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Review

Combating cellular senescence by sirtuins: Implications for atherosclerosis☆

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ABSTRACT

Cellular senescence is the permanent cell cycle arrest induced either by chronological ageing or extrinsic stimuli. Recent researches have identified cellular senescence as an important mechanism for atherosclerosis, which is the essential pathophysiological contributor to cardiovascular diseases (CVDs). The sirtuins are a family of cellular deacetylases with fundamental abilities to regulate cellular metabolism and a variety of physiological activities. Previous studies have revealed the anti-ageing functions of sirtuins as the longevity-associated proteins. These advances indicate the potential beneficial functions of sirtuins in atherosclerosis by affecting cellular senescence. Herein, we review the recent findings about sirtuins in regulating atherosclerotic cellular senescence, and discuss the possibility of activating sirtuins as a therapeutic strategy for combating atherosclerosis.

1. Introduction

Atherosclerosis, with fatty streaks gradually developing into atheroma and characteristic plaques inside the arteries, is the main pathophysiological condition resulting in cardiovascular disease (CVD) [1, 2]. Despite of the emerging pharmacological interventions and lifestyle changes, atherosclerotic cardiovascular disease (ASCVD) remains to be a heavy health and economic burden globally [3, 4]. The pathologic mechanisms of atherosclerosis are complex, including elevated concentrations of lipoprotein cholesterol, chronic inflammatory responses, and arterial wall cell dysfunctions [5]. Among all the triggering factors for these mechanisms, ageing consistently presents the strongest association with atherosclerosis prevalence, and continues to be the major determinant of 10-year ASCVD risk [6–8]. One plausible explanation is that mechanisms related to ageing play vital roles in the pathophysiologic process of atherosclerosis.

Among the various mechanisms, cellular senescence has been considered as a major contributor to tissue ageing [9]. In 1970s, Hayflick and Moorhead first defined "cellular senescence" as they discovered the limited capacity of dividing before entering a stable proliferative arrest in cultured normal human cells, also termed as "Hayflick limit" [10–12]. Cellular senescence is currently defined as the arrest during the cell cycle, which could be driven by either chronological ageing (endogenous sources) or multiple stimuli including oxidative stress, DNA damage and inflammation (exogenous sources) [13, 14]. In recent years, the association between cellular senescence and atherosclerosis has gained much attention, as more evidence has been brought that senescent cells (SNCs) exist in atherosclerotic plaques, and that SNCs could alter the pro-atherogenic events.

Silent information regulator 2 (Sir2) proteins (sirtuins), is a conserved nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase family [15–17]. Mounting researches have demonstrated the beneficial role of sirtuins in cardiovascular diseases *via* regulating cellular metabolism and a wide range of cellular functions [18–20]. The association between sirtuins and ageing begins with the finding that overexpression of sirtuins increased life span in yeast [21, 22]. Ever since, more studies have demonstrated the beneficial effects of sirtuins and senescence-related pathologies [23].

Over the past decades, the wide use of lipid-modifying drugs like statins has led to the reductions in atherosclerosis-associated cardiovascular events [24]. However, the risk of ASCVD is still high, fueling the development of new targets toward the treatment of atherosclerosis. This review aims to work toward an exploration of the link between cellular senescence and atherosclerotic progression, and to point a way forward toward the application of sirtuins-associated pharmaceutical controls over atherosclerosis.

2. Cellular senescence in atherosclerosis

2.1. Characteristics of senescent cells (SNCs) in atherosclerotic plaques

There are several markers and morphological changes that

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distinguish SNCs from other non-dividing cells in atherosclerotic lesions. The most used assay for cellular senescence is the β-galactosidase activity at PH6.0, termed as senescence-associated β-galactosidase (SAβGAL) [25]. Additionally, *in vitro* cultured SNCs usually undergo some morphological changes of becoming larger, flat, vacuolized and multinucleated, which is not obviously observed under *in vivo* conditions due to the tissue architecture. One more SNCs features include increased expressions of p16, p53, p21 and other senescence markers. Moreover, SNCs are capable of producing pro-inflammatory and extracellular molecules, known as senescence-associated secretory phenotype (SASP). Detection of these inflammatory cytokines and chemokines could also provides evidence for cellular senescence [26, 27]. Currently, the use of the above senescence-related markers and features in combination is the best practice for identifying SNCs [28].

Atherosclerosis is considered as an age-related disease, with age dominating as an independent factor for human atherosclerosis. Mounting studies demonstrated the accumulation of SNCs in atherosclerotic lesions from both experimental model and human plaques, providing insights into the association between cellular senescence and plaque progression [29]. More than a decade ago, Minamino T et al. revealed the presence of senescence-associated vascular endothelial cells within human atherosclerotic lesions [30]. Later on, more evidence of cellular senescence from human atherosclerotic plaques are obtained from patients with ASCVD [30–35]. Notably, the progression of atherosclerotic lesions is a complex process with several cell types involved, namely, endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and inflammatory cells. And the presence of senescence-associated changes has been observed in these multiple cell types, raising the multistep role of senescent cells in atherogenesis.

2.2. The role of SNCs in atherosclerosis

Interestingly, the detrimental effects of SNCs on atherosclerosis are twofold. The first is that the accumulation of SNCs within atherosclerotic lesions leads to cell dysfunction and the loss of tissue-repair capacity. Second, the SASP effect of SNCs causes excessive pro-inflammatory factor secretion and inflammatory cell migration, which contributes to the argument of plaque vulnerability (shown in Fig. 1).

Endothelial cellular senescence is an essential contributor to atherogenesis (see Fig. 1, *Senescent ECs*). On one hand, cellular senescence correlates with the declination in endothelial function, such as leaky endothelium and reduced nitric oxide production. On the other hand, the SASP effect of senescent endothelial cells (ECs) induces more monocyte recruitment and inflammatory response, contributing to the progression of plaque vulnerability [36–38]. The regulation of senescent ECs may hold promise for anti-atherogenic properties. Results by Toshio Hayashi et al. demonstrated that liver X receptors (LXRs) agents exerted anti-atherogenic effects through the inhibition of endothelial cellular senescence, evidenced by decreased SA-β-GAL activity and the reversion of the decrease in telomerase activity [39]. Kheloufi M. recently proposed that adequate endothelial flux prevented cellular senescence and limited atherosclerotic plaque formation [40]. Also, *in vivo* experimental evidence suggests that the control of endothelial senescence could improve endothelial function and reduce atherosclerotic lesion formation [41].

Vascular smooth muscle cells (VSMCs) in advanced atherosclerotic lesions and cultured from plaques present features of senescence [42] (see Fig. 1, *Senescent VSMCs*). The proliferation of VSMCs that produce extracellular matrix is beneficial in enhancing atherosclerotic fibrous cap and plaque stability [43]. While, VSMCs senescence cause cellular dysfunction and loss of tissue-repair capacity, which is associated with the initial plaque formation and advanced plaque vulnerability, including decreased fibrous cap and increased necrotic core areas [44].

The fundamental role of foamy cell macrophage senescence has been well illustrated in recent years (see Fig. 1, *Senescent foamy macrophages*). By using transgenic and pharmacological approaches to eliminate senescent cells *in vivo*, Childs BG et al. demonstrated that senescent intimal foam cells are deleterious throughout all stages of atherosclerosis, from the onset of atherogenesis to advanced lesions [45]. Their results revealed the detrimental role of SNCs in atherosclerosis and indicated that the clearance of these senescent cells might hold promise for combating atherosclerosis.

Of note, the SASP effect of senescent cells within atherosclerotic lesions plays a major role in mediating both the atherogenesis and the increase in plaque vulnerability. SNCs isolated from advanced lesions show increased levels of pro-atherogenic secreted factors (monocyte chemotactic protein1 (MCP1), matrix metalloprotein 12 (MMP12), matrix metalloprotein 13 (MMP13), IL-6, and IL-1α) [46, 47]. This SASP effect is responsible for the deterioration of vascular structure and function, and for the chronic inflammation microenvironment within the atherosclerotic lesions [48, 49]. It is widely accepted since 1980s that fatal cardiovascular events are predominantly attributed to the rupture of vulnerable or high-risk plaques, of which excessive inflammatory response is a major characteristics [50–53]. In this context, SASP harbors the detrimental effects, and pharmacological manipulation of the SASP effect within atherosclerotic lesions presents great therapeutic potential.

3. Sirtuins: a chemotherapeutic target for atherosclerosis?

Sirtuins (SIRT1-7) are a family of NAD^+-dependent cellular deacetylases, acting as nutrient and metabolic sensors [54–56]. The critical role of sirtuins is potently involved in multiple metabolic processes including inflammation, gluconeogenesis, insulin sensitivity and renin-angiotensin-aldosterone system (RAAS) system [57–59]. The best evidence comes from the studies by M. Lagouge and J. A. Baur et al. that SIRT1 activation by resveratrol treatment improved metabolic profile in mouse model [60, 61]. Over the past 20 years, numerous studies have revealed the beneficial role of sirtuins in anti-ageing, as animal models with genetically sirtuins over-expression or treated with sirtuins activators or NAD^+ precursors present improved organ function and longevity [62]. These evidences from yeast [21, 63, 64], worm [65–68], fruit fly [69–71] and mouse [72–75] have demonstrated that sirtuin knockout shortened longevity, while genetically-manipulated sirtuin over-expression or sirtuin activators extended longevity.

The seven mammalian sirtuins, SIRT1-SIRT7, hold differences in subcellular location and function. SIRT1, SIRT6 and SIRT7 are predominately located in the nucleus. These three nuclear sirtuins act as transcription regulators, and are involved in additional regulatory activities including energy metabolism, DNA repair, cell survival and inflammation [59, 76]. While SIRT2 is a cytosolic protein, SIRT3, SIRT4 and SIRT5 are mainly located in mitochondria. Unlike the nuclear sirtuins (SIRT1, SIRT6 and SIRT7) which target histones, these sirtuins interact with cytosolic and mitochondrial non-histone proteins. Notably, nuclear sirtuins such as SIRT1, could also target and deacetylase non-histone proteins, including p53, nuclear factor-kappa B (NF-κB), PPARγ coactivator 1α (PGC1-α), Ku70 and poly (ADP-ribose) polymerase-1 (PARP1), making sirtuins a complex network.

The biological activity of sirtuins could be regulated by a variety of upstream factors, which occurs at multiple levels including transcription, translation, post-translation modifications, protein-protein interactions and natural compounds or molecules [77]. As a metabolism-associated protein family, the expression of sirtuins changes depending on different energy status. For instance, S. Nemoto et al. reported that in mammalian cells, acute nutrient deprivation simultaneously elevated the expression of SIRT1 [78]. Furthermore, the activity of sirtuins could be affected by the post-translation modifications of phosphorylation and SUMOylation [79–84]. For pharmacological interventions considerations, a variety of sirtuin-activating compounds (STACs) have been discovered and developed [85], including natural compounds (*e.g.* resveratrol) and synthetic STACs (*e.g.* SRT1720, SRT2104) [23]. Another feasible method to activate sirtuins is the application of NAD^+

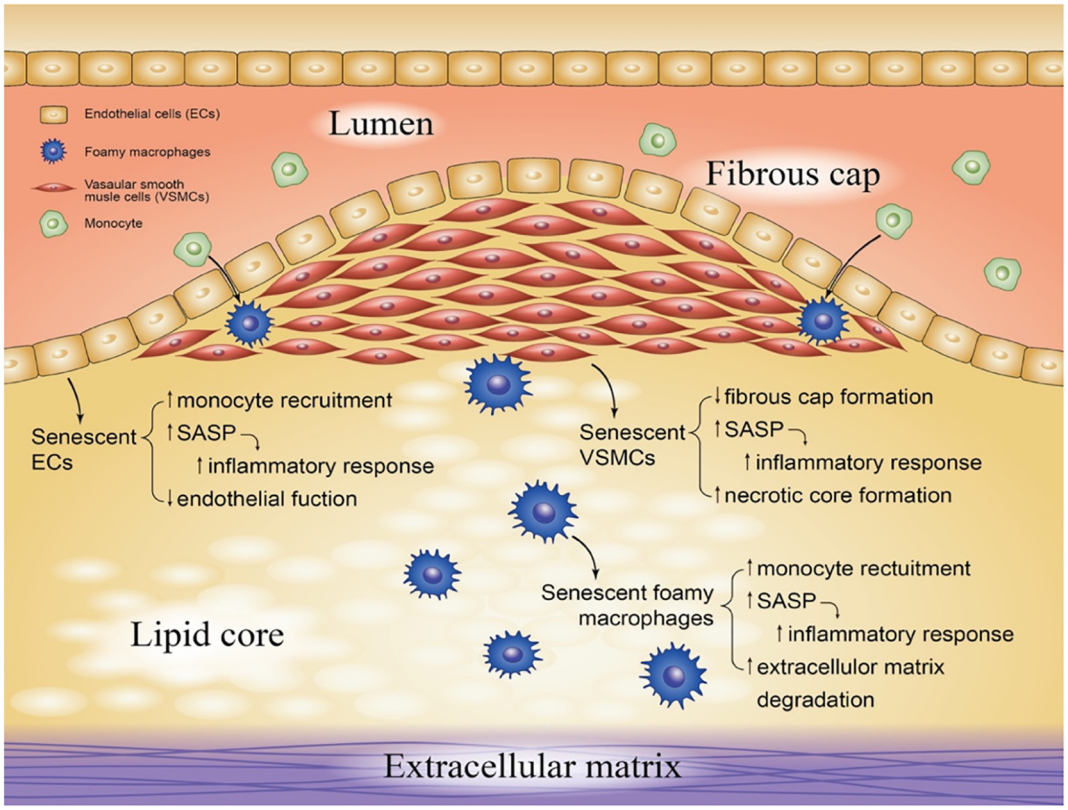

Fig. 1. Cellular senescence contributes to the progression of atherosclerotic plaques.
The three main types of SNCs, namely senescent ECs, senescent VSMCs and senescent foamy macrophages contribute to atherogenesis and atherosclerotic plaque vulnerability *via* the cellular dysfunction and SASP effects.
Abbreviations: SNCs: senescent cells; ECs: endothelial cells; VSMCs: vascular smooth muscle cells; SASP: senescence-associated secretory phenotype.

boosters (*e.g.* nicotinamide riboside), as sirtuins being a NAD^+-dependent enzyme.

Currently, a considerable amount of researches has demonstrated the key regulatory role of sirtuins in ageing and age-related diseases [86, 87]. As atherosclerosis is an age-related disease *per se*, researchers have been considered sirtuins as a promising target for atherosclerosis.

3.1. Sirtuins in regulating cellular senescence

Table 1 lists some of the major findings about the anti-senescence effects of sirtuins in the field of cardiovascular diseases (including but not limited to atherosclerosis) in the past five years, with SIRT1 still being the research hotspot, studies of other sirtuins emerging [88–108]. In addition to these studies, evidence from sirtuin-knockout mouse model appears to be more convincing. By using a transgenic mouse model with endothelial-specific overexpression of SIRT1, Y. Zu et al., demonstrated that SIRT1 prevented ECs senescence, which was a potent contributor to endothelial dysfunction and atherogenesis [109]. Similar conclusions were also drawn by Radovan Vasko et al. using a ECs-specific SIRT1 knockout mice model and Hidetaka Ota et al. using a SIRT1-heterozygous knockout mice model [110, 111].

As mentioned above, the casual role of cellular senescence in atherosclerosis implies that treatments aimed at both the prevention of cellular senescence and reducing its consequences are therapeutically viable [112]. Herein, we propose an overview of the sirtuins in association with cellular senescence in atherosclerosis (Fig. 2). For sirtuins specifically, studies are predominantly concentrated in the involvement of sirtuins in the prevention of cellular senescence, either by directly regulating senescence-associated proteins (p53-p21 and p16 pathway), or by regulating mechanisms that contribute to the induction of cellular senescence (such as telomere shortening, DNA damage, and mitochondrial ROS homeostasis). If the biological ageing and cardiovascular risk factors are the alpha (labeled with yellow font in Fig. 2), and the onset of cellular senescence within atherosclerotic plaques is the omega, then the four key mechanisms, namely DNA damage, p53-p21/p16 signaling, oxidative stress and telomere shortening, are the intervening alphabet (labeled with blue font in Fig. 2). And sirtuins, as has been demonstrated in numerous studies, are the longevity proteins with the abilities to re-arrange the alphabet. This beneficial effect is mediated by regulating several mechanisms. First, telomere shortening is an essential characteristic and contributor to cellular senescence [13, 113, 114]. SIRT1 is a positive regulator of telomere length, and is responsible for reducing telomere shortening associated with ageing [115, 116]. SIRT6, another nuclear sirtuin member, also functions as telomere maintainer, thus inhibiting the triggering of cellular senescence [117–119]. Second, effective repair mediated by SIRT1, SIRT6 and SIRT7 in response to DNA damage, attenuated the amount of SNCs in atherosclerotic plaques [88, 120, 121]. Third, in the case of ROS triggered cellular senescence, sirtuins members including SIRT1 and SIRT3 appear to control the cellular response to stress by regulating antioxidant enzymes (*e.g.*, FOXOs signaling, SOD2), contributing to the maintaining of mitochondrial homeostasis [122–125]. Last but not the least, p53-p21 and p16 signaling are the two main effector pathways that block cycle progression and drive entry into senescence [126, 127]. By modulating the acetylation level in p53 and p21, sirtuins alter the activity of these senescence-associated proteins, thereby directly inhibiting the entry of proliferative arrest in SNCs [104, 128–130]. In addition to the above four mechanisms that trigger cellular senescence process, sirtuins may also protect against atherosclerosis by retaining the detrimental consequences of SNCs, that is inhibiting the SASP effect (labeled with green font in Fig. 2). SASP related pro-inflammatory signals play a key role in perpetrating atherogenesis and plaque

Table 1
Recent findings about the anti-senescence effects of sirtuins in cardiovascular diseases.

Sirtuin name	Cellular localization	*In vivo* model	Cell type	Associated signaling pathway/mechanism	Year	Authors
Sirt1	Ubiquitous, mainly nucleus	Mice ageing model	Endothelial cells	cAMP-CREB pathway	2016	N Fujitsuka et al.
		Mice ageing model	HUVECs	Histone H4 lysin 16 (H4K16)	2014	Wan YZ et al.
		Atherosclerosis model in ApoE$^{-/-}$ mice	Vascular smooth muscle cells	Nijmegen Breakage Sydrome-1/DNA damage	2013	Isabelle Gorenne et al.
		Abdominal aortic aneurysms model in ApoE$^{-/-}$ mice	Vascular smooth muscle cells	Nuclear factor-κB pathway	2016	Chen HZ et al.
		Mice xenograft model	Human fibroblasts	Nuclear factor-κB pathway	2017	Wang P et al.
			SH-SY5Y cells	Nuclear factor-κB pathway	2017	Nopparat C et al.
			Human aortic smooth muscle cells	P21 signaling pathway	2014	Badi I et al.
		Atherosclerosis model in LDLR$^{-/-}$ mice	Endothelial cells	P53/p21 signaling pathways	2014	Warboys CM et al.
			Human mammary epithelial cells	pRb pathway	2015	Sedic M et al.
			Endothelial progenitor cells		2018	Wang C et al.
		High-fat-diet in ApoE$^{-/-}$ mice	Endothelial cells		2014	Liao YC et al.
		Vascular senescence model in mice	Endothelial progenitor cells		2017	Guo Y et al.
Sirt3	Mitochondria		Mesenchymal stem cells	Maintaining mitochondrial ROS homeostasis	2017	Jung YH et al.
		Senescence-accelerated mice model	HepG2 cells	Regulating oxidative stress and mitochondrial function	2014	Tian G et al.
		Mice ageing and Sirt3 KO mice model		p53/Parkin-mediated mitophagy	2018	Li Y et al.
		Aged WT and p16 KO mice model	Mesenchymal stem cells		2016	Son MJ et al.
Sirt4	Mitochondria		Trophoblast stem cells		2017	Castex J et al.
Sirt6	Nucleus	Intervertebral disc degeneration model	Nucleus pulposus cells	Autophagy induction	2018	Chen J et al.
		Atherosclerosis model in ApoE$^{-/-}$ mice	Macrophages and endothelial cells	H3K9 and H3K56/inflammatory cytokines expression	2016	Zhang ZQ et al.
			Human 293T and U2OS cells	K18 of histone H3 (H3K18)	2016	Luisa Tasselli et al.
		Progeria mouse model		MDM2-mediated ubiquitination and proteasomal degradation	2018	Qian M et al.
			Chondrocytes	Nuclear factor-κB pathway	2015	Wu Y et al.
			Mesenchymal stem cells	NRF2 signaling pathway	2016	Pan H et al.
			HUVECs, aortic endothelial cells	Protection from telomere and genomic DNA damage	2013	Cardus A et al.

Abbreviations: HUVECs: human endothelial vein cells; WT: wild-type; KO: knock-out; NRF2: nuclear factor erythroid 2-related factor 2.

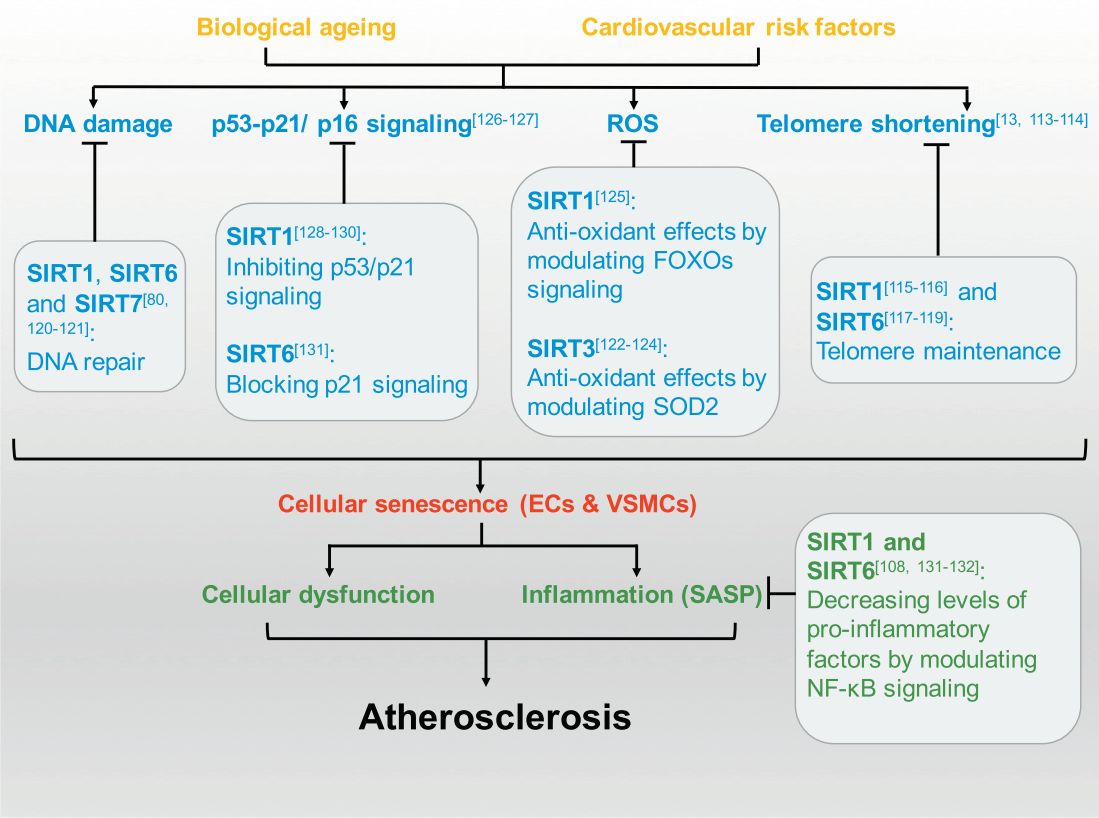

Fig. 2. Overview of sirtuins in association with cellular senescence in atherosclerosis.
The biological ageing and cardiovascular risk factors contribute to the activation of cellular senescence-associated mechanisms, namely telomere shortening, DNA damage, oxidative stress and p53-p21/p16 signaling. Sirtuins could regulate these mechanisms, thereby inhibiting cellular senescence in ECs and VSMCs. In addition, sirtuins ameliorate the SASP effect of senescent cells, leading to the reduction of inflammatory response in atherosclerotic lesions.
Abbreviations: ROS: reactive oxygen species; FOXO: Forkhead box class O; SOD2: superoxide dismutase 2; ECs: endothelial cells; VSMCs: vascular smooth muscle cells; SASP: senescence-associated secretory phenotype.

instability [131, 132]. An *in vivo* study using transgenic mouse model showed that SIRT6$^{+/-}$ ApoE$^{-/-}$ mice presented increased plaque formation and vulnerability, with increased expressions of NKG2D ligands and pro-inflammatory cytokines [108]. Therefore, targeting SASP-associated pro-inflammatory signaling by sirtuins may be another promising approach to tackle cellular senescence in atherosclerosis.

Notably, vascular senescence-independent effects of sirtuins could also contribute to the suppression of atherosclerosis. In a recent study by Gorenne I et al., they demonstrated that pharmacological activation of SIRT1 induced reduction in Pcsk9 secretion, LDL-cholesterol, and atherosclerosis in apolipoprotein E-deficient (Apoe$^{-/-}$) mice [133]. Also, the research by Sokrates Stein et al. suggested that protective effects of SIRT1 in atherogenesis could be attributed to the reduction in macrophage foam cell formation. By using a heterozygous SIRT1 knockout mice model, they revealed that SIRT1 in macrophages is sufficient to reduce foam cell formation and atherogenesis [134]. Another inevitable function of sirtuins was the inflammation-inhibition effect that was not associated with cellular senescence. It was reported that SIRT1 activation by resveratrol attenuated endothelial inflammation by inducing autophagy, thus inhibiting the pathological process of atherosclerosis. Moreover, Balestrieri ML et al. indicated the involvement of SIRT6 in the inflammatory pathways of atherosclerotic lesions in diabetic patients [135]. Although these studies confirmed the promising effects of sirtuins in inhibiting atherosclerosis, they also revealed the complexity of sirtuins function, which may be regarded as a crucial limitation of sirtuins therapy in clinical application.

3.2. Therapeutic considerations and challenges

The anti-atherogenic effects of sirtuins have lent credence to the therapeutic possibility of sirtuins on atherosclerosis by regulating cellular senescence. Currently, a number of clinical studies have been initiated to evaluate the efficacy of STACs in cardiovascular diseases in human beings [62]. Among them, several clinical have been evaluating the safety and efficacy of resveratrol in humans. Specifically, a randomized double blinded placebo controlled study regarding the clinical benefits of resveratrol in heart disease has reached phase III (NCT01914081). These advances bring excitement on the therapeutic potential of sirtuins for atherosclerosis for translational applications in clinical settings. However, considerations and challenges still exist.

One big question is the specificity of STACs. Most of the natural STACs such as resveratrol are nonspecific compound, which could influence the activity of various protein within the cell. Furthermore, the specificity of synthetic STACs cannot be over-estimated due to the broad deacetylation effect of sirtuins with the involvement in a variety of cellular activities as mentioned above.

Another potential problem posed by inhibiting cellular senescence in atherosclerosis is how to exert anti-atherosclerotic effects without elevating cancer risk. One important point we should keep in mind is that cellular senescence supports the beneficial function of tumor suppression [28, 136]. The association of cellular senescence inhibition and cancer risk is currently unclear *per se*. Furthermore, the application of STACs in cancer models generates mixed results [137]. It was reported that one of the STACs SRT1720 promoted tumor cell migration in mice breast cancer [138]. This undesired effect of cancer risk should be a crucial consideration. Hopefully, combination of therapy with

medications, which could exert tumor suppression effect, may provide prospective insights for this consideration. For instance, metformin, a widely used biguanide for the management of type 2 diabetes mellitus, has been considered as a potential anticancer agent by both preclinical and clinical evidence [139–141]. The anti-tumor ability of metformin may be attributed to the ability to lower circulating insulin level in certain cancer types associated with hyperinsulinemia, as well as to the growth inhibitory effects in cancer cells [142–144]. Similarly, extensive studies have revealed that statins, a widely prescribed cholesterol-lowering medication, exhibited important anti-tumor activities [145–147]. As growing evidence has emerged to show the anti-cancer effects of these medications, the concomitant therapy on certain patients may serve as a promising tool for combating the tumor-promotion risk of inhibiting cellular senescence in atherosclerosis.

Moreover, the challenges remain to determine the degree to which the murine data could be translated into human disease. Researches on the mouse atherosclerosis model began in the late 1970s, and since then, mouse has been the classic animal model for atherosclerotic studies [148, 149]. Even though the development of atherosclerotic lesions in mouse ApoE$^{-/-}$ or Ldlr$^{-/-}$ models are similar to those in human disease conditions, disparities do exist [150]. First, the cholesterolemia level in experimental mouse model is markedly higher than human, as studies of human atherosclerosis lesions revealed less lipid accumulation due to the wide application of statin therapies [151]. Furthermore, human atherogenesis usually evolve over many years instead of a few months in rodent model, meaning that the human atheromata are considerably more complicated [29].

4. Conclusions and outlook

The analysis of the current knowledge and findings clearly demonstrates that sirtuins are beneficial against atherosclerosis *via* the regulation of cellular senescence. Moreover, multiple experimental models and ongoing clinical trials have indicated the therapeutic potency of sirtuins. The path forward seems clear. First, though previous researches have identified SNCs in atherosclerotic plaques as detrimental, the cell origins of the SNCs and the underlying mechanisms are still blurry. And it is still an unfinished task to precisely identify SNCs and evaluate the functions of SNCs in atherosclerotic lesions *in vivo*. Second, although many questions in association with sirtuins and cellular senescence in the settings of atherosclerosis have been resolved, a large number of them still remain. The last question is the exploration of effective STACs, with improved bioavailability and less side-effects. With ASCVD still being a health and financial burden globally, these questions should be addressed soon.

Transparency document

The Transparency document associated with this article can be found, in online version.

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