [8]. Of these, Sir2 is widely present from bacteria to eukaryotes. Mammalian homologues of Sir2, ie, sirtuins, are composed of seven members (SIRT1–SIRT7) that are ubiquitously expressed and contain a highly conserved deacetylase domain [9]. Among the sirtuins, SIRT1 has been the most extensively studied. SIRT1 is the most representative homologue, as it has the highest homology with basic members of the Sir2 family in yeast [10]. In 1999, it was found that the human *SIRT1* gene is located at 10q21.3 [11]. Its coding region is 33715 bp long, is highly conserved and has nine exons encoding a protein of 747 amino acids, including an N-terminal nuclear localization signal and a catalytic core composed of 275 deacetylated amino acids [12]. The catalytic core consists of a large Rossmann fold domain characterized as an NAD^+/NADH binding protein [13] and a small zinc finger domain. There are NAD binding sites at the junction of the two domains and an acetylated substrate is bound to the end of the gap close to an NAD glycosylation site. The structure of SIRT1 determines its role in cellular activities such as gene transcription, DNA replication, DNA repair and metabolic regulation. SIRT1 regulates a wide array of cellular processes crucial to cell survival, apoptosis, cell growth, cell senescence and metabolism, by deacetylating histones and many non-histone proteins [14]. Histone tail deacetylation alters the electrostatic properties of DNA–histone interaction resulting in transcriptional regulation. Additionally, numerous other non-histone SIRT1 protein targets have been reported and include peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α), forkhead transcription factor O (FoxO), nuclear factor κB (NF-κB) and tumor protein 53 (p53) [15,16]. SIRT1 is a master metabolic regulator in different tissues (Fig. 1).

Recent studies have shown that subcellular localization of SIRT1 differs among cells. In the heart, nuclear and cytoplasmic localization of SIRT1 was found to be regulated developmentally and during stress [17]. In young mice, SIRT1 was expressed in cardiomyocyte nuclei only, but in adult rats, cardiac SIRT1 was expressed in both nuclei and cytoplasm [17]. Nuclear SIRT1 presents in different models of heart failure, such as post myocardial infraction in rats and dilated cardiomyopathy in patients [18]. SIRT1 controlled endothelia angiogenic functions during vascular growth [19], and another study has found that abnormal cardiac development in SIRT1-knockout mouse model [20], indicating that SIRT1 has crucial roles in the formation of the heart. These observations suggest that myocardial cell differentiation and apoptosis may be associated with SIRT1 [17].

3. Protective roles of SIRT1 in cardiovascular disease

SIRT1 is dispensable for the survival of adult cardiomyocytes. Increased SIRT1 levels were found in hypertrophied and failing hearts [21,22]. Though cytoprotective, SIRT1 promotes cardiomyocyte growth under stress conditions, a study has found that blocking of SIRT1 activity with inhibitors increased the propensity of cardiomyocytes to death, but prevented hypertrophy of myocytes in response to stress stimuli. SIRT1 can protect cells from death in response to serum starvation, but causes an overall increase in size of cardiomyocytes [23]. SIRT1 homozygous knockout mice in an inbred genetic background exhibit severe developmental defects in the heart and they mostly die after birth [24,25]. A study on Tg-Sirt1 mice which were generated on an FVB background using the α-myosin heavy chain (α-MHC) promoter has found that a low to moderate expression of SIRT1 (2.5–7.5 fold over endogenous levels) was found to be protective against age dependent increase in cardiac hypertrophy, apoptosis, and cardiac dysfunction; whereas

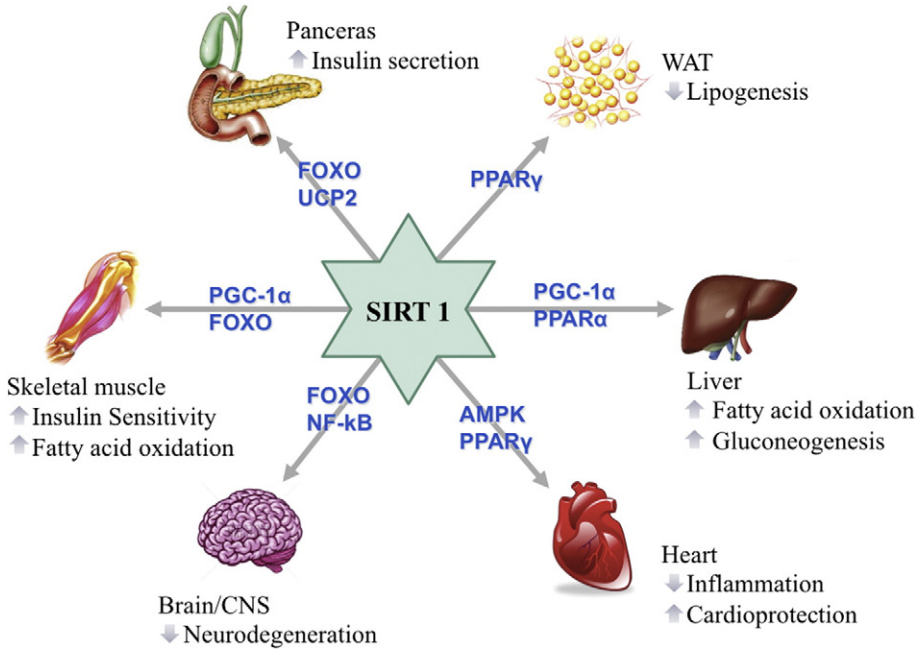

Fig. 1. SIRT1 is a master metabolic regulator in different tissues. SIRT1 plays a vital role in cardiomyocytes, white adipose tissue (WAT), liver, fat, neurons and skeletal muscle, which will ultimately affect the processes of aging and disease.