SIRT1 Activators and Their Effects on Atherosclerosis Progression

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Abstract

Atherosclerosis is the main cause of Cardiovascular Disease (CVD), which is the leading cause of death worldwide. Hyperlipidemia and associated lipid metabolic disorders are the major risk factors involved in the progression of atherosclerosis. Sirtuins (SIRT1-SIRT7) are a family of NAD+-dependent deacetylases that catalyze the deacetylation of both histone and non-histone protein substrates. Among sirtuins, Siruin 1 (SIRT1) has been intensively investigated due to its broad regulatory effects on lifespan and cellular metabolism. Accumulating recent evidence has shown that activating SIRT1 genetically and pharmacologically has broad atheroprotective effects. Discovery of SIRT1-activating compounds (STACs, such as SIRT1720, resveratrol, SRT3025, E1231, etc) are practicable and emerge as new therapeutic strategies to treat atherosclerosis and its related cardiovascular disease which are the main lethal geriatric diseases.

Keywords: Atherosclerosis; Cardiovascular Disease (CVD); Resveratrol (RSV); SIRT1 Activators

Abbreviations

Ac-LXRα : Acetylated LXRα
CVD : Cardiovascular Disease
eNOS : Endothelial Nitric Oxide Synthase
H2S : Hydrogen Sulfide
LDL-C : Low-Density Lipoprotein Cholesterol
LDLR : Low Density Lipoprotein Receptor
Lox-1 : Lectin-Like Ox-LDL Receptor 1
LXR : Liver X Receptor
NAD+ : Nicotinamide Adenine Dinucleotide
NBS-1 : Nijmegen Breakage Syndrome-1
NF-κB : Nuclear Factor-Kappa B
PCSK9 : Proprotein Convertase Subtilisin/Kexin Type 9
RSV : Resveratrol

Introduction

The yeast silencing information regulator complex (Sir complex) regulates transcriptional repression or silence, thus playing an important role in lifespan extension [1]. In mammals, there are seven members in the sirtuin family (SIRT1-SIRT7) which are ubiquitously expressed and share a highly conserved deacetylase domain [2]. Among them, SIRT1 is the most extensively studied. SIRT1 regulates a wide range of cellular processes which are crucial to cell survival, apoptosis, cell growth, cell senescence, and metabolism through deacetylating histones and many non-histone proteins [3]. Accumulating studies have demonstrated that activating SIRT1 expression/activity have extensive cardiovascular protecting effects [2,4]. For example, endothelial SIRT1 inhibits
endothelial apoptosis, and improves vascular endothelial function through increasing Endothelial Nitric Oxide Synthase (eNOS) expression, thereby exerting anti-atherosclerotic effects [5]. At the vascular smooth muscle cell level, SIRT1 protects against DNA damage and inhibits atherosclerosis, in part, through activation of the repair protein Nijmegen Breakage Syndrome-1 (NBS-1) [6]. SIRT1 may also have a prominent role in vascular biology, and regulate aspects of age-dependent atherosclerosis. Li et al. demonstrated that SIRT1 is a positive regulator of Liver X Receptor (LXR) activation and cholesterol efflux, suggesting that the interaction between diet and genetic factors could affect the progression of age-associated atherosclerosis through direct deacetylation of LXR by SIRT1 [7]. SIRT1 may also prevent atherothrombosis by downregulating the endothelial expression of tissue factor [8,9]. Additionally, SIRT1 inhibits inflammation by negatively regulates nuclear factor-kappa B (NF-κB) signaling pathway thus exerting anti-atherosclerosis effects [10].

Due to the cardioprotective effects, several SIRT1 activators have been studied both in vivo and in vitro. Most of these molecules are phenolic compounds, such as resveratrol (RSV), curcumin, etc [3]. Though RSV was questioned with some researchers proposing that it was dependent on the fluorophore utilized to label the evaluated peptide, but later, it was proved to be an allosteric activator of SIRT1 [11]. The anti-atherosclerotic function of RSV was evaluated in several animal models. RSV decreases oxidative stress, inhibits cardiac hypertrophy, promotes cell survival, and inhibits cell apoptosis [3]. Some synthetic SIRT1-Activating Compounds (STACs) have been developed and successfully tested [12], such as SRT1720, SRT1460, etc. SRT1720 was proved to attenuate angiotensin II-induced atherosclerosis in Apolipoprotein E knockout (ApoE−/−) mice through inhibiting vascular inflammatory response [13]. Also, SRT1720 could reverse vascular endothelial dysfunction, excessive superoxide production, and inflammation with aging [14]. SRT3025 provided atheroprotection in ApoE−/− mice by reducing hepatic Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) secretion and enhancing Low Density Lipoprotein Receptor (LDLR) expression [15]. Hydrogen Sulfide (H₂S) has a protective role in the pathogenesis of atherosclerosis. Recent study showed that H₂S was a novel SIRT1 activator, and endogenous H₂S directly sulfhydrated SIRT1, increased its deacetylation activity and stability, thus reducing atherosclerotic plaque formation [16]. Our recent study showed a new small molecule compound E1231 as a SIRT1 activator [17]. E1231, 1- {4-[2-(5-methylfuran-2-yl) quinoline-4-carbonyl] piperazin-1-yl} ethanone, may regulate cholesterol and lipid metabolism and thus play anti-atherosclerotic role in both foam macrophage and ApoE−/− mice. This study also revealed the anti-atherosclerotic mechanism of E1231 was through SIRT1-LXRs-ABCA1 (ATP-binding cassette transporter A1) pathway. According to recent studies, the atherosclerosis protective effects of SIRT1 activators are summarized in Figure 1.
The binding sites were simulated by Discovery studio software and are now under investigating by mutated SIRT1 proteins. We hypothesized that E1231 promoted the deacetylation activity of LXR and enhanced the activity of downstream ABCA1 in view of LXR as the direct deacetylation target of SIRT1 [7]. Thus, the first aim was to ensure where E1231 could elevate the activity of LXRs. Co-immunoprecipitation assay indicated that it could deacetylate LXRs. Moreover, RNA interference (RNAi) and luciferase reporter gene assays indicated E1231-induced LXRa targeted ABCA1 expression was SIRT1-dependent. This stimulates the ABCA1 promoter in vitro, thus promoting cholesterol efflux and inhibiting liquid accumulation in macrophages. More importantly, ApoE−/− mice fed an atherogenic diet treated with E1231 decreased total cholesterol and triglyceride levels in both serum and liver, and reduced atherosclerotic plaque development compared with untreated mice, suggesting that E1231 can serve as a promising SIRT1 activator which modulates lipid and cholesterol metabolic disorder-related diseases. The principal results are summarized in Figure 2.

In summary, our recent study and many others studies have demonstrated the necessity to harness high throughput compound screening to identify putative SIRT1 activators with atheroprotective functions. Further studies are warranted to translate the pre-clinical findings to clinical settings for therapeutic purposes.

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References


Figure 2: Working model of depicting identification of E1231 and its mechanism on regulating cholesterol and lipid metabolism. Ac-LXRs: Acetylated LXRs; Nicotinamide Adenine Dinucleotide: NAD+; + (green color) indicates activate; green upward arrow indicates the increase; red upward arrow indicates the decrease.


