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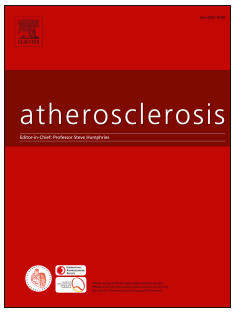

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The sirtuin family members SIRT1, SIRT3 and SIRT6:

their role in vascular biology and atherogenesis

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ABSTRACT:

The sirtuins, silent mating-type information regulation 2 (SIRTs), are a family of nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases with important roles in regulating energy metabolism and senescence. Activation of SIRTs appears to have beneficial effects on lipid metabolism and antioxidants, prompting investigation of the roles of these proteins in atherogenesis. Although clinical data are currently limited, the availability and safety of SIRT activators such as metformin and resveratrol provide an excellent opportunity to conduct research to better understand the role of SIRTs in human atherosclerosis. Encouraging observations from preclinical studies necessitate rigorous large, prospective, randomized clinical trials to determine the roles of SIRT activators on the progression of atherosclerosis and ultimately on cardiac outcomes, such as myocardial infarction and mortality.

Keywords: Atherosclerosis, CVD, Sirtuin, SIRT1, SIRT3, SIRT6, Oxidative Stress, Lipid metabolism.

Abbreviations: ABC, Adenosine triphosphate binding cassette; ABCG, ABC sub-family G member; ADP, Adenosine diphosphate; AMPK, Adenosine monophosphate-activated protein kinase; eNOS, Endothelial nitric oxide synthase; FOXO, Forkhead transcription factor subclass O; HDL-C , High-density lipoprotein cholesterol; HIF1A, Hypoxia-inducible factor 1A; HUVEC, Human umbilical vein endothelial cells; LDL-C, Low-density lipoprotein cholesterol; LDLR, Low-density lipoprotein receptor; LOX-1, Lectin-like oxidized low-density lipoprotein receptor-1; LXR, Liver X receptor; MnSOD, Manganese-dependent superoxide dismutase; NAD, Nicotinamide adenine dinucleotide; NADPH, Nicotinamide adenine dinucleotide phosphate (reduced form) ; N-CoR, Nuclear receptor co-repressor; NF-κB, Nuclear factor κB; NFATc2, Nuclear factor of activated T cells 2; ox-LDL,Oxidized low-density lipoprotein; p53, Tumor protein 53; PCSK9, Proprotein convertase subtilisin/kexin 9; PGC-1α, Peroxisome proliferator-activated receptor-γ co-activator-1α; ROS, Reactive oxygen species; SIRT, Silent mating-type information

regulation; SOD2, Superoxide dismutase 2; SR-B1, Scavenger receptor class B type I; STAT3, Signal transducer and activator of transcription-3; VCAM-1, Vascular cell adhesion molecule-1,

1. Sirtuins family

The sirtuins, silent mating-type information regulation 2 (SIRTs), are a family of nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases. SIRTs are activated in response to low cellular energy stores and have been implicated in the control of many physiological processes including senescence (1). The life-prolonging effects of SIRTs were first described in *Saccharomyces cerevisiae* (2). The regulation of SIRTs by NAD^+ dictates that the activity of these enzymes alters in response to changes in prevailing intracellular redox potential (1) and SIRTs have been found to have important roles in energy regulation (3). The main chemical reactions catalyzed by sirtuin enzymes are protein lysine deacetylations. Sirtuins couple the deacetylation of lysine to the hydrolysis of NAD+ by transferring the acetyl group to the adenosine diphosphate (ADP)-ribose moiety to form O-acetyl-ADP-ribose, releasing free nicotinamide (4). Seven closely-related SIRT family members have been identified and these are divided into four classes: class I (consisting of SIRT1, SIRT2, and SIRT3), class II (SIRT4), class III (SIRT5), and class IV (SIRT6 and SIRT7) (5, 6). The SIRTs have a conserved core catalytic domain, but they differ with respect to their distribution in tissues and their intracellular locations (7). SIRT1, SIRT6 and SIRT7 are predominantly located in the nucleus, SIRT2 is unique in its cytoplasmic location, and SIRT3, SIRT4 and SIRT5 are mitochondrial SIRTs (8). Of the seven SIRT subtypes, SIRT1, SIRT3, and SIRT6 have been most extensively characterized and are the focus of this narrative review.

1.1.1. SIRT1

SIRT1 is a highly conserved NAD-dependent histone deacetylase (6) and is the best characterized member of the SIRT family. SIRT1 is highly expressed in human vascular endothelial cells (9), where it resides in the nucleus of the cell and is associated with euchromatin (10). SIRT1 regulates many cellular processes essential for cell survival, apoptosis, inflammation, stress resistance, cell growth, cell senescence and metabolism, by deacetylating histones and many non-histone proteins such as forkhead transcription

factors (FOXOs), nuclear factor κB (NF-κB), tumor protein 53 (p53), peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α), and several DNA damage repair proteins including Ku70 (11-14). SIRT1 deficiency contributes to increased inflammation, oxidative stress, foam cell formation, impaired nitric oxide (NO) production and autophagy, thereby promoting vascular aging and atherosclerosis (11-14).

1.1.2. SIRT3

SIRT3 regulates several mitochondrial functions and it has important roles in maintaining homeostasis, particularly under conditions of stress (15). However, SIRT3 does not appear to be a prerequisite for life, as demonstrated by knockout mice models which showed an almost normal phenotype at birth - although these animals displayed excessive acetylation of mitochondrial proteins (16). SIRT3 participates in the control of fatty-acid metabolism, and SIRT3 knockout mice demonstrate abnormal lipid metabolism which is associated with abnormal accumulation of acylcarnitines and triglycerides in the livers of these animals during fasting (17). Multiple cellular targets including manganese-dependent superoxide dismutase (MnSOD), NADH dehydrogenase sub-complex 9, and succinate dehydrogenase complex subunit A have been identified as being modulated by SIRT3 (18, 19). SIRT3 provides protection against oxidative stress by deacetylation and activation of superoxide dismutase 2 (20). Roos *et al.* indicated that loss of SIRT3 does not change endothelial function in advanced atherosclerosis, but may lead to augmentation of osteogenic signaling and accelerated progression of vascular calcification (21).

1.1.3. SIRT6

The core domain of SIRT6 is flanked by a N-terminal which is necessary for histone deacetylation and chromatin association and a C-terminal which is required for the nuclear localization of this SIRT subtype (22). Primarily characterized as an NAD+-dependent histone deacetylase (23), SIRT6 targets the histones H3K9 (10) and H3K56 (24) and also directly deacetylases a variety of proteins (24, 25). SIRT6 expression

is decreased in atherosclerotic lesions from ApoE−/− mice (26) and human patients (27). However, the role of SIRT6 in regulating vascular endothelial function and atherosclerosis is not well understood. Recently Xu *et al.* reported that SIRT6 reduces the formation of atherosclerotic lesions *via* the attenuation of endothelial dysfunction and vascular inflammation (28) .

1.1.4. Putative therapeutic roles of SIRTs

SIRTs regulate a variety of genes which encode proteins that regulate inflammation and endothelial cell function (10). The importance of SIRTs in many physiological processes has led to pathophysiological and therapeutic roles being investigated in a variety of conditions including cancer, diabetes mellitus, and cardiovascular disease (1), all leading causes of morbidity and mortality (29). Cardiac (3, 30, 31) and cardiovascular (1, 32) effects of SIRTs have been extensively reviewed elsewhere. SIRT1 has been implicated in protection against endothelial dysfunction, thrombosis, myocardial infarction and reperfusion injury. SIRT3 appears to have beneficial effects on the myocardium, ameliorating cardiomyopathy and left ventricular hypertrophy by preserving mitochondrial function (33). SIRT6 has similar effects and additionally may have beneficial effects on lipid profiles. Hepatic Sirt6 might suppress transcription of Pcsk9, which prevent hepatic low-density lipoprotein receptor (LDLR) degradation and subsequently reduce plasma LDL cholesterol (LDL-C) levels in mice (34).

2. Atherosclerosis

Atherosclerosis is a progressive disorder, which develops from foam cells and fatty streaks in arterial walls through several stages of development, ultimately resulting in atherosclerotic plaques. The plaques can obstruct blood flow. In the coronary circulation this can result in symptoms of angina pectoris. If the plaques rupture, they expose the platelets to pro-aggregatory stimuli leading to thrombogenesis and its sequelae: coronary thrombosis and myocardial infarction. A similar process in cerebral arteries results in

ischaemic stroke (35). Research in recent decades has increasingly highlighted the roles of oxidative stress, inflammation (36-38), macrophage infiltration and deposition of oxidized low-density lipoprotein (ox-LDL) cholesterol in the walls of blood vessels and endothelial dysfunction in the pathophysiology of atherosclerosis (35, 39). Results from preclinical studies suggest that SIRTs are involved in the regulation of many of these pathways. This review focuses on the vascular biology of SIRT1, SIRT3 and SIRT6, with a focus on the roles of these enzymes and their modulators on biological molecules and processes involved in atherogenesis, including lipid metabolism, inflammation and endothelial function.

3. Potential for SIRTs to modulate factors involved in the development atherosclerosis

3.1. Lipid modification

The deposition of oxidized lipids in arterial walls is a characteristic of atherosclerosis (35, 39). Pharmacological modification of plasma lipid profiles, in particular the reduction of low-density lipoprotein cholesterol (LDL-C), has been shown to be effective in the primary (40) and secondary (41) prevention of cardiovascular events. Epidemiological studies have repeatedly demonstrated associations between HDL-C and reduced risk of cardiovascular disease, although the causal relationship of this relationship has been called into question by careful studies including a large, well-conducted Mendelian randomization investigation (42). Lipid-modifying effects of SIRTs have been described, and, therefore SIRTs may have the potential to alter the course of atherogenesis (43) (**Figure 1**).

SIRT1 modulates cholesterol biosynthesis in the liver (44) resulting in reduction of serum lipid levels(45). These effects is associated with the fact that SIRT1 is a positive regulator of the liver X receptor (LXR) proteins, important regulators of the metabolism of fatty acids, cholesterol, and glucose. LXR regulates reverse cholesterol transport, a process that removes cholesterol from macrophages and prevents foam cell formation. SIRT1 may promote deacetylation of LXRs at lysine K432 (44). Deacetylation and subsequent activation of LXR increase the expression of ATP-binding cassette (ABC) sub-family A member (ABCA)

1 and ABC sub-family G member (ABCG) 1, which contribute to the reverse cholesterol transport and the suppression of foam cell formation and cholesterol loading in macrophages (44). Moreover, SIRT1 interacts with transcription factors including peroxisome proliferator-activated receptor gamma (PPARγ), nuclear receptor co-repressor (N-CoR) (46), and peroxisome proliferator-activated receptor gamma co-activator 1-alph (PGC-1a) (47), and may also contribute to activation of LXR in cells via the NF‑κB pathways (14).

Of particular interest is the observation that pharmacological activation of SIRT1 can increase LDLR expression in mice through a reduction in secretion of proprotein convertase subtilisin/kexin 9 (PCSK9) (48), which targets LDL receptors for internalization in hepatic cells and thereby reduces the capacity of the liver to take up circulating LDL (49, 50). Monoclonal antibodies directed against PCSK9 have shown great efficacy in lowering circulating LDL-C concentrations and are very promising agents in the prevention of cardiovascular disease (CVD) (49, 50). Also, SIRT6 can reduce LDL-C levels through regulation of the PCSK9 gene (34). Deficiency of hepatic SIRT6 increased PCSK9 gene expression and LDL-C. SIRT6 can be recruited by forkhead transcription factor FOXO3 to the proximal promoter region of the PCSK9 gene and deacetylates histone H3 at lysines 9 and 56, which suppress the gene expression. Moreover, overexpression of SIRT6 in mice fed a high-fat diet lowers LDL-C (34). FOXO3 and SIRT6 also suppress the *Srebp2* gene expression, a major regulator of cholesterol biosynthesis in the liver. SIRT6 and FOXO3, have an impact on total cholesterol levels in the circulation *via* regulation of the *Srebp2* gene (51).

3.2. Reduction of oxidative stress

Anti-atherosclerotic actions of SIRTs may derive from their potential to reduce the severity of oxidative stress and stress-induced endothelial injury (52) (53). SIRT1 exerts antioxidant effects by modulating FOXO signaling (54). FOXO proteins have many functions, including cell cycle, metabolism, apoptosis,

stress resistance, DNA repair, and aging (55). Deacetylation and then activation of FOXO1, 3 and 4 transcription factors by SIRT1 reduces oxidative stress by induction of anti-oxidative enzymes in endothelial cells (56). SIRT1 promotes the expression of FOXO target genes associated with stress resistance, and decreases the transcription of genes associated with apoptosis (57). Genetic variations at the SIRT1 and FOXO1 loci have been found to be associated with carotid atherosclerosis. A pronounced effect was found for two SNPs (rs10507486 and rs2297627) at FOXO1 and common carotid intima-media thickness (58). SIRT1 has been shown to promote the ubiquitination and degradation of FOXO3a, which protects endothelial progenitor cells against oxidative stress-induced apoptosis (59).

SIRT3 reduces intracellular activity of reactive oxygen species (ROS) via deacetylation and stimulation of mitochondrial superoxide dismutase 2 (SOD2) (19), an enzyme responsible for the conversion of superoxide to molecular oxygen or hydrogen peroxide. (53). Correspondingly, it has been demonstrated that SIRT3 deficiency in murine and human pulmonary artery smooth muscle cells was associated with induction of the transcription factors involved in the pathogenesis of pulmonary artery hypertension hypoxia-inducible factor 1A (HIF1A), signal transducer and activator of transcription-3 (STAT3), and nuclear factor of activated T cells 2 (NFATc2) (60). Moreover, SIRT3 deficiency induces a mild, superoxide-dependent endothelial dysfunction in mice fed a high-cholesterol diet (61).

3.3. Anti-inflammatory actions

SIRTs have the potential to reduce the inflammatory component of atherosclerotic disease. In particular this may occur through regulation of nuclear factor-kB (NF-kB), which regulates the expression of cytokines, chemokines and other pro-inflammatory agents (62).

SIRT6 is an important regulator of inflammation. In endothelial cells, the down regulation of SIRT6 is associated with enhanced expression of NF-kB, while overexpression of SIRT6 is associated with diminished NF-kB activity. SIRT6 thus appears to modulate the up-regulation of genes involved in

inflammation, vascular remodelling, oxidative stress and angiogenesis including interleukin1β (IL-1β) (7).

In a murine model, haploinsufficiency of SIRT6 results in more rapid atherosclerotic plaque formation and greater carotid plaque instability than in homozygous SIRT6 controls. The homozygote animals had greater expression of inflammatory cytokines (63). Interestingly, the study also found that expression of SIRT6 was lower in carotid arteries from patients with atherosclerotic disease, compared to normal controls (63)

3.4. Macrophage migration and foam cell deposition

Uptake of ox-LDL into endothelial cells, an important stage in the development of atherosclerosis, is achieved via several scavenger receptors, for example lectin-like oxidized low-density lipoprotein receptor-1 (Lox-1) and CD36 (64). Inhibition of Lox-1 expression would appear to be a potential therapeutic strategy against atherosclerosis (65). SIRT1 reduces the expression of the scavenger receptor Lox-1 in macrophages (66), and may thereby act to slow the development of foam cells. Reduction of Lox-1 expression by SIRT1 is associated with suppression of NF-signaling by deacetylation of RelA/p65 (66). SIRT1 also exerts CD36 dependent and independent activities related to ox-LDL uptake (57). Moreover, it was also indicated that SIRT1 does not affect scavenger receptor class B type I (SR-B1) which mediates cellular HDL cholesterol uptake (44). In addition, SIRT1 may stabilize existing atherosclerotic plaques by enhancing the activity of tissue inhibitor of metalloproteinase 3 in vascular smooth muscle cells (67).

3.5. Autophagy

Autophagy is catabolic process through which damaged organelles and macromolecules are degraded and recycled within the cell. Macrophage autophagy plays a protective role in atherosclerosis by reducing

inflammation and promoting cholesterol efflux (68). SIRT1 can regulate autophagy by both epigenetic mechanisms through histone modification and by posttranslational mechanisms through the action of forkhead transcription factors (FOXO) (69). The primary deacetylation target of SIRT1 is lysine 16 on histone H4 (H4K16). H4K16 deacetylation inhibits the transcription of genes involved in the initial and late stages of autophagy (70). SIRT1 may directly interact with ATG5, ATG7, and Atg8/LC3 (71). Indirectly, SIRT1 might regulate autophagy by deacetylation of FOXO1 and FOXO3, which cause increased expression of molecules associated with autophagy. FOXO1 activation stimulates the expression of Rab7, which leads to the maturation of autophagosomes (72). Deacylation of FOXO3 increases the expression of Bnip3, which is critical for the induction of autophagy (73).

SIRT6 also protects against atherosclerosis by reducing foam cell formation through an autophagy-dependent pathway. He *et al.* indicated that SIRT6 overexpression lowers the level of miR-33, which not only increases autophagy flux but also upregulates ABCA1 and ABCG1 expression, promoting cholesterol efflux and preventing macrophage foam cell formation at the same time (74).

3.6. Vascular function

Two recent studies conducted in mouse models have investigated the effects of SIRT6 upon vascular function using similar methods (26, 28). Endothelial derived relaxation, provoked by an acetylcholine challenge, was impaired in haploinsufficient $SIRT6^{+/-}$ mice (28) and when the function of SIRT6 was attenuated by small hairpin RNAs. Haploinsufficiency $SIRT6^{+/-}$ mice had increased rates of atherogenesis associated with elevated vascular cell adhesion molecule-1 (VCAM-1), an inflammatory cytokine. Correspondingly, SIRT6 overexpression was associated with reduced expression of pro-atherosclerotic genes (including tumour necrosis factor (TNF) family members and reduced adhesion of monocytes to endothelial cells) (28)

4. SIRTs and cigarette smoke

Cigarette smoke causes generalized endothelial dysfunction (75, 76), which is usually an indicator of an increased oxidative stress. In smokers and in subjects with diabetes, SIRT1 expression and/or activity may be decreased, despite the fact that the protective effects of SIRT1 against oxidative stress would be especially helpful in this situation. It was found that the SIRT1 activator SRT2104 is safe and well tolerated in otherwise healthy cigarette smokers and positively effects on lipid profiles through reducing LDL-cholesterol concentrations in serum by 11%, but did not indicate beneficial effects on vascular, endothelial, or platelet function compared with placebo (77). Resveratrol, probably via a SIRT1-dependent mechanism, may prevent the adverse vascular effects of cigarette smoking by reducing cigarette smoke-induced oxidative stress and preventing pro-inflammatory phenotypic alterations in vascular tissues (78). Additionally, it was shown that SIRT1-PARP-1 axis plays a pivotal role in regulation of autophagy induced by cigarette smoke (79).

5. SIRTs and statins

In addition to their well-documented lipid-modifying effects, statins (3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors) have pleiotropic vascular protective effects associated with improvement or restoration of endothelial function, enhanced activity of endothelial nitric oxide synthase (eNOS), and reduction of oxidative stress (80). eNOS protects the cardiovascular system from atherosclerosis by regulating vascular relaxation (81). A positive correlation was found between eNOS and SIRT1 expression in subjects receiving statins. Ota *et al.* indicated that an increase in eNOS activation caused by statins could promote SIRT1 (82). Kilic *et al.* shown that SIRT1 expression is increased and eNOS expression is decreased in patients with atherosclerosis and statin, atorvastatin and rosuvastatin, therapy may reduce SIRT1 expression and increase eNOS expression, to the similar levels as in healthy

population, independent from the studied SIRT1 gene variants (rs7069102C>G and rs2273773C>T) (83). Therefore, statin treatment could exert its protective effect on cardiovascular disease through the inhibition of SIRT1 expression. Conversely, previous studies, demonstrated an increase in SIRT1 expression with statin treatment (84, 85).

6. Pharmacological modulators of SIRTs

SIRTs present an interesting and attractive therapeutic target in the prevention of atherosclerotic cardiovascular disease. The wide-ranging anti-atherosclerotic effects of SIRT activation afford an opportunity simultaneously to influence multiple components of the development of atherosclerotic cardiovascular disease with a single drug target. Furthermore, a number of currently available drugs and nutraceuticals have been demonstrated to activate SIRTs directly or via allosteric activation (86, 87). Thus, the clinical manipulation of SIRTs may be achievable without the costly and time-consuming process of discovering new drug targets. Pharmacological modulators have been best characterized for SIRT1 and several of these are discussed below. In order to test the hypotheses that these agents may be beneficial in the treatment and prevention of cardiovascular disease, possibly long-term, outcomes-based placebo-controlled clinical trials would be necessary. However such studies are likely to be expensive and relatively difficult to conduct. The short-term studies, which simultaneously measure expression of SIRTs and different parameters of cardiovascular risk in patients taking SIRT modulators, may go some way to addressing the question.

6.1. Metformin

Metformin is a safe and widely used antidiabetic drug. In addition to its well-characterized reductions in plasma glucose, it has anti-inflammatory properties with the potential to modulate important components of the pathophysiology of atherosclerosis. (88, 89). Metformin increases SIRT1 expression and activity

and represses the expression of inflammatory markers such as I1-6 and TNF-alpha in patients with carotid artery atherosclerosis (90). Metformin has been shown to promote phosphorylation of 5' adenosine monophosphate-activated protein kinase (AMPK), which leads to protection against oxidative injuries (91). The signaling pathways of metformin-mediated anti-atherosclerotic effects involve inhibition of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and the ROS formation, which impair the LOX-1 up-regulation and AKT/eNOS deactivation. Importantly, these protective mechanisms are attenuated when SIRT1 and AMPK are repressed (92).

6.2. Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a polyphenol found in natural products including grapes (93). Resveratrol is a strong activator of SIRT1 and it is potentially anti-atherosclerotic (2, 94, 95). Disappointingly, a well-conducted and extensive meta-analysis did not find any evidence of resveratrol supplementation impacting plasma lipids, or other risk factors (96).

6.3. Genistein

Genistein (4',5,7-trihydroxyisoflavone) is an isoflavone which is present mainly in soybeans and red clover. It has anti-atherosclerotic activities (97-99). Genistein increases the activity of endothelial nitric oxide synthase (eNOS) and the production of nitric oxide (NO) (100). NO is a vasodilator and reduced endothelial NO production is a hallmark of endothelial dysfunction and atherosclerosis. In human umbilical vein endothelial cells (HUVECs), genistein has been shown to reverse eNOS uncoupling induced by ox-LDL, a process modulated by a SIRT1-dependent pathway (100). This observation provides an important potential mechanism for the anti-atherosclerotic actions of genistein and SIRT activators in general.

6.4. Quercetin

Quercetin is a flavonoid with anti-oxidative and anti-inflammatory activities. It is present in vegetables, fruits, herbs and red wine (101). Like genistein, quercetin suppresses ox-LDL-induced endothelial dysfunction by activating SIRT1 (102).

6.5. Berberine

Berberine is a botanical alkaloid mainly isolated from the Chinese herb *Coptis chinensis* which has been proposed as an anti-atherosclerotic agent (103). In a cell-culture model, berberine has been shown to reduce the formation of foam cell formation by activating the AMPK-Sirt1-PPAR-γ pathway and by reduction of the uptake of ox-LDL by monocytes (104).

6.6. Curcumin

Curcumin is a polyphenol extract of *Curcuma longa*. Curcumin enhances cholesterol efflux from macrophages, an important step in reverse cholesterol transport, whereby cholesterol is returned to the liver for metabolism. This effect of curcumin may result from an increase of ABCA1 expression through activation of AMPK-Sirt1-LXRα signaling in THP-1 macrophage-derived foam cells (105). Such effects may reduce the development of atherosclerosis and indeed curcumin has been proposed as an anti-atherosclerotic agent (106).

6.7. Delphinidin-3-glucoside

Delphinidin-3-glucoside is a natural anthocyanin which is found in a variety of fruits, vegetables, and cereals (107). Several studies have demonstrated potentially beneficial effects of anthocyanins on atherosclerosis, but the mechanisms have not been fully elucidated (108). It has been shown that

delphinidin-3-glucoside protects against ox-LDL-induced injury in HUVECs (108). This effect may be mediated via an adenosine monophosphate-activated protein kinase/Sirt1 signaling pathway (109).

6.8. Ginkgolide B

Ginkgolide B is an extract of the ginkgo leaf and is a natural inhibitor with potentially protective effects on endothelial cells (110) Ginkgolide B can protect against endothelial cell injury by reducing LOX-1 and increasing Sirt1 (111) and it has been suggested as a potential agent for the prevention of atherosclerosis (111, 112).

6.9 Evaluation of clinical effects of pharmacological modulators of SIRTs

The compounds described above have shown promise in varying degrees in the modulation of SIRT function. More rigorous evaluation of these compounds is needed before any recommendations can be made with respect to their clinical use. Metformin is probably the most promising candidate in this respect, because its widespread availability as a pharmaceutical preparation would make a large randomised controlled trial realatively easy to facilitate (88-92). Such a trial could be used to measure the effect of the drug on SIRT function and clinical outcomes, to determine whether these effects were correlated with one another. Natural products such as resveratrol, genistein, quercetin, berberine, curcumin, delphinidin-3-glucoside and ginkgolide B may be harder to investigate robustly owing to difficulties in measuring dietary intake in observational studies and because of the difficulty in eliminating variability between batches of supplements used in controlled studies (94-112). Perhaps the most practical approach to further research would be to investigate metformin initially as a ‘proof of concept’ and then to investigate natural products if studies with metformin suggested a SIRT-mediated benefit of metformin.

7. Conclusions

SIRTs appear to have a prominent role in vascular biology, and in preclinical models they promote a variety of physiological effects, which would be expected to oppose atherogenesis. Preclinical studies suggest roles for SIRTs in protecting vascular smooth muscle and endothelial cells from the deleterious effects associated with lipid deposition, oxidative stress, and inflammation. Although clinical data are currently limited, and caution must be applied when extrapolating from the results of preclinical studies, the availability and safety of SIRT activators such as metformin and resveratrol make possible the studies that will be necessary to better understand the role of SIRTs in human atherosclerosis. These encouraging observations necessitate rigorous large clinical trials to determine the roles of SIRT activators on cardiac outcomes such as incident myocardial infarction and mortality.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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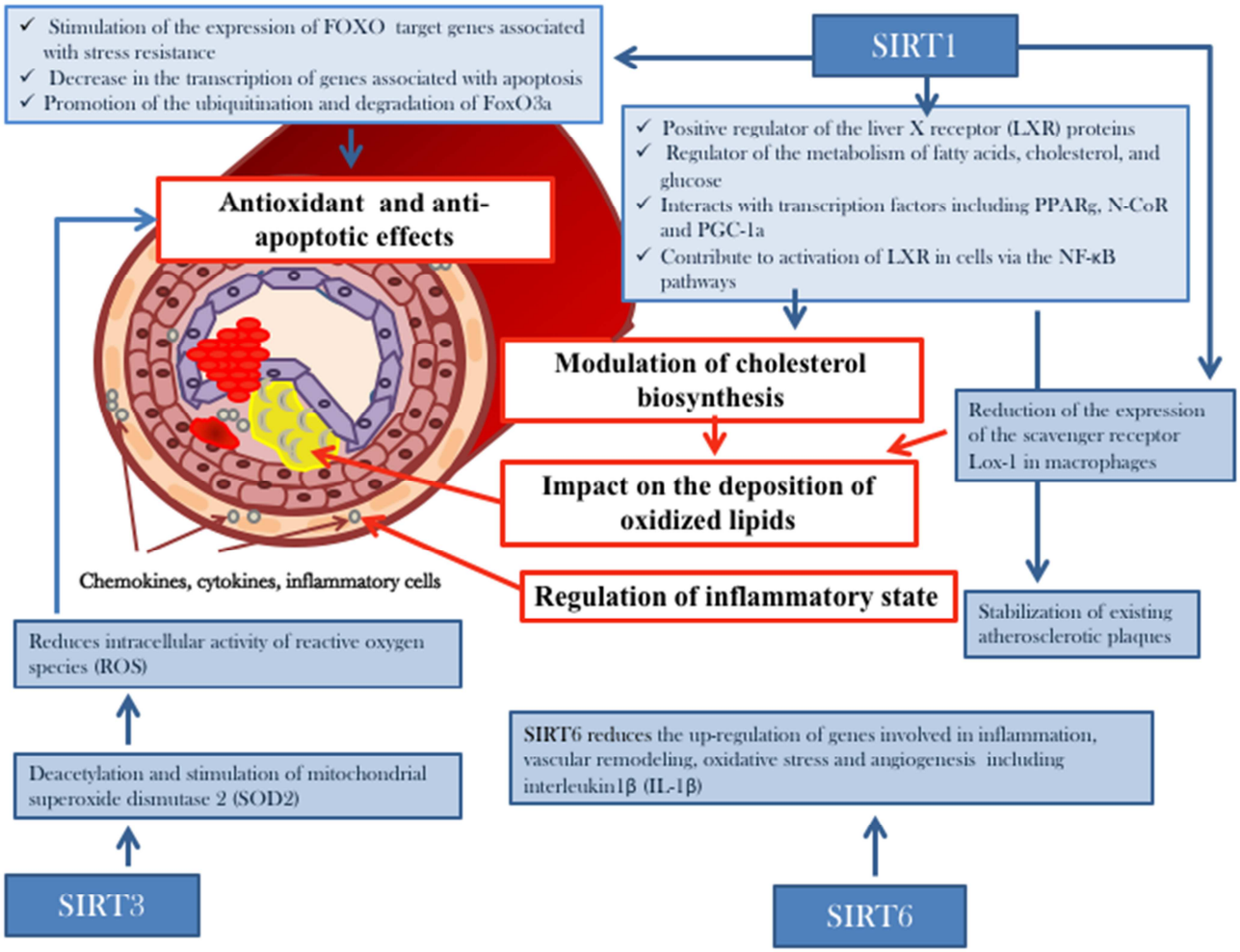
Figure 1: An overview of potential interactions of SIRTS with pathophysiological processes in atherosclerosis.



HIGHLIGHTS:

- The sirtuins, silent mating-type information regulation 2 (SIRTs), are a family of nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases
- SIRTS have important roles in regulating energy metabolism and senescence.
- Activation of SIRTs appears to have beneficial effects on lipid metabolism and antioxidants
- The availability and safety of SIRT activators such as metformin and resveratrol provide an excellent opportunity to conduct research to better understand the role of SIRTs in human atherosclerosis.