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Caloric restriction, Sirtuins, and cardiovascular diseases

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Abstract

Caloric restriction (CR) is a well-established dietary intervention known to extend healthy lifespan and exert positive effects on aging-related diseases, including cardiovascular conditions. Sirtuins, a family of nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases, have emerged as key regulators of cellular metabolism, stress responses, and the aging process, serving as energy status sensors in response to CR. However, the mechanism through which CR regulates Sirtuin function to ameliorate cardiovascular disease remains unclear. This review not only provided an overview of recent research investigating the interplay between Sirtuins and CR, specifically focusing on their potential implications for cardiovascular health, but also provided a comprehensive summary of the benefits of CR for the cardiovascular system mediated directly via Sirtuins. CR has also been shown to have considerable impact on specific metabolic organs, leading to the production of small molecules that enter systemic circulation and subsequently regulate Sirtuin activity within the cardiovascular system. The direct and indirect effects of CR offer a potential mechanism for Sirtuin modulation and subsequent cardiovascular protection. Understanding the interplay between CR and Sirtuins will provide new insights for the development of interventions to prevent and treat cardiovascular diseases.

Keywords: Caloric restriction; Sirtuins; Cardiovascular diseases; Healthy lifestyle; Dietary

Introduction

Cardiovascular diseases (CVDs) are a major cause of mortality globally. In China, current estimates indicate a prevalence of 330 million CVD cases, with the disease representing the foremost cause of mortality among urban and rural populations.[1] The management and prevention of CVDs include the adoption of a healthy lifestyle, appropriate use of medications, surgical interventions, and systematic monitoring. Among the diverse treatments, caloric restriction (CR) has emerged as a promising non-pharmacological therapy for preventing of CVDs.[2]

CR is a dietary intervention characterized by daily food intake reduced to a level that does not result in malnutrition. Numerous studies have consistently demonstrated that CR is the most effective non-pharmacological intervention for extending the healthy lifespan of diverse organisms.[3] CR also has beneficial effects on several aging-related conditions, including cancer, metabolic disorders, neurodegenerative, autoimmune, and CVDs.[2,4–7] In particular, mounting evidence supports that CR may significantly reduce the risk of CVDs through multiple mechanisms,[8] such as improving the risk factor profile, lowering circulating inflammatory cytokine levels, reducing oxidative stress, and enhancing endothelial function.

As major protein mediators of the response to CR, Sirtuins are a family of highly conserved nicotinamide adenine dinucleotide (NAD^+) cofactor-dependent histone deacetylases, consist of seven mammalian forms, namely Sirtuin (SIRT)1 to SIRT7. They regulate a wide range of physiological functions and cellular processes, including DNA repair, gene expression, and metabolism.[9] The role of Sirtuins in aging has garnered significant attention, particularly because the activity of individual Sirtuins in cells typically decreases with age.[10] Furthermore, the duplication of the Sir-2.1 gene in *Caenorhaditis elegans*, also known as SIRT1 in mammals, results in a remarkable 50% extension of the worm's lifespan.[11] In the process of CR, members of the Sirtuin family may be involved in the cardiovascular protective effects across various cell types.[12–17]

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In this review, we aimed to evaluate existing evidence on the interplay between CR and Sirtuins, focusing on the mechanisms through which this interplay might contribute to improve cardiovascular health. We hypothesized two novel pathways that may help to understand the intricate mechanism *in vivo*, in which interactions among different organs contribute to the functions of Sirtuins. Furthermore, this review is expected to provide possible avenues for future research focusing on elucidating the relationship among CR, Sirtuins, and CVD.

Beneficial Effects of CR on the Cardiovascular System

Cardiovascular risk factors alleviating by CR

CR affects multiple cardiovascular risk factors, reduces blood pressure, improves lipid profile, decreases inflammation, alleviates oxidative stress, and enhances endothelial function. In the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) trial, a randomized controlled trial, a cohort of healthy non-obese individuals was assigned to a 25% CR diet or an ad libitum control diet, and the effects of the CR diet on cardiometabolic risk factors were evaluated.[18] After two years of CR, all assessed conventional cardiometabolic risk factors were consistently and significantly reduced, including low-density lipoprotein-cholesterol, total cholesterol to high-density lipoprotein-cholesterol ratio, and systolic and diastolic blood pressures. Studies conducted on individuals with metabolic syndrome or obesity have shown that a 6-month CR diet reduced peripheral cytokine levels, inflammatory markers,[19] and oxidative stress parameters in leukocytes.[20] These improvements in cytokine profiles and vascular disease markers may have significant implications for cardiovascular health. In aged mice, impaired endothelium-dependent dilation of the carotid artery was restored by an 8-week CR diet. This restoration was accompanied by increased nitric oxide (NO) bioavailability and reduced superoxide production.[21]

The results obtained in the clinical trial and non-cardiovascular disease animal model mentioned above suggest that favorable changes in cardiovascular risk factors contribute to the overall cardioprotective effects of CR and imply its potential as an effective strategy for preventing and managing CVDs.

Protective effects of CR against heart disease

In healthy cardiac tissue, there is greater utilization of fat as an energy source compared to that in other organs, with cardiac hypertrophy and heart failure inducing a metabolic shift from the preferential consumption of fatty acids to glucose to meet energy demands. During CR, energy generation and utilization shift, leading to a shift from fat storage to enhanced fat utilization. The regulatory molecules involved in this shift may be associated with the prevention and remission of heart disease. Moreover, metabolic reprogramming induced by CR may alleviate the abnormal metabolic features observed in disease states.

In an isoproterenol-induced cardiac hypertrophy model, CR protected against alterations in the cardiac lipidome, mitochondrial disturbances, and oxidative stress.[22] In a mouse model of chronic hypertensive cardiac remodeling, a carbohydrate-restricted diet with a high percentage of fat or protein mitigated the progression of hypertrophy. Specifically, the high-fat, low-carbohydrate (Fat-LC) diet upregulated ketone body levels and inhibited the mammalian target of rapamycin (mTOR) signaling pathway, while the high-protein, low-carbohydrate (Pro-LC) diet activated glycogen synthase kinase (GSK)-3β.[23] Leptin-deficient and leptin-resistant mice also exhibit ventricular hypertrophy, and a 12-week CR diet has been shown to attenuate myocyte hypertrophy, cardiac inflammation, fibrosis, oxidative stress, and remodeling in obese (ob)/ob and diabetic (db)/db mice. These beneficial effects may be mediated by the regulation of iron homeostasis.[24]

In a rat model of postischemic heart failure, prolonged CR over the course of one year has been shown to enhance sympathetic cardiac innervation and β-adrenergic receptor function in the failing myocardium. These improvements contribute to the amelioration of cardiac dysfunction and enhancement of the inotropic reserve.[25] Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure in older people, particularly in overweight or obese individuals. In a randomized, attention-controlled, 2 × 2 factorial trial involving 100 elderly obese patients with chronic stable HFpEF, the effects of a 20-week CR diet, aerobic exercise, and their combination were evaluated. All three interventions, applied alone or in combination, improved the peak oxygen consumption (VO_2) and other measures of physical function in these patients.[26]

Alterations in cardiac energy metabolism contribute to improved postischemic recovery. During myocardial ischemia, there is a significant increase in circulating plasma fatty acids, resulting in accelerated fatty acid oxidation during reperfusion. High fatty acid oxidation rates can inhibit glucose oxidation. CR effectively relieves myocardial ischemia–reperfusion injury in various animal models.[27,28] One study found that in mice under CR, there was an improvement in functional recovery after myocardial ischemia, associated with an increased rate of glucose oxidation, while the rates of fatty acid oxidation and glycolysis remained unchanged.[29] In 26-week-old Fischer344 rats, a 6-month CR diet led to the preservation of postischemic mitochondrial respiration and the reduction in postischemic mitochondrial hydrogen peroxide (H_2O_2) production.

CR exerts a notable influence on diverse cardiac conditions, including cardiac hypertrophy, heart failure, and post-ischemic myocardial injury. The epigenetic influence of CR on the cardiovascular system, especially on metabolic modifications mediated by the metabolic enzymes, may constitute a pivotal mechanism in this process. Additionally, the impact of CR on genetic heart diseases, such as cardiomyopathies arising from mutations in metabolism-related genes, remains unclear. Thus, in-depth investigations using well-designed clinical trials

and animal experiments are warranted to elucidate the mechanisms of cardiac function improvement during CR.

Protective effects of CR against vascular disease

The efficacy of CR in lowering atherosclerosis risk has been proven in various models, including rodents[30], non-human primates, and humans[31]. Fewer atherosclerotic lesions in the aorta, increased collagen content in plaques, reduced macrophage numbers, and decreased plaque calcium build-up induced by the CR diet facilitate greater plaque stability. The effect of CR on abdominal aortic aneurysm (AAA) mitigation has been confirmed in angiotensin Ⅱ (Ang Ⅱ)-infused, Apoe$^{-/-}$ mice.[12,32]

CR has been demonstrated to promote vascular health and alleviate vascular aging by affecting systemic risk factors and modulating the microenvironment of the vascular wall, including endothelial and smooth muscle cells. The combination of reduced inflammation, improved lipid and glucose metabolism, enhanced nitric oxide (NO) bioavailability, regulation of proliferation, autophagy, and age-related endothelial progenitor cell (EPC) dysfunction underlies beneficial effects.

Vascular endothelium plays critical roles in modulating vascular function, homeostasis, and permeability. The effect of CR on the vascular endothelium is closely related to endothelial nitric oxide synthase (eNOS), a key enzyme that produces NO, which is a potent vasodilator and regulator of vascular function. A study conducted on Zucker obese male rats, under a 2-week 20% CR diet, found that vascular H_2O_2 may be a link between AMP-activated protein kinase (AMPK) and eNOS activation. Calcium/calmodulin-dependent protein kinase II (CAMKII) was identified as a key mediator of CR-induced AMPK activation by increasing H_2O_2 levels.[33] Additionally, CR promotes autophagy and plays cytoprotective effects in vascular endothelial cells by removing dysfunctional cellular components and accelerating cellular renewal. Especially, autophagy appears to augment eNOS expression and further enhance the function of CR.[34,35]

In the aged arterial wall, the migration and invasion of vascular smooth muscle cells (VSMCs) contribute to intimal thickening, and CR mitigates the proliferation of VSMCs in old arterial wall through suppressing platelet-derived growth factor-BB signaling, which preserves a youthful phenotype.[36]

EPCs play a crucial role in safeguarding the structure and function of the endothelium, while the depletion and dysfunction of circulating EPCs lead to the vascular dysfunction in obesity. *In vitro* starvation of EPCs enhanced migration, adhesion, and angiogenesis via activating autophagy.[37] However, further research is required to validate these findings *in vivo*.

Taken together, CR exerts beneficial effects on vascular health, with a particular emphasis on preserving endothelial function. This intervention shows promise for various vascular diseases, such as atherosclerosis, aortic aneurysm, and others that require further investigation. The specific mechanisms in mediating these effects warrant further comprehensive research, including studies in rodents, pigs, and non-human primates, and clinical trials.

Potential Mechanisms Linking CR, CVDs, and Sirtuins

Direct benefits of CR on the cardiovascular system mediated by Sirtuins

Sirtuins are a class of enzymes characterized by NAD^+-dependent protein lysine deacetlase activities, which intricately regulate metabolic processes. They may potentially be involved in mediating the epigenetic impact of CR on the cardiovascular system. Currently, seven mammalian Sirtuins have been identified based on their cellular localization. Nuclear Sirtuins, namely SIRT1, SIRT6, and SIRT7, are primarily responsible for the regulation of gene expression. SIRT3, SIRT4, and SIRT5 localize to the mitochondrial compartment, where they modulate cellular metabolism and mitigate oxidative stress. Cytoplasmic Sirtuin SIRT2, plays a pivotal role in DNA repair and apoptosis. Furthermore, Sirtuins are capable of migrating between organelles, enabling them to integrate and coordinate various cellular signals, ultimately facilitating the convergence and orchestration of diverse intracellular cues and corresponding cellular responses.[9] As previously mentioned, Sirtuins serve as critical mediators of the direct cardiovascular benefits observed during CR. Changes in Sirtuins expression within cardiovascular tissue are pivotal for facilitating antioxidant effects, mitigating inflammation, improving endothelial function, and inducing favorable metabolic alterations within the cardiovascular system. The direct effects of CR on the cardiovascular system mediated by Sirtuins are illustrated in Figure 1.

SIRT1

SIRT1 is a nuclear Sirtuin considered the ortholog of Sir2, an NAD^+-dependent deacetylase in yeast, which was among the first genes to be associated with the response to CR.[38] Sir2/SIRT1 is a crucial mediator of the beneficial effects of CR. Notably, the lifespan-promoting effect of reduced glucose levels is not observed in yeast strains lacking Sir2.[39] Studies on flies and worms have also provided insights into the impact of Sir2 orthologs on lifespan, supporting the conserved mechanism triggered by CR. Mice lacking SIRT1 exhibit attenuated longevity responses to CR, whereas transgenic mice with constitutive SIRT1 expression display multiple phenotypes, similar to those observed in mice undergoing CR, including leanness, enhanced metabolic activity, improved metabolic status, and delayed reproduction.[40] Additionally, the beneficial effects of CR and CR mimetics on various diseases including hepatic steatosis,[41] CVDs,[13,14] and neurodegenerative disorders,[42] are mediated by SIRT1, which highlight its essential role in multiple organs and tissues. Studies have also reported the participation of SIRT1 in the health-promoting effects observed in individuals undergoing CR. SIRT1 protein levels are elevated in muscles[43] and serum[44,45], influenced by factors such as sex and body mass index.[45] In contrast, decreased

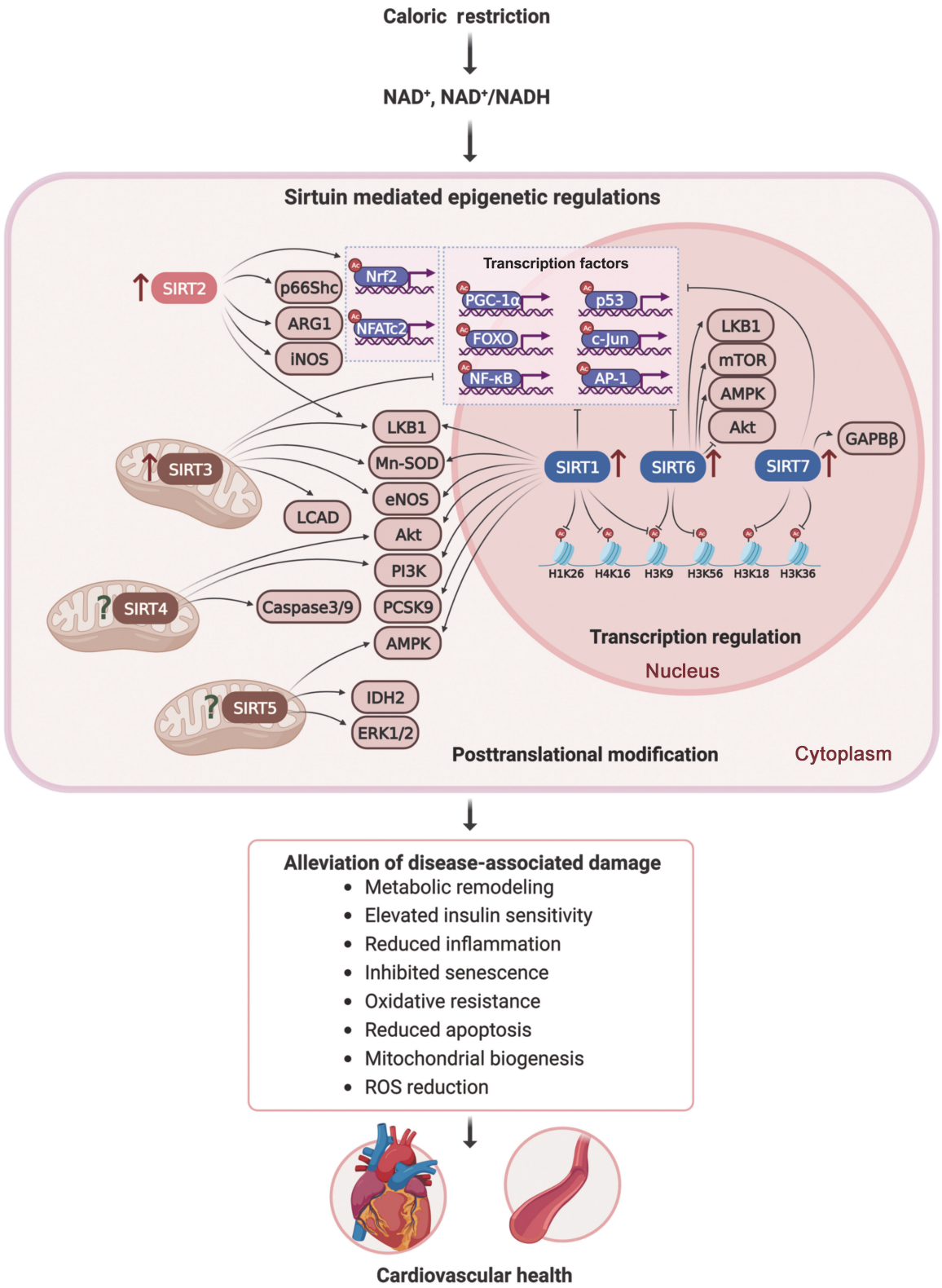

Figure 1: Direct benefits of CR on the cardiovascular system mediated by Sirtuins. CR induces a series of beneficial effects on the cardiovascular system mediated by Sirtuins. CR triggers an elevation in NAD^+ levels and the NAD^+/NADH ratio, thereby modulating the expression and activity of Sirtuin family members localized in different cellular compartments. The altered protein deacetylation activity of Sirtuins leads to changes in acetylation status and activity of downstream proteins, including histones, transcription factors, transcriptional coregulators, metabolic enzymes, and proteins involved in signaling pathways and those associated with mitochondrial function. These direct effects mediated by Sirtuins collectively contribute to the alleviation of disease-associated damages, and the overall improvement and maintenance of cardiovascular system function. They play a crucial role in preventing cardiac hypertrophy, myocardial remodeling, heart failure, myocardial ischemia, reperfusion injury, atherosclerosis, and aneurysm development. Akt: Protein kinase B; AMPK: AMP-activated protein kinase; AP-1: Activator protein-1; CR: Caloric restriction; eNOS: Endothelial nitric oxide synthase; ERK: Extracellular regulated protein kinases; FOXO: Forkhead box O; IDH2: Isocitrate dehydrogenase 2; MnSOD: manganese superoxide dismutase 2; mTOR: Mammalian target of rapamycin; NAD: nicotinamide adenine dinucleotide; NF-κB: Nuclear factor kappa B; PCSK9: Proprotein convertase subtilisin/kexin type; PGC-1α: Proliferator-activated receptor-γ coactivator-1α; PI3K: Phosphosphatidylinositol-3-kinase; ROS: Reactive oxygen species; SIRT: Sirtuin.

SIRT1 levels have been observed in the adipose tissue of obese individuals[46] and the brain tissue of individuals with Alzheimer's disease.[47]

SIRT1 has a protective role against CVDs during CR. We found that CR increased, whereas high-fat diet decreased SIRT1 expression in mouse aortas.[17] The activity of SIRT1 declined in the hearts of Ang II-treated db/db mice, whereas CR attenuated deleterious perturbations and prevented the development of cardiomyopathy. Notably, the SIRT1–PGC-1α–HO-1 axis assumes a pivotal role in countering oxidative stress arising from hyperglycemia, thereby protecting the diabetic heart.[13] Similar outcomes were observed in the aorta of aged ad libitum (AL)-fed mice, in which SIRT1 protein levels were reduced compared to those in their young AL-fed counterparts. Meanwhile, aged CR-fed mice exhibited SIRT1 levels that were not significantly different from those of young AL- or CR-fed mice.[21] Our group performed a study on angiotensin II (AngII)-induced AAA and demonstrated that SIRT1 was upregulated in VSMCs upon CR. Further more, the specific ablation of SIRT1 in VSMCs abolished the prophylactic effect of CR on AAA formation in Apoe$^{-/-}$ mice, indicating the essential role for SIRT1 in CR-mediated vasoprotective effects.[12]

The mechanism through which CR affects the expression and activity of Sir2/SIRT1 remains a subject of ongoing debate. Given its dependence on NAD^+, the modulation of NAD^+ levels and NAD^+/NADH levels is likely to play a significant role in this process.[48] The low energy status induced by CR alters the production and consumption of NAD^+ during cellular metabolism, leading to an elevation in intracellular NAD^+ levels. The increased NAD^+ can bind to and activate SIRT1, thereby facilitating its deacetylation activity. Furthermore, emerging evidence suggests that dietary supplementation with NAD^+ or NAD^+ precursors can activate SIRT1 and potentially promote healthy aging.[49] CR modulates the activity of multiple signaling pathways and transcription factors that interact with SIRT1, including AMP-activated AMPK, mammalian target of rapamycin (mTOR), insulin/insulin-like growth factor 1 (IGF-1), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PFC-1α), thereby further enhancing the function of SIRT1.[50] Through deacetylation, SIRT1 modifies downstream target proteins including transcription factors, histones, and metabolic enzymes, which allows cells to adapt to energy-restricted environments through changes in metabolic processes and gene expression.

Other members of the Sirtuins family

SIRT2 is predominantly localized within the cytoplasm, co-localizing with microtubules and facilitating the deacetylation of α-tubulin. It can also transiently translocate to the nucleus during the G2/M transition to deacetylate histone H4.[51] SIRT2 plays a pivotal role in various metabolic processes and is widely expressed in multiple metabolically active tissues.[52] Our group previously demonstrated that SIRT2 plays important roles in pathological cardiac hypertrophy and age-related vascular remodeling.[53,54] During CR, the expression of SIRT2 is upregulated in renal and white adipose tissue, where it deacetylates FOXO transcription factors, thus suppressing ROS production.[55,56] SIRT2 is also implicated in the protective effect of CR against tumorigenesis, with SIRT2 deficiency abolishing the CR-induced increase in survival of mouse tumor models.[57] Additionally, SIRT2 plays a crucial role in vascular diseases, with its effects on endothelial cell damage dependent on the degree of oxidative stress.[58] Yu *et al*[59] found that the mRNA and protein levels of SIRT2 were increased in rat cardiomyocytes after short-term CR. Notably, in aortic smooth muscle cells treated with resveratrol, a compound that mimics the effects of CR, SIRT1, SIRT3, and SIRT4 expression was upregulated, while SIRT6 was downregulated, and SIRT2 expression remained unaltered.[60] Taken together, further investigation is warranted to determine whether SIRT2 plays a mediating role in CVDs during CR.

SIRT3 is primarily localized in the mitochondria where it regulates mitochondrial function, cellular metabolism, and antioxidant defense. It also participates in the process of cell death and has been implicated in cardiac hypertrophy, myocardial infarction, as well as heart failure.[61,62] During CR, SIRT3 has been demonstrated to deacetylate and activate mitochondrial isocitrate dehydrogenase 2 (IDH2), resulting in elevated nicotinamide adenine dinucleotide phosphate (NADPH) levels and an increased reduced-to-oxidized glutathione ratio in mitochondria, which highlight the importance of SIRT3 in enhancing the mitochondrial glutathione antioxidant defense system.[63] Another study revealed that the protective effects of CR against oxidative stress were diminished in mice lacking SIRT3, and SIRT3-induced reduction of cellular ROS was dependent on superoxide dismutase 2 (SOD2).[64] A quantitative mass spectrometic study investigating the hepatic mitochondrial acetyl-proteome during CR revealed that SIRT3 deacetylates proteins involved in various metabolic pathways and mitochondrial maintenance, demonstrating the orchestrated regulation of multiple biological processes.[65] Collectively, these findings highlight the essential role of SIRT3 in the intricate modulation of mitochondrial function, oxidative stress response, and metabolic adaptations during CR. SIRT3 expression in cardiac tissues was shown to increase during CR.[59] The protective effect of CR mimetic resveratrol was not observed in SIRT3 knockout mice.[66] However, a direct evaluation of the contribution of SIRT3 to the CR-dependent alleviation of CVDs is lacking.

SIRT4 and SIRT5 are also mitochondrial Sirtuins. Unlike other Sirtuin family members, SIRT4 enhances pathological cardiac hypertrophy. Our group unveiled that SIRT4 can compete with SIRT3 for manganese superoxide dismutase 2 (MnSOD) binding and accelerate Ang II-induced pathological cardiac hypertrophy by inhibiting MnSOD activity and promoting ROS accumulation.[67] CR induces the expression of SIRT3 and SIRT5,[68] while SIRT4 appears to have the opposite effect. Instead of functioning as an NAD-dependent deacetylase, SIRT4 utilizes NAD to produce adenosine diphosphate (ADP)-ribosylated glutamate dehydrogenase (GDH), a key enzyme involved in the metabolism of glutamate and glutamine for adenosine triphosphate (ATP) production.

Through the ADP-ribosylation of GDH, SIRT4 inhibits its enzymatic activity and downregulates insulin secretion in response to amino acids. The effects of CR on GDH activity were consistent with the changes observed in the pancreas of SIRT4 knockout mice, implying that the activity of SIRT4 is downregulated during CR.[69] SIRT5 interacts with carbamoyl phosphate synthetase 1 (CPS1), an enzyme that catalyzes the initial step of the urea cycle for the detoxification and disposal of ammonia, and upregulates its activity. SIRT5 deficiency exacerbates cardiac hypertrophy in response to cardiac pressure overload by impairing fatty acid oxidation, glucose oxidation, and the mitochondrial NAD^+/NADH balance.[70] Moreover, CR triggers SIRT5-mediated deacetylation of CPS1 and adaptation to increased amino acid catabolism, whereas SIRT5 knockouted mice are unable to upregulate CPS activity during CR, which leads to elevated blood ammonia levels.[71]

SIRT6 plays a critical role in inflammation, glucose metabolism, and lipid metabolism, and SIRT6 dysfunction has been linked to the onset of various pathologies, including CVDs,[72] cancer, neurodegenerative diseases, and diabetes.[73] Previous studies have demonstrated that overexpression of SIRT6 in male transgenic mice significantly extends lifespan compared to that of wild-type mice.[74] Moreover, SIRT6 expression is elevated after 6-month CR in aged mice.[75] In a study investigating the effect of CR on the ovarian lifespan of rats, it was observed that a 25% CR regimen upregulated SIRT6 expression in the ovary, whereas a 45% CR regimen had no effect.[76] Therefore, further investigation is needed to fully understand the underlying mechanisms and the precise role of SIRT6 in promoting longevity and the response to CR.

SIRT7 maintains transforming growth factor receptor I by modulating autophagy and contributing to myocardial tissue repair.[77] The expression of SIRT7 under CR conditions varies depending on age and tissue type, with inconsistencies between mRNA and protein expression.[78] SIRT7 can also catalyze ADP-ribosylation. Under CR, SIRT7 interacts with the ADP-ribose reader mH2A1.1, leading to the enrichment of mH2A1.1 in a specific group of neighboring genes. Studies on SIRT7-deficient mice subjected to CR revealed that the expression patterns of these genes were disrupted, consequently impairing autophagy activation.[79]

Collectively, the direct contribution of CR to cardiovascular health is intricately linked to Sirtuins. In experimental studies using murine models, Sirtuins, notably SIRT1, have been shown to mediate the beneficial effects of CR on diverse CVDs, including diabetic cardiomyopathy,[13] myocardial ischemia/reperfusion injury,[14,15] myocardial fibrosis,[80] atherosclerosis,[81] and AAA.[12] Studies involving larger animals, such as non-human primates, have also provided compelling evidence supporting the cardiovascular benefits of CR.[82] And Sirtuins may play a crucial role in the process while further experimental verification is required. Small SIRT1 activators, such as SRT2104, SRT2379, and SRT3025, which are undergoing clinical trials,[83] may simulate the CR state *in vivo* and be potential drugs for the treatment of CVDs. At present, considerable attention is focused on SIRT1, and further extensive research is warranted to elucidate the contribution of other Sirtuin isoforms to changes in the cardiovascular system during CR. The Sirtuin-mediated beneficial effects of CR in the cardiovascular system are summarized in Table 1.

Indirect effects of CR on cardiovascular prevention mediated by Sirtuins through circulating small molecules

Although certain changes induced by CR are shared across various organs and tissues, most appear to be organ-specific. The extent to which organs respond to CR varies significantly, suggesting that the impact of CR on organ function and metabolism is complex and influenced by organ-specific factors. In light of these findings, we hypothesized that aside from the direct Sirtuin-mediated benefits of CR on the cardiovascular system, beneficial effects in other tissues and organs may indirectly affect the cardiovascular system. The modulation exerted by small molecule metabolites in the circulation may be involved in this process. The indirect effects of CR on the cardiovascular system are shown in Figure 2.

Metabolic organ response to CR

Liver

During the initial stages of CR, the liver exhibits an adaptive response. Hepatocytes upregulate gluconeogenesis, a process in which glucose is synthesized from non-carbohydrate precursors. This response ensures a steady supply of glucose to meet the energy demands of various tissues during periods of reduced caloric intake. A significant increase in SIRT1 levels was observed in the liver after overnight fasting, suggesting its involvement in the regulation of glucose production.[93] In another study, the regulation of SIRT1 expression in response to a 3-month CR diet showed divergent patterns between the liver and other tissues. Specifically, SIRT1 protein levels were increased in white adipose and muscle tissues, and decreased in the liver.[94] This decrease in hepatic SIRT1 during CR was consistent with the observed reduction in the ratio of NAD^+ to NADH, indicating an altered cellular redox state. Analysis of the liver metabolome in response to CR revealed that a wide range of metabolites were significantly affected. These include metabolites involved in glycolysis, fatty acid oxidation, and tryptophan metabolism. Importantly, they can be exported from the liver into plasma, indicating their systemic impact beyond the hepatic tissue.[95]

Adipose tissue

Adipose tissue dysregulation has been implicated in the development of systemic metabolic dysfunction and an increased susceptibility to CVDs. CR exerts notable effects on adipose tissue, influencing its morphology, adipokine secretion, and levels of metabolic regulatory factors. Despite the general reduction in adipose tissue mass during CR, functional beige adipocytes continue to develop. This phenomenon, known as the browning of

Table 1: Sirtuin-mediated beneficial effect of CR in the cardiovascular system

Sirtuins	CR and CR mimetics	Sirtuin levels	Sirtuin targets	Effect and mechanism involved	Functions	References
SIRT1	10% restriction for 2 weeks followed by 35% for 2 weeks	Activity↑	PGC-1α/PPARγ	Cardioprotective effects of CR operating through SIRT1 and PGC-1 α, thereby decreasing oxidative stress, fibrosis, and inflammation.	Regulation of diabetic cardiomyopathy.	[13]
	10% restriction for 2 weeks followed by 30% for 6 weeks	↑	PGC-1α/PPARγ	CR activates the expression of the AMPK/SIRT1/PGC-1α signaling pathway and optimizes myocardial energy metabolism in the elderly and alleviates the adverse consequences of I/R.	Resist myocardial ischemia/reperfusion.	[15]
	10% restriction for 2 weeks followed by 40% for 12 weeks	↑	Cardiac C3	Cardiac SIRT1 suppresses local complement system activation after ischemia-reperfusion.	Attenuate myocardial ischemia-reperfusion injury.	[14]
	Glucose deprivation for cultured cardiac myocytes; 48h food starvation for mice	↑	FOXO1	Deacetylation of foxo1 by SIRT1 is required for starvation-induced autophagy in mouse hearts.	Mediate starvation-induced autophagy and maintain cardiac function.	[84]
	Resveratrol	↑	MnSOD	MnSOD induced by RSV via nuclear SIRT1 reduces oxidative stress.	Cardiomyocyte protection.	[85]
	Resveratrol	↑	TGF-β/Smad2/3	Attenuated compensatory myocardial hypertrophy and reduced interstitial collagen deposition.	Attenuate myocardial fibrosis.	[80]
	30% restriction for 1 year	↑	eNOS	Improving endothelial cell survival and function.	Decrease atherosclerosis.	[17]
	57.4 kcal/week diet for 3 weeks	Untested	eNOS	SIRT1 regulates endothelial NO and endothelium-dependent vascular tone by deacetylating eNOS.	Promote endothelium-dependent vasodilation.	[86]
	SRT3025	Activity↑	Pcsk9	Pharmacological SIRT1 activation mimics CR phenotype, reduced Pcsk9 secretion, increased Ldlr expression, and decreased plasma LDL-cholesterol in $Apoe^{-/-}$ mice.	Decrease atherosclerosis.	[81]
	28-month-old rat with lifelong 40% CR	↑	NF-κB	Improved endothelial function, attenuated vascular ROS production, inhibited NF-κB activity, and down-regulated inflammatory genes.	Vasoprotective effects in aging.	[16]
SIRT2	40% restriction for 3 weeks	↑	Unknown	Unknown	Unknown	[59]
SIRT3	25% restriction for 8 weeks	↑	Unknown	Unknown	Improve cardiac function.	[87]
	40% restriction for 3 weeks	↑	Unknown	Unknown	Unknown	[59]
	Exogenous addition of NAD	↑	LKB1	SIRT3 deacetylates and activates LKB1, thus augmenting the activity of the LKB1-AMPK pathway.	Inhibit cardiac hypertrophy and heart failure.	[88]
	Resveratrol	↑	TGF-β/Smad3	RSV activates SIRT3 in the mouse heart and can exert antifibrosis effects via the TGF-β/Smad3 pathway.	Ameliorate cardiac fibrosis and improve cardiac function.	[66]
	Resveratrol	↑	NF-κB	RSV negatively regulated H_2O_2-induced NF-κB activation, and SOD2, Bcl-2, and Bax were involved in this pathological process.	Protect cardiomyocytes from oxidative stress-mediated cell death.	[89]
SIRT4	40% restriction for 3 weeks	↑	Unknown	Unknown	Unknown	[59]
	Resveratrol	↑	Unknown	Unknown	Protect cardiomyocytes from H_2O_2-induced apoptosis by activating SIRT1, 3, 4, 7.	[90]
SIRT5	24h fasting	Unchanged	–	–	Sirt5 mRNA levels in the liver were increased by fasting but were unchanged in the kidney or heart.	[91]
SIRT6	40% restriction for 12 months	↑	Unknown	Unknown	Nutrient limitation extends lifespan by increasing SIRT6 levels.	[92]
SIRT7	Resveratrol	↑	Unknown	Unknown	RSV protects cardiomyocytes from H_2O_2-induced apoptosis by activating SIRT1, 3, 4, 7.	[90]
	40% restriction for 3 weeks	↑	Unknown	Unknown	Unknown	[59]

AMPK: AMP-activated protein kinase; CR: Caloric restriction; eNOS: Endothelial nitric oxide synthase; FOXO: Forkhead box O; H2O2: Hydrogen peroxide; MnSOD: manganese superoxide dismutase 2; NAD: nicotinamide adenine dinucleotide; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; PCSK9: Proprotein convertase subtilisin/kexin type 9; PGC-1α: Proliferator-activated receptor-γ coactivator-1α; PPAR-γ: Peroxisome proliferator-activated receptor γ; ROS: Reactive oxygen species; RSV: Resveratrol; SIRT: Sirtuin; SOD: Superoxide dismutase 2; SRT3025: A SIRT 1 activitor; TGF-β: Transforming growth factor β; ↑: Expression increased; Activity ↑: Expression not changed but activity increased; –: Not available.

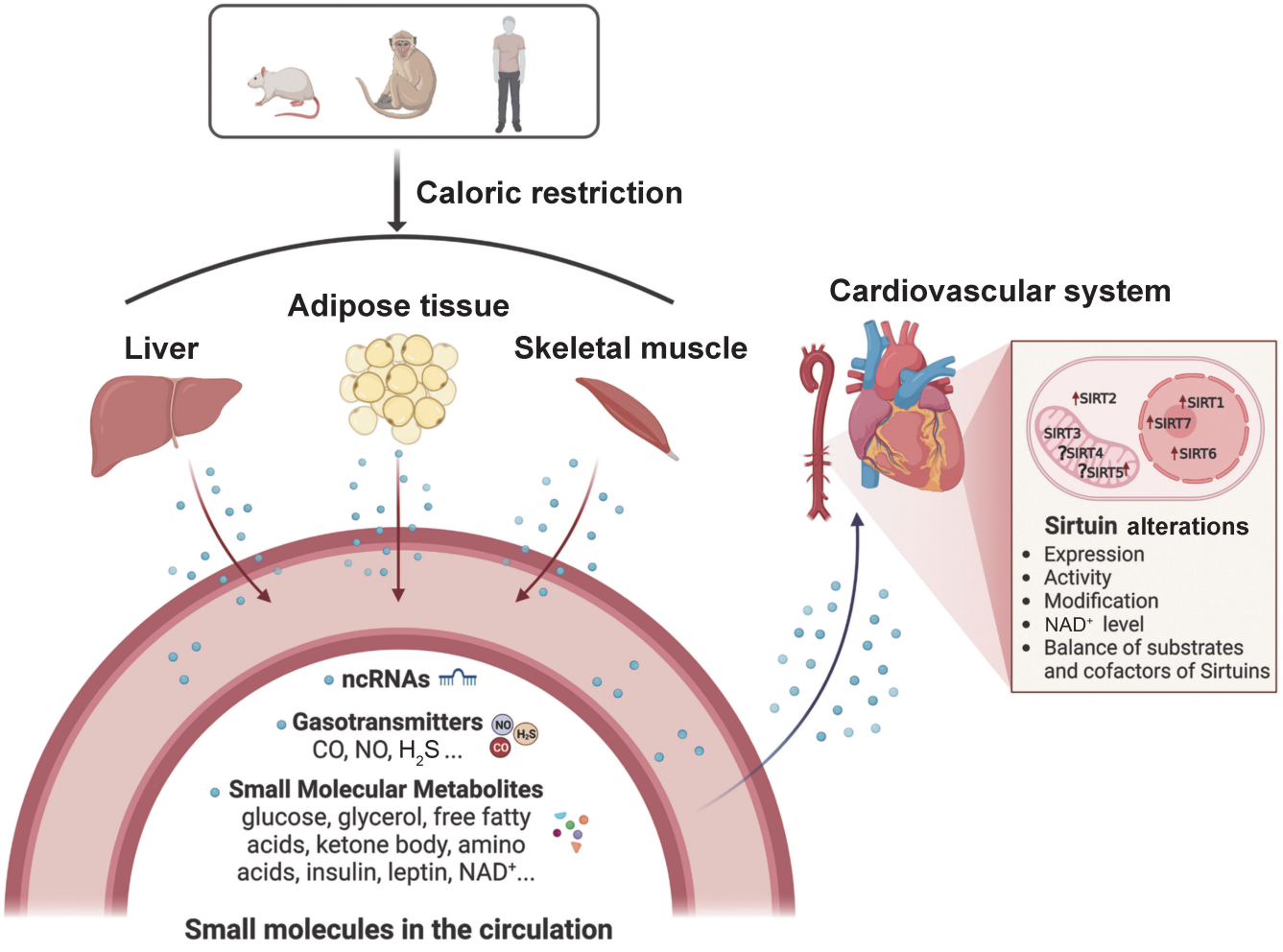

Figure 2: Indirect effects of CR on cardiovascular system through circulating small molecules. During the initial stage of CR, metabolic organs such as the liver, skeletal muscle, and adipose tissue undergo adaptive changes. Subsequently, small molecules derived from these organs, including gasotransmitters, ncRNAs, and small molecular metabolites, are released into the bloodstream. These circulating small molecules can then be transported to the cardiovascular system, where they exert influence on the Sirtuins present. The activation of Sirtuins in the cardiovascular system by these circulating small molecules contributes to their protective effects mediated by Sirtuins, including reduced risk factors, inflammation, and oxidative stress, improved lipid and glucose metabolism, and increased NO bioavailability, leading to improved cardiovascular health. This indirect mechanism highlights the interplay between metabolic organs and the cardiovascular system mediated by circulating molecules, elucidating the multi-organ communication involved in the benefits of CR on cardiovascular function. CO: Carbon monoxide; CR: Caloric restriction; H2S: Hydrogen sulfide; NAD: Nicotinamide adenine dinucleotide; NO: Nitric oxide; ncRNAs: Non-coding RNAs; SIRT: Sirtuin.

white adipose tissue, is prevalent in response to a negative energy balance and plays a vital role in maintaining overall energy homeostasis during periods of energy scarcity.[96] CR leads to distinct changes in serum lipid signatures derived from adipose tissue, consequently affecting the systemic lipid profile. Downstream factors associated with adiponectin signaling, such as SIRT1, AMPK, and PGC-1α, play crucial roles in mediating the favorable effects of CR across various tissues and organs.[97]

Skeletal muscle

Skeletal muscle is a highly metabolically active tissue that plays a crucial role in maintaining glucose homeostasis. During the aging process, the skeletal muscle undergoes significant deterioration and is characterized by various detrimental changes. These effects include muscle atrophy, decreased protein synthesis, increased protein degradation, impaired mitochondrial function, chronic inflammation, and insulin resistance. CR promotes greater glucose uptake by skeletal muscles, leading to a decrease in blood glucose levels.[98] This can contribute to the maintenance of glucose homeostasis and potentially provide metabolic benefits in the context of aging and certain metabolic disorders. Short-term CR has also been demonstrated to enhance the availability and activity of stem cells in skeletal muscles, mitochondrial abundance, and induce conserved metabolic and longevity regulators.[99] CR also induces changes in the secretion of myokines such as interleukin 8, matrix metalloproteinase-2, and irisin, which have anti-inflammatory and metabolic regulatory properties.[100] The improved metabolic function of skeletal muscles induced by CR can enhance energy utilization, increase fat oxidation, reduce adiposity, improve lipid profiles, and maintain systemic metabolic homeostasis.

Small molecules from metabolic organs to plasma

During CR, metabolic organs, such as the liver, adipose tissue, and skeletal muscle, undergo changes, leading to the production and release of specific metabolites. These metabolites can then be transported to the cardiovascular system via the bloodstream, where they exert systemic effects. Herein, we summarize the selection of small molecules that confer significant benefits during CR, including gasotransmitters, non-coding RNAs, and small molecule metabolites, emphasizing their pivotal roles in mediating the beneficial effects of CR on systemic metabolism and cardiovascular health.

Gasotransmitters

Gasotransmitters, such as NO, carbon monoxide (CO), and hydrogen sulfide (H_2S), are endogenously synthesized and can diffuse across cell membranes. They exhibit high reactivity and do not require degradation or reuptake. These gasotransmitters exhibit dynamic fluctuations in their concentrations and distributions in response to CR.[101–103]

NO plays a pivotal role in vasodilation and the maintenance of vascular homeostasis, thereby influencing blood flow dynamics and nutrient distribution in diverse tissues. Obesity has been associated with a decrease in eNOS levels, and studies have demonstrated that HFD-induced obesity leads to reduced eNOS expression in both the liver and adipose tissues.[104] By contrast, CR increases eNOS expression, resulting in elevated NO levels.[102]

Endogenous CO is generated via heme degradation, resulting in the production of CO, iron, and biliverdin. This transformation is catalyzed by heme oxygenase (HO), and the HO/CO system exerts robust protective effects on the vascular system. CR has been associated with enhanced heme catabolism, resulting in endogenous CO production.[101]

H_2S participates in blood vessel relaxation and the regulation of liver perfusion. Aging is associated with the dysfunction of cystathionine gamma-lyase (CSE) and cystathionine beta-synthase (CBS), resulting in reduced H_2S production and concentration. In a study involving rats of different ages fed an AL or a 40% CR diet for four months, it was observed that CR exerted beneficial effects on CSE and CBS protein levels in the aorta and liver, potentially counteracting the age-related decline in H_2S concentration.[105] In another study, CR upregulated the expression of cystathionine gamma-lyase (CGL), an enzyme involved in the transsulfuration pathway, resulting in increased H_2S production and protection against hepatic ischemia-reperfusion injury. By contrast, supplementation with sulfur amino acid (SAA), the activation of mTORC1, or inhibition of CGL reduced H_2S production and abolished the beneficial effects of CR.[103] Furthermore, the abundance of H_2S-producing microbes within the gut microbiota has been implicated in the increased production of H_2S during CR.[106,107] H_2S signals via a post-translational modification, termed "persulfidation", which acts as a molecular mediator of the pleiotropic benefits of CR, including longevity and stress resistance. By preserving the H_2S signaling system, CR may help maintain cellular homeostasis during aging.

Numerous studies have investigated the impact of CR on gasotransmitters, with particular emphasis on H_2S. Owing to their pronounced reactivity and remarkable diffusibility, gasotransmitters can exert their effects throughout entire body.

Non-coding RNAs (ncRNAs)

ncRNAs constitute a heterogeneous group of RNA molecules that lack protein-coding capacity but play pivotal regulatory roles in cellular processes. They exhibit structural and functional diversity, which allows them to participate in various molecular mechanisms involved in gene regulation and cellular homeostasis. Through their interactions with DNA, RNA, and protein, ncRNAs can modulate gene expression at the transcriptional, post-transcriptional, and epigenetic levels. Several recent genome-wide studies have provided evidence of the influence of CR on the expression profiles of diverse classes of ncRNAs, including microRNAs, long non-coding RNAs (lncRNAs), and the relatively less understood 5′ transfer RNA(tRNA) halves. These studies demonstrate that CR can modulate and reverse age-associated alterations in the expression patterns of these ncRNA classes.[108] RNA-sequencing analysis of skeletal muscle tissues from young and old rhesus macaques revealed that CR could reverse age-associated alterations in a significant number of miRNAs.[109] A previous study found that CR increased mitochondrial miRNAs in the mouse liver, and caused overproduction of mtDNA-encoded proteins, resulting in mild proteostatic stress within the mitochondria and the induction of the mitochondrial unfolded protein response to enhance mitochondrial proteostasis and function.[110] Consistent findings have been described for circulating miRNAs during CR, highlighting their potential as non-invasive biomarkers of aging and age-related diseases.[111]

Small-molecule metabolites

CR elicits a myriad of changes in small-molecule metabolites, including metabolites associated with energy metabolism such as glucose, glycerol, free fatty acids, and ketone bodies; hormones involved in energy balance such as insulin and leptin; NAD^+ and its precursors; and specific amino acids. These changes reflect metabolic adaptations that occur in response to reduced calorie intake. Alterations in serum small molecule metabolites during CR provide valuable insights into systemic metabolic changes.

Functioning as a substrate for NAD^+-dependent reactions, NAD^+ is a crucial cellular coenzyme that plays a pivotal role in fundamental metabolic pathways, such as glycolysis, the tricarboxylic acid cycle, β-oxidation, and oxidative phosphorylation. NAD^+ synthesis can occur via *de novo* pathways, from tryptophan or through salvage pathways utilizing NAD^+ precursors such as nicotinic acid, nicotinamide (NAM), or nicotinamide riboside.[112] A comprehensive analysis was conducted to ascertain the

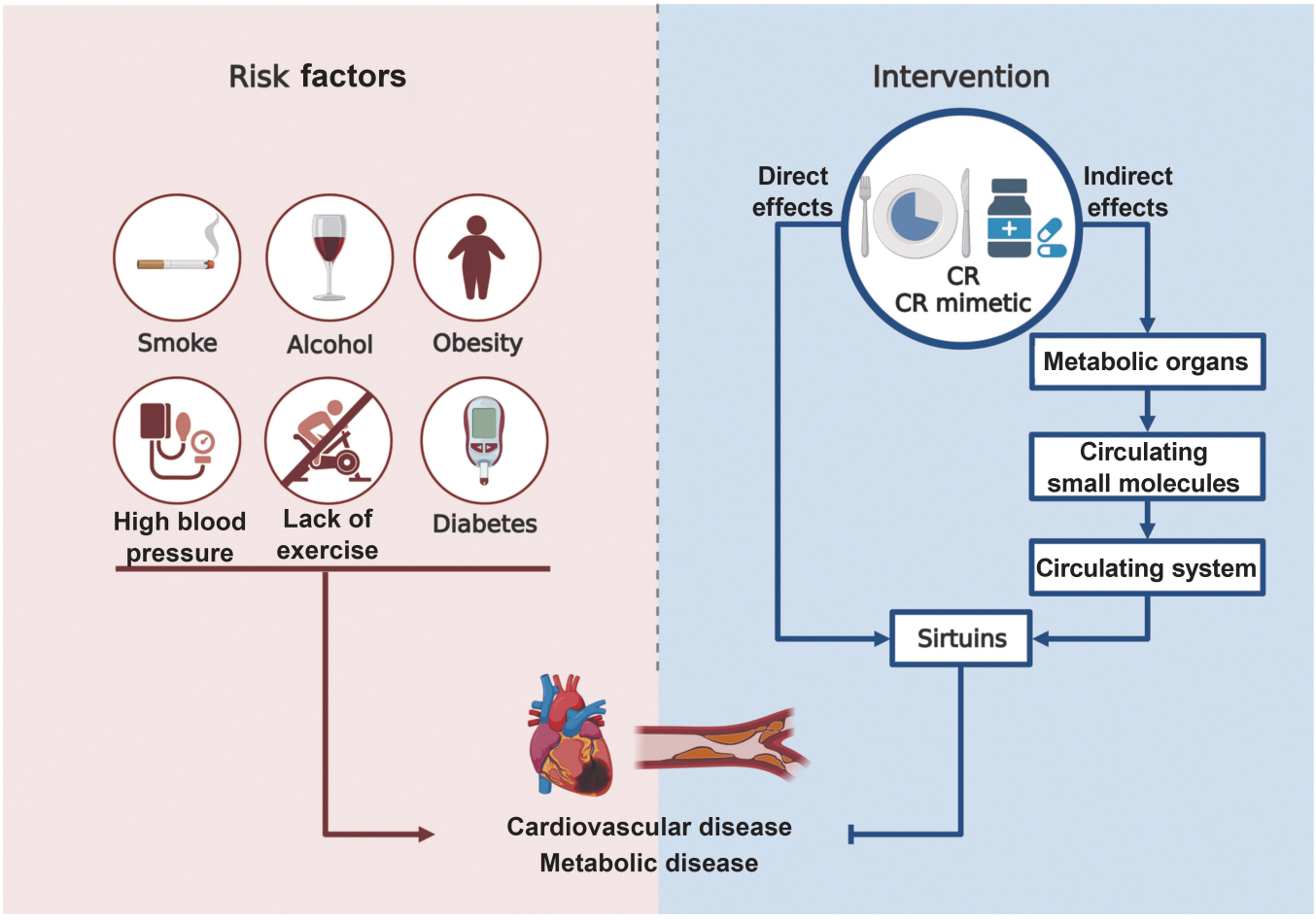

Figure 3: Graphical abstract of the direct and indirect effect of CR and CR mimetic. Numerous risk factors can lead to metabolic diseases and CVDs. CR and CR mimetics have been shown to mitigate these risk factors, thereby promoting cardiovascular health. We hypothesize that CR exerts its benefits on the cardiovascular system through both direct and indirect pathways. The direct impact of CR involves the modulation of NAD^+ levels and the NAD^+/NADH ratio in the heart and vascular, thereby leading to alterations in Sirtuin levels. The indirect effects on the cardiovascular system impact the metabolic organs firstly, including the liver, skeletal muscle, and adipose tissue. These organs then produce numerous small molecules that enter the circulatory system. Additionally, the circulating molecules conversely interact with other organs, further promoting their protective effects, and causing the alterations of Sirtuins in the cardiovascular system. Sirtuins, as the energy sensors, respond to the change of the energy status and interact with the circulating small molecules, mediating the beneficial effect of CR on the cardiovascular system. CR: Caloric restriction; CVD: Cardiovascular diseases; NAD: Nicotinamide adenine dinucleotide.

shared pathway alterations among brown adipose tissue, liver plasma, and the brain, with L-carnitine biosynthesis, NAD biosynthesis from 2-amino-3-carboxymuconate semialdehyde, S-methyl-5′-thioadenosine degradation II, NAD biosynthesis II (from tryptophan), and tRNA charging were revealed as the most prominently modulated canonical pathways.[113] The observed elevation of NAD^+ levels in various tissues under CR may not only arise from the de novo biosynthesis pathway but could also involve the salvage pathway. Recycling of NAD^+ precursors such as NAM and 1-methyl nicotinamide (meNAM) is upregulated during CR, indicating a potential contribution to the increased NAD^+ levels.

Metabolic organs might be the main source of small molecules, releasing them into the bloodstream. However, the intricate interplay between these molecules within metabolic organs and their interactions with other tissues and organs during CR remains elusive. The tissue-specific effects of these small molecules and the signaling pathways that span different tissues during CR warrant further study. Moreover, modulating the release and interactions of these small molecules may be a viable approach for devising therapeutic interventions targeting cardiovascular diseases and other age-related disorders.

Changes in circulating small-molecule levels regulate overall Sirtuins

Alterations in circulating gasotransmitters, ncRNAs, and metabolites have the potential to exert systemic effects by reaching tissues and organs throughout the body and significantly affecting Sirtuin expression and activity.

Studies have demonstrated that increased levels of H_2S, a gasotransmitter, can lead to sulfhydration of Sirtuins, including SIRT1[114] and SIRT3[115]. These modifications enhanced the interactions between Sirtuins and zinc ions, thereby promoting their deacetylation activity and contributing to their increased stability. H_2S has been reported to increase the levels of NAD^+, which then enhances Sirtuin activity.[116] Other gasotransmitters, such as NO and CO, also regulate Sirtuin function.[117,118]

Several studies have shown that ncRNAs directly target Sirtuins and regulate their function. Micro-199a induces the differentiation of pluripotent stem cells into endothelial cells, inhibits VSMC differentiation by targeting SIRT1, and induces angiogenesis.[119] Micro-34a induces EPC senescence and impedes angiogenesis by suppressing SIRT1.[120] In addition to microRNAs, Inc RNAs have also been documented to interact with Sirtuins and play a role in the development and progression of CVDs.[121,122]

Circulating metabolites also modulate the activity and function of Sirtuins. CR or supplementation with NAD^+ precursors, such as nicotinamide mononucleotide and nicotinamide riboside, leads to an increase in NAD^+ levels. This increase is linked to the activation of SIRT1, enhanced oxidative metabolism, and protection against a high-fat diet in mice.[123] Additionally, other metabolites, such as acetyl-coenzyme A, can affect Sirtuin activity by altering the balance of substrates and cofactors involved in Sirtuin-catalyzed reactions.

Indirect effects exert cardiovascular protection

The intricate interplay between gasotransmitters, ncRNAs, and small-molecule metabolites, and their interactions with Sirtuins elucidates the multifaceted mechanisms underlying the cardiovascular benefits associated with CR. These circulating small molecules, originating from diverse organs and tissues, actively participate in physiological and pathological processes within the cardiovascular system. Moreover, they play crucial roles in modulating the expression and activity of Sirtuins, thereby mediating the beneficial effects of CR on cardiovascular health.

Sirtuins, which function as sensors of energy status, respond to the overall changes in metabolism within the organism and exert cardiovascular protective effects through various epigenetic mechanisms. Further research is required to elucidate the precise mechanisms underlying these regulatory effects. Growing knowledge of CR and Sirtuins presents substantial opportunities for the development of novel Sirtuin-targeting therapeutic strategies against CVDs.

Conclusion and Perspectives

The current review provides a comprehensive summary of the effects of CR on Sirtuin protein family members and their cardiovascular protective properties. There have been emerging studies on the epigenetic role of SIRT1 in the alleviation of CVDs during CR. However, the diverse roles of other members within the Sirtuin protein family in this process warrant further investigation. Here, we describe the direct effects of CR on Sirtuin-mediated cardiovascular health and propose that CR modulates the metabolic status and homeostasis of metabolic organs, leading to systemic changes in circulating factors. These systemic changes influence Sirtuin expression and activity within the cardiovascular system, and contribute to improvements in cardiovascular function. Notably, molecules, such as H_2S, miRNAs, and NAD^+, have emerged as critical mediators that bridge the systemic changes induced by CR and the resultant benefits observed in specific organs. Figure 3 shows the direct and indirect effects of CR and CR mimetics. The interplay between these effects yields important insights that may contribute to the design and development of novel CR mimetics.

The existing studies on Sirtuins and CR merely represent the tip of the iceberg. The evidence supporting Sirtuin as the sensor or mediator of CR is still insufficient, and the distinct functions of each molecule within the family have not been clearly analyzed. Moreover, the conclusions drawn from mouse experiments are still not clear, and further experiments in primates is yet to be conducted. The increasing attention focused on the interplay between different organs necessitates the incorporation of advanced methodologies, including single-cell sequencing, high-throughput technologies, and machine learning models, in future research endeavors. The development of such strategies will effectively address the pressing need for comprehensive studies in the field of multi-organ metabolism. Moreover, the ongoing exploration of various CR mimetics and a deeper understanding of the intricate interplay between systemic factors and specific organs hold immense promise for the development of innovative therapeutic approaches aimed at managing cardiovascular aging and disease.

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Conflicts of interest

None.

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