A Review on the Emerging Role of SIRT6 in Cardiovascular Diseases

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
May 2023

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “A Review on the Emerging Role of SIRT6 in Cardiovascular Diseases” submitted by Md. ShahOwaly Ullah Dinar (18346028), of Summer, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on May 2023.

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Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

The fundamental reasons behind cardiovascular diseases are exacerbated by a vast number of signaling molecules. Sirtuin 6 (SIRT6) is a highly conserved NAD^+ dependent enzyme and essential in regulating a number of cellular events, including telomeric balance, gene expression, DNA repair as well as management of metabolism. As a matter of importance, SIRT6 not only aids in atherosclerosis and cardiac remodelling but also protects against the onset and progression of CVDs. Hypertrophy of cardiomyocytes, atherosclerosis, and fibroblast transformation are all suppressed by SIRT6. When it comes to the beginning and progression of different cardiovascular illnesses, the involvement of SIRT6 in glucose and lipid balance, genomic stability, and inflammation are crucial. This study provides a detail discussion on existing molecular mechanism, prevention as well as available treatment and prospective therapeutic modulators to control SIRT6-mediated CVDs.

Keywords: Hypertension, Polypill, Revascularization, Bradyarrhythmia, Atherogenesis.

Dedication

I dedicate this work to everyone who inspired me in my work and especially to my parents.

Acknowledgement

Before anything else, I want to thank Allah (SWT) for each of the bounties He has bestowed upon me and for making it possible for me to finish the thesis.

My deepest appreciation goes out to Dr. Raushanara Akter (Professor, School of Pharmacy, Brac University) for serving as my project supervisor and providing invaluable assistance and advice over the duration of this project. I want to thank her for having faith in me and giving me the freedom to write my thesis on a topic of my own choosing. I am immensely thankful for her constant support, knowledge, consistent optimism, and inspiration throughout this journey, with all of its difficulties and triumphs.

In addition, I owe a great debt of appreciation to Professor Dr. Eva Rahman Kabir (Dean of the School of Pharmacy, Brac University) for all of the support, advice, and patience she has shown me during the process of writing my thesis. Without their direction and input at every stage, this work would not have been completed. Also, I'd want to express my deep appreciation to Dr. Hasina Yasmin, Associate Dean and Program Director, School of Pharmacy, Brac University.

Lastly, I would want to acknowledge my family and companions for their support, encouragement, and faith in me, as well as all of my teachers who helped me along the way.

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List of Acronyms

SIRT6	Sirtuin6
VEGF-B	Vascular Endothelial Growth Factor B
T3	Triiodothyronine
GH	Growth Hormone
IGF-1	Insulin-like Growth Factor 1
NRF2	Nuclear Factor Erythroid 2-related Factor 2
MCP-1	Monocyte Chemotactic Protein 1
PAI-1	Plasminogen Activator Inhibitor 1
ICAM-1	Intercellular Adhesion Molecule 1
HUVECs	Human Umbilical Vein Endothelial Cells
Col-I	Type I collagen
CTGF	Connective Tissue Growth Factor
AMPK	Adenosine Monophosphate-Activated Protein Kinase
IL	Interleukin
MMP	Matrix metalloproteinase
TGF	Transforming Growth Factor
SMC	Smooth Muscle Cell
EC	Endothelial Cell

NFATc4	Nuclear Factor of Activated T cells family 4
NF-kB	Nuclear Factor kappa B
STAT3	Signal Transducer and Activator of Transcription 3
CaN	Calcineurin
ERK	Extracellular signal Regulated Kinase
MAPK	Mitogen Activated Protein Kinase
c-JNK	c-Jun N-terminal Kinase
ACS	Acute Coronary Syndrome
TLR	Toll Like Receptor
ICAM-1	Intercellular Adhesion Molecule-1
VCAM-1	Vascular Cell Adhesion Molecule-1
HMSC	Human Mesenchymal Stem Cell
Bach1	BTB domains and CNC homolog 1
CRC	Colorectal Cancer
CHD	Coronary Heart Disease
HF	Herat Failure
AS	Atherosclerosis
LDL-c	Low Density Lipoprotein cholesterol
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9

ACE-Is	Angiotensin Converting Enzyme Inhibitors
ARBs	Angiotensin Receptor Blockers
CAD	Coronary Artery Disease
PCI	Percutaneous Coronary Intervention
CABG	Coronary Artery Bypass Graft
SGC-2	Sodium Glucose Cotransporter-2
IMT	Intima-Media Thickness
HIF-1α	Hypoxia-Inducible Factor 1-alpha
FOXO3	Foreheads Box O3
TNFSF4	Tumor Necrosis Factor Superfamily member 4
ECM	Extra-Cellular Matrix
MMP-9	Matrix Metalloproteinase 9
HMSCs	Human Mesenchymal Stem Cells
CR	Calorie Restriction

Chapter 1: Introduction

1.1 Cardiovascular Diseases

Death and disability are exacerbated by cardiovascular diseases. Cardiovascular and vascular diseases primarily afflict the elderly due to extended exposure to multiple risk factors, however they can also affect toddlers and teenagers (Ianni et al., 2018). Multiple signal molecules participate significantly in the etiology of CVD (Saiyang et al., 2021). The incidence of heart failure in the community over 80 is almost 15 times higher than in those between the ages of 20 to 39. When it comes to fatalities, heart disease is always first, and impacting both men and women equally. Around 795 thousand people worldwide suffer from a first or subsequent stroke every year. Ischemic strokes account for 87%, cerebral hemorrhages for 10%, and subarachnoid hemorrhages for 3% of all strokes (Tsao et al., 2022). According to Carrizales-Seplveda et al. (2018), the overall incidence rate in Mexico is 232.2 per 100,000 people, with a frequency of 18.2 per 1000 citizens aged 60 and up (Carrizales-Sepúlveda et al., 2018). Myocarditis and cardiomyopathy affect 6.11 million people globally at a prevalence rate of 76.92 per 100,000 people, according to American Heart Association (AHA) reports. Myocarditis and cardiomyopathy occurred more often with increasing age in the southern sub-Saharan region of Africa, the eastern and tropical regions of Latin America. According to the results of the INTER-CHF (International Congestive Heart Failure) cohort trial, the leading root-cause analysis of cardiac arrest as well as death after a diagnosis of HF differed among regions. Ischemic heart diseases (IHD) accounted for 20% of deaths in Africa, 25% of deaths in South America, 45% of deaths in China, 46% of deaths in India, 50% of deaths in the Arab world, and 56% of deaths in Southeast Asia (Tsao et al., 2022).

1.2 Molecular Pathogenesis of CVDs

At its outset, hypertrophy occurs in response to both healthy and unhealthy stimuli.; nevertheless, abnormal growth of tissue (pathological hypertrophy) typically develops into HF regulated by distinct cellular signaling pathways (X. Li et al., 2021; Nakamura & Sadoshima, 2018). It has been established that factors other than myocardial hypertrophy—such as severe fibrosis, aberrant induction of IGF (Insulin-like Growth Factor) Akt Signaling, β-adrenoceptor-mediated cardiac elevated stress, and autophagy damage; contribute to maturation of cardiac failure (X. Li et al., 2021; Lu et al., 2016). Abnormal stimulation of the Insulin-like growth factor-Akt cascade is connected to many diseases, including heart failure (X. Li et al., 2021).

Atherosclerosis (AS) is linked to a variety of causes, such as aberrant lipid metabolism, dysfunctional endothelial cells, and others (Michael A. & Guillermo, 2016; Musunuru & Kathiresan, 2016). Atheromatous plaques are largely made up of VSMCs (Vascular-Smooth-Muscle cells). Changes in energy metabolism, inflammation along with death are all observed in VSMCs from human atherosclerotic plaques (Grootaert et al., 2018; X. Li et al., 2021). The aging of VSMCs in human atherosclerotic plaques contributes to the development of the diseases and to the instability of the plaques (J. Wang et al., 2015). Because of LDL-c is also a significant danger sign with the onset of AS (Korman & Wisløff, 2018). It is also well established that macrophage foam cell production is an early atherosclerotic pathogenic alteration (X. Li et al., 2021).

1.3 Risk Factors of Cardiovascular Diseases

1.3.1 Ageing

A natural consequence of living is getting older. When it comes to the elderly, several of the primary causes of death are directly linked to aging itself, such as atherosclerosis-based cardiovascular illnesses and type 2 diabetic mellitus (T2DM). Currently, both the life expectancy and the elderly population are on the rise, which has led to a dramatic rise in the incidence of age-related chronic disorders. There is currently no viable method to predict aging or even reverse its associated conditions (Zhao et al., 2021). The AHA reports that the frequency of cardiovascular illness in the United States is 48.0% among those aged 20 and up, and that this percentage rises with age in both men and women. Heart diseases, heart failure, stroke, hypertension, and other cardiovascular illnesses and their risk factors account for more fatalities annually than both cancer and chronic lung diseases combined (Virani et al., 2020).

1.3.2 High Blood Cholesterol Level

The presence of cholesterol in the circulatory system is a major sign of atherosclerosis (Grundy et al., 2019). Blood levels of LDL-c are more vital in modern times for assessing cardiovascular risk and, by extension, for developing effective treatment strategies to mitigate that risk (Chapman et al., 2020). One of the seven components of excellent cardiovascular health, according to the AHA, is having a TC level below 200 mg/dL without treatment (Benjamin et al., 2019). In the years between 2015 and 2018, the average TC level for children ages 6-11 averaged 157.3 milligram/desiLitre, with men having a level of 157.4 milligram/desiLitre and women averaging 157.1 milligram/desiLitre. In 2020, the highest age-standardized death rates from high LDL-C were in Central Asia and Eastern Europe. By 2020, high concentration of LDL cholesterol would have contributed to 4.51 million deaths, having 7.96% of PAF (Population Attributable Fraction) (Tsao et al., 2022).

1.3.3 Diabetes Mellitus

Diabetes is a heterogeneous set of disorders in which blood glucose level is abnormal. In the United States, 90–95% of all instances of diabetes are attributable to diabetes of type 2, and 5-10% of all instances of diabetes are classified as type 1, are indeed the two most frequent kinds of diabetes. (Tsao et al., 2022). As clinical and epidemiological studies have progressed in last twenty years, it has been clear that One's risk of developing heart failure is dramatically increased if one has diabetes than those who do not have diabetes. There is growing evidence that heart failure can develop in diabetic patients despite the absence of coronary artery diseases and associated adverse outcomes. Experimental studies suggest multiple processes are at play because of a decline in systolic and diastolic activity in these patients (Lehrke & Marx, 2017).

1.3.4 High Blood Pressure (HBP)

High blood pressure is linked to an increased risk of many different health problems, not just heart diseases and stroke but also kidney diseases, dementia, aortic abnormalities, and disorders of the heart's valves, according to large cohort studies. The three most important modifiable risk factors for type 2 diabetes and cardiovascular diseases are tobacco use, hypertension, and abnormal lipid levels. There is a higher incidence of hypertension than any other condition as well as most convincing causation evidence (Fuchs & Whelton, 2020).

1.4 Treatment Option for Cardiovascular Diseases

1.4.1 Prevention

1.4.1.1 Lowering Cholesterol

Statins are very effective in avoiding ACS, stroke, and cardiac mortality because they cut cholesterol, particularly LDL cholesterol. Reducing LDL levels further lessens CVD risk, as

shown by recent findings with statins as well as by using the newer PCSK9 inhibitors (Mihaylova et al., 2012; Sabatine et al., 2017).

1.4.1.2 Lifestyle Factor

The policy emphasis on a healthy diet, regular exercise, and abstinence from tobacco and alcohol use must be preserved. Positively influencing behavior through policy is more likely to succeed than through individual therapy. (Leong et al., 2017). Several therapeutic interventions have been investigated for their potential to help smokers give up the habit. Studies have showed that using NRT, varenicline, bupropion, or cytisine can increase temparence rates by as much as forty percent to seventy percent., but this estimate is constrained by probable publication prejudices and short follow up periods (Leong et al., 2017; Stanley & Massey, 2016).

1.4.1.3 Polypill as a Fixed-Dose Combination Drug Therapy

Antihypertensive medicines, aspirin, and statins are often combined into a single pill (a "polypill"), which has been demonstrated to increase treatment adherence and blood pressure (BP) and cholesterol levels more so than standard care alone (Thom et al., 2013). It has been demonstrated that the polypill has the ability to lower the prevalence of CVD in the population at a reasonable cost (Wald et al., 2016). It is clinically valuable, especially for secondary prevention, that in theory, taking a polypill can cut your risk of cardiovascular disease by over 70–80%. Within 6 months following a myocardial infarction, patients who were treated with a polypill including aspirin, ramipril, and atorvastatin had a considerably decreased risk of serious adverse cardiovascular events compared to those who received basic treatment (Castellano et al., 2022).

1.4.1.4 Treatment of Hypertension

Reducing blood pressure in those with hypertension of stage 1 or higher decreases danger of having a stroke, heart diseases, and cardiac failure (Ettehad et al., 2016). Research has shown that lowering systolic blood pressure by merely 10 mm Hg is related with a 41% lower chance of a stroke and a 22% lower danger of CHD (Leong et al., 2017). This benefit is shown even when additional dangers are present. Calcium channel blockers, β-blockers, ARBs, diuretics as well as ACE-Is are all potent antihypertensive medicines. It has been demonstrated that each one of them lowers mortality and cardiovascular disease. For the treatment of chronic vascular illnesses, certain of these medications—such as beta-blockers, diuretics as well as ACE-Is—are also given significant importance. The optimal BP goal remains debatable. Variations in baseline CVD risk and in the procedures employed to measure blood pressure and adjust the dosage of antihypertensive drugs were observed among the study populations (Yusuf et al., 2016). Most hypertension patients require more than two drugs to support efficient blood pressure control. Since doctors rarely prescribe a second medication and patients often want to forgo follow-up appointments, a single-drug regimen might lead to clinical inertia. There is growing evidence that starting treatment for high blood pressure with two medications is the most effective and efficient approach (Chow et al., 2017). Hypertensive patients have risk of experiencing a cardiovascular disease event can be reduced by 40% to 50% when statins are used in addition to decreasing BP (Leong et al., 2017).

1.4.2 Surgical Strategies

1.4.2.1 Arterial Revascularization

When the left main, triple, or double coronary arteries, including the proximal left anterior descending artery, are affected by coronary artery diseases, revascularization surgery is advantageous. Contrary to popular belief, PCI has not been demonstrated to be any more

effective than standard therapy at reducing mortality or morbidity in patients with chronic stable CAD (Sedlis et al., 2015). There are concerns about the financial viability of PCI and CABG surgery, according to the available analyses. Conversely, people who have recently displayed symptoms of cerebrovascular diseases and 70% to 99% carotid stenosis have an absolute reduction of 16% in their 5-year risk of ipsilateral ischemic stroke after undergoing carotid endarterectomy. On the other hand, carotid endarterectomy's function in asymptomatic carotid diseases is less certain. In individuals at high risk for carotid endarterectomy, an acceptable alternative to carotid endarterectomy is carotid angioplasty/stenting to treat symptomatic carotid disorders (Abbott et al., 2015; Leong et al., 2017).

1.4.2.2 Symptomatic Bradyarrhythmia

Electrocardiograms are used to determine the root of bradyarrhythmia. Diagnosing bradyarrhythmias, especially in rural areas of low-income countries, may be made easier with the advent of novel, lightweight, hand-held, single-lead electrocardiography. The median survival time for those with symptomatic full atrioventricular block without permanent pacing is 2.5 years. Mortality and morbidity from high-grade atrioventricular block are greatly diminished when permanent pacemakers are implanted. Pacemakers cost US$773 per life-year, making them among the most cost-benefit therapies.

1.4.3 Medication

1.4.3.1 Medication for Atrial Fibrillation

One of the most dangerous outcomes of atrial fibrillation is thrombus embolism. Antiplatelet drugs lessen the likelihood of a thrombosis occurring in people with atrial fibrillation. Stroke risk is reduced by 22% when using aspirin and 64% when taking warfarin for nonvalvular atrial fibrillation. Even while clopidogrel raises the risk of bleeding by 57%, an extra 28% protection

against stroke is achieved by this. When other risk factors are present, stroke danger can be reduced with warfarin more significantly compared with dual antiplatelet medication. Reduced symptoms and progression of tachycardia-induced cardiomyopathy can be achieved with proper ventricular rate management in atrial fibrillation. Since drugs that slow the heart rate (β-blockers, diltiazem, and verapamil) are just as successful as other methods of treating atrial fibrillation (AF), they should be used first (Leong et al., 2017).

1.4.3.2 Medication for Heart Failure

There are a number of effective generic therapeutic techniques for treating HF that are not specific to any one cause of the condition. When treating peripheral edema associated with HF, loop diuretics like furosemide are necessary. ACE-I/ARBs and β-blockers, each of which causes dysfunctional neuroendocrinal reactions to HF, decrease the risk of dying in individuals with HFrEF (HF with reduced ejection fraction) (Xie et al., 2016). Priority should be given to the consumption of ACE-Is, beta-blockers, spironolactone, and furosemide in all contexts. Patients who have heart failure and a modest fraction of ejection, digoxin reduces hospitalization and symptoms while having no effect on mortality (Leong et al., 2017). Starting current guideline-directed pharmacological therapy (Vaduganathan et al., 2020).

1.4.3.3 Medication for Atherosclerosis

Vegetable and fruit-rich diets are linked to a lower incidence of CVD. When compared to controls, participants randomized at random to a Mediterranean diet that included almonds in the PREDIMED small randomized cohort study had significantly slower progression of carotid intima-media thickness and carotid plaque after a median of 2.4 years (Virani et al., 2020). The carotid intima-media thickness of an older female was found to be inversely correlated with the number of servings of vegetables per day, especially cruciferous vegetables (Blekkenhorst et al., 2018). When compared to eating only less than two servings of vegetables per day, eating

greater than three or equal vegetable consumption daily had a five percent lower chance of developing carotid atherosclerosis (Virani et al., 2020). Additionally, CAC testing indicated suitable people who could improve most from aspirin medication.

1.5 SIRT6

Currently, seven Sirtuin family members have been recognized from SIRT1 to SIRT7 (Fuchs & Whelton, 2020). These have a NAD+ binding site and a highly catalytically preserved domain, nonetheless, there are regions at the N and C ends. These proteins have a wide range of physiological functions and localize to different parts of cells. Comparatively, SIRT1 is exclusively nuclear, while SIRT2 is predominantly cytoplasmic. In mitochondria, proteins belonging to the SIRT family (SIRT3, 4, and 5) are founded, while in nucleus only SIRT6 and 7 are detected (Chang et al., 2020; G. Liu et al., 2021). Both isomers of SIRT6 are encoded by exons 8 and 7, respectively, on human chromosome 19. Research on SIRT6's role in CVDs and the development of SIRT6 therapeutic targets has been a hot topic in recent years (Huang et al., 2018; Saiyang et al., 2021). Recently published studies show that SIRT6, a deacetylase that is only found in very small amounts in chromatin, protects against CVDs in a fashion analogous to that of SIRT1 (D'Onofrio et al., 2018). H3K9ac and H3K56ac acetylation are two substrates for SIRT6's deacetylase activity. Additionally, in the cytoplasm and nucleus, non-histone proteins are deacetylated by SIRT6. In addition to its ADP-ribosyl transferase activity, it may undergo hydrolysis of fatty acyl lysines with a long chain length like presence of myristoyl in the ER. Therefore, The epigenetic protein SIRT6 has several potential applications as a result (Chang et al., 2020; Ren et al., 2022). SIRT6 controls metabolism as well to help in cardiac remodeling. Activation of FOXO3 by SIRT6 protects against ischemia-induced damage, and SIRT6's inhibition of IGFAKT signaling delays cardiac senescence and enlargement (X. X. Wang et al., 2016). Furthermore, doxorubicin-induced cardiomyocyte death is prevented by SIRT6 cooperates with GATA-binding polypeptide 4 and epigenetic activation of transcription

by acting independently of deacetylases (Ren et al., 2022). About 250 amino acids make up the highly conserved core catalytic domain of SIRT6, which is surrounded by various N- and C-terminal (respectively NTE and CTE) length extensions. Nucleosome binding, essential for chromatin association in cells, requires SIRT6's NTE domain in addition to the enzyme's inherent catalytic properties (G. Liu et al., 2021; Sacconnay et al., 2016). According to evidence, several different types of mammalian tissues express SIRT6, such as, kidney, brain or heart, and is mostly found both in the nucleus and cytoplasm, along with its known targets (Huang et al., 2018; Rezazadeh et al., 2019; R. Zhang et al., 2018). The aging and inflammatory signaling pathways NF-kB, HIF-1α and c-JUN have their activity stifled by SIRT6. In endothelial cells, where SIRT6 is predominantly expressed, it prevents DNA damage to telomeres and the genome, postponing the onset of aging (Y. Li et al., 2017). A few senescence-related physiological functions, such as oxidative stress, lipid and sugar balance, systemic inflammation, cell death, genomic stability as well as telomere preservation, are regulated by SIRT6, which is highly expressed in all mammalian tissues (Abdellatif et al., 2018; X. Li et al., 2021; Tasselli et al., 2017). Having SIRT6 overexpressed offers protection from metabolic problems associated with dietary obesity. Calorie restriction which is a diet strategy that guards against numerous aging-related alterations, induces SIRT6 expression (Tasselli et al., 2017).

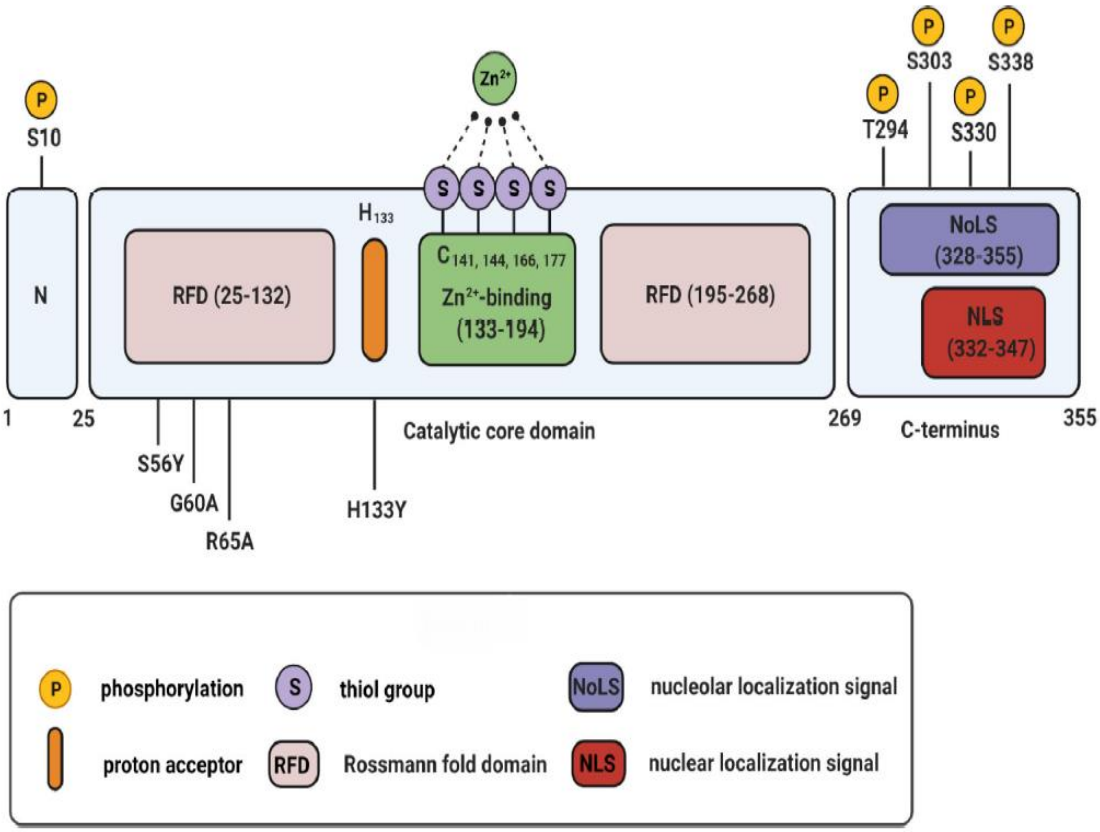

Figure 1: Structure of SIRT6 (Korotkov et al., 2021).

1.6 Purpose of the Study

Telomere maintenance, DNA repair, breakdown and storage of fat, and glucose homeostasis are just some of the many processes that SIRT6 controls. In addition, SIRT6 controls ventricular hypertrophy, inflammation, and oxidative stress, all of which have a role in the etiology of a number of cardiovascular illnesses. SIRT6 has recently been found to offer protection from CVDs, according to mounting data. Intense study of SIRT6's roles in atherosclerosis, heart failure, cancer, and vascular remodeling identified novel therapeutic targets inside complex mechanisms. Although SIRT6 has been shown to have a preventive effect on certain cardiovascular diseases, studies examining its agonists and inhibitors are still in their infancy. The information gleaned from this research can be used to make SIRT6 drugs, which may give a novel approach to treating CVDs, more effective in their activation or development.

1.7 The study's Goals and Objectives

The primary goal of this research is to shed light into the molecular and cellular pathways mediated by SIRT6 in cardiovascular disorders. This study looks into the function of SIRT6 in heart failure, atherosclerosis, cardiac fibrosis, and hypertension as a promising therapeutic approach for CVDs.

Chapter 2: Methodology

This study reviews the emerging role of SIRT6 in cardiovascular diseases along with pathogenesis, prevention and treatment options for cardiovascular diseases as well as the advance pharmacological modulator of SIRT6. All the information and data used for this comprehensive review were obtained from reliable scientific articles indexed in PubMed, ELSEVIER, WILEY, Springer and PubMed Central. The articles published in the journals that served as the source of information for this review study are, The Lancet, Molecular Cell, Frontiers, Nature, BioMed, Pharmacology, Medicinal Chemistry, Cell Biology, Cardiology, American Heart Association, New England Journal, European Heart Journal, etc. An outline was first created for the purpose of collecting the material in a methodical way, after which information was gathered by carefully reading numerous research articles. A huge number of research papers were reviewed, and then 136 publications were selected for the study since they had the necessary information.

Chapter 3: Cardiovascular Diseases and SIRT6

3.1 Important Function of SIRT6 in Cardiovascular Disorders

SIRT6 is expressed in a wide variety of mammalian organs, including the brain, kidney, and heart, and it is mostly located in the nucleus and cytoplasm. SIRT6 is a key hub controlled by several pathways that impact lifespan and CVDs. Patients with chronic heart failure have drastically reduced SIRT6 expression in the heart. The activation of adhesion molecules and inflammatory factors are both negatively regulated by SIRT6, which also reduces LDL-c levels. SIRT6 inhibits the production of adhesion factors and inflammatory factors by deacetylating histones on H3K9 and H3K56, respectively, and so modulates downstream gene expression, thereby exerting anti-CVDs actions.

Table 1: Role of SIRT6 in Cardiovascular Diseases.

Cardiovascular Diseases	Mechanism of action of SIRT6	References
Heart Failure	Reduces IGF expression and FOXO1 de-acetylation.	(Saiyang et al., 2021)
Atherosclerosis	Reduces the levels of aging-related angiocrine factors such plasminogen activator inhibitor-1 and tumor necrosis factor superfamily member 4.	(Ren et al., 2022; Yepuri & Ramasamy, 2019)
Cardiac fibrosis	Through deacetylating H3K9, it reduces NF-kB enzymatic scheme.	(X. Li et al., 2021)
Hypertension	H3K9ac deacetylation inhibits Nkx3.2 (NK3 homeobox 2) activity.	(Ren et al., 2022)

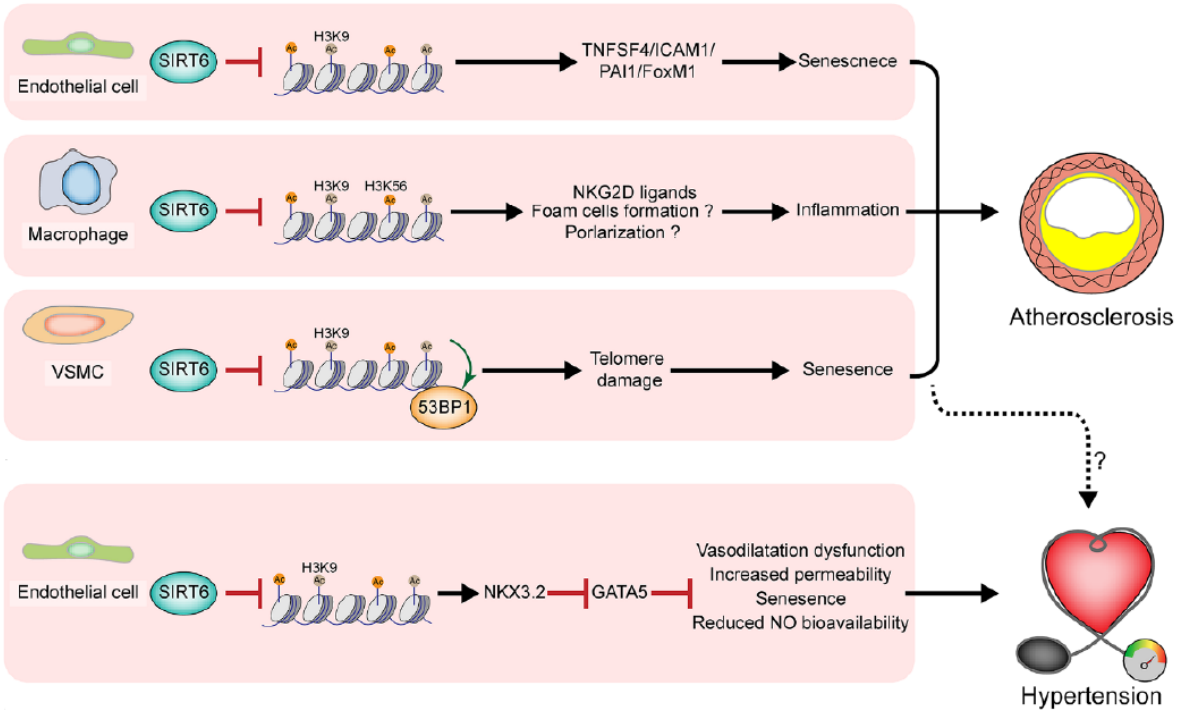

Figure 2: Function of SIRT6 in cardiovascular diseases (Ren et al., 2022).

3.1.1 Myocardial Enlargement and Congestive Heart Failure: The Involvement of SIRT6

Hypertrophy is a compensatory reaction to both biological and pathological stressors; unchecked by Signaling at the cellular level pathways, it typically results in heart failure (Nakamura & Sadoshima, 2018). Many chronic cardiovascular diseases (CVDs) progress to heart failure as their final stage, marked by increased morbidity, death, and rehospitalization (Metra & Teerlink, 2017). According to reports, when it comes to heart hypertrophy, SIRT6 acts as an anti-regulator. Heart enlargement and heart failure are seen in SIRT6 deficient animals, but not in SIRT6 mutant animals (X. Li et al., 2021). Cardiac fibrosis, enlarged cardiomyocytes, and elevated apoptosis are all signs of malfunction in SIRT6 knockout animals (Saiyang et al., 2021). Researchers have discovered further that SIRT6 upregulation safeguarded against heart failure by lowering cardiac remodeling and dysfunction (Winnik et al., 2015). Moreover, research has linked the evolution of heart failure to severe fibrosis, problems with apoptotic damage, cardiac overstress mediated through β-adrenoceptors as well

as inappropriate IGF-Akt signaling (X. Li et al., 2021; Lu et al., 2016; Tian et al., 2015). SIRT6 had also been found to limit PI3K/Akt signaling in order to decrease EP300 (also known as p300) function by promoting their demise (Shen et al., 2016; Tang et al., 2019). Downregulating p300 protein decreased NF-κB p65 transcriptional activity, shielding cardiomyocytes against Ang II or phenylephrine-induced hypertrophy (G. Liu et al., 2021; Shen et al., 2016). Further, this one was verified that SIRT6 limited NF-kB enzymatic reactions via H3K9 deacetylation in angiotensin II-stimulated cardio fibroblasts, hence blocking cardiovascular fibrosis by attempting to prevent fibroblasts of heart from evolving into myofibroblasts (X. Li et al., 2021; Tian et al., 2015). The enzyme nicotinamide adenine mononucleotide adenylyltransferase 2 (Nmnat2), which is essential in the production of NAD, regulates SIRT6's protective action. Nmnat2 overexpression increases SIRT6 activation and inhibits cardiac enlargement caused by angiotensin II (X. Li et al., 2021; G. Liu et al., 2021). The substrate NAD is degraded by an abundance of PARP-1 activity, which ultimately leads to apoptosis (X. Li et al., 2021; M. Liu et al., 2014). Cardiovascular failure and pathological remodeling caused by β-adrenergic receptor stimulation need STAT3 activation. It has been proposed that SIRT6 prevents PE-induced STAT3 activation, hence protecting cardiomyocytes from hypertrophy (X. X. Wang et al., 2016).

3.1.2 Role of SIRT6 in Atherosclerosis (AS)

Ischemic coronary artery diseases is a leading consequence of atherosclerosis, the cause of most vascular illnesses in the globe (Herrington et al., 2016). Myocardial infarction (MI) and other forms of coronary arterial diseases (CAD) are symptoms of a more complex illness called atherosclerosis (G. Liu et al., 2021). SIRT6 synthesis was elevated in specialized cells that have been linked to atherosclerotic plaque development. These cells include macrophages, smooth muscle cells (SMCs), and endotheliocytes (Huang et al., 2018; W. Zhang et al., 2018). Reduced LDL cholesterol (LDL-c), lowering the production of foam cell of macrophage and avoidance

of endothelial dysfunction are the three primary mechanisms through which SIRT6 has indeed been identified as having anti-atherosclerosis benefits. (G. Liu et al., 2021). Moreover, LDL cholesterol is a key factor in the onset of AS, and PCSK9 controls LDL cholesterol breakdown (Saiyang et al., 2021). Signaling pathways of lipogenic respectively, SREBP1 and SREBP2 were found to be suppressed to inhibits cholesterol levels and also the activation AMPK signaling pathway by SIRT6 (G. Liu et al., 2021). It has been shown that FoxO3 recruits SIRT6 to the SREBP2 gene, there it generates a suppressive chromatin environment through removal of acetyl group from histones H3K9 and H3K56, hence repressing the activation of Srebp2 and its molecular targets (G. Liu et al., 2021). An upregulation of PCSK9 was seen when FOXO3 was involved in the gene's close-by promoter area and reduced LDL-c generation after liver SIRT6 ablation. Further evidence showed that SIRT6 regulates cholesterol metabolism by activating phosphorylated AMPK and blocking the cleavage of SREBP1/SREBP2 and the lipogenic transcription factors SREBPs 1 and 2 (Saiyang et al., 2021). SIRT6's role in AMPK-mediated antioxidant defense systems may help to keep your heart safe from the effects of ischemia and reperfusion (I/R) (X. X. Wang et al., 2016). Overexpression of SIRT6 stimulates autophagy and improves cholesterol excretion by suppressing miR-33 and its host gene Srebp2 (J. He et al., 2017). The durability of atherosclerotic plaques was shown to be enhanced when SIRT6 was used to boost to decrease macrophage influx by promoting macrophage decomposition and blocking their interaction with endothelial cells. (T. Wang et al., 2020). Atherogenesis is characterized initially by endothelial cell (EC) dysfunction (Michael A. & Guillermo, 2016). The expression of various genes involved in atherosclerosis, including TNFSF4, is suppressed by SIRT6 overexpression, which protects against atherosclerosis. SIRT6 deacetylated TNFSF's H3K9 at the atherosclerotic TNFSF4 gene promoter and halted TNFSF4 production in endothelial cells (Xu et al., 2016). These results suggest that SIRT6 has a detrimental function in regulating the development of AS via reducing LDL-c and adhesion

molecule synthesis. Overall, SIRT6's deacetylated activity or upregulation could be a new method to treating AS due to its anti-atherosclerotic benefits. For the treatment of AS, it would be a novel method (Saiyang et al., 2021).

3.2 SIRT6 in Cardiovascular Remodeling

Cardiac remodeling may occur for pathological or physiological reasons. In the end, the beneficial changes that characterize the heart's physiological remodeling lead to decreased wall stress, better vascularization or better efficient pumping. Within the framework of individual molecules, biological cardiac remodeling involves the thyroid hormone T3, growth factor VEGF-B, GH, insulin also IGF1, as well as other well-known signaling pathways. Cardiac myocyte contractility, cell survival, metabolic and electrical remodeling, mitochondrial adaptations, angiogenesis and sarcomere remodeling are all tightly controlled by these signal transduction (Bernardo & McMullen, 2016; Spaich et al., 2015). Pathological remodeling, which ultimately leads to heart failure, is a consequence of fibrosis, inflammation, and cellular dysfunction including oxidative and endoplasmic reticulum stress, alterations in autophagy, and impairment of metabolism and signaling pathways (Wu et al., 2017).

Vascular remodeling also includes anomalies in vessel structure and function. A multicellular autocrine/paracrine network facilitates vascular remodeling. Some of the key participants of pathological vasculogenesis include assembling of fat, cell growth, redox disequilibrium, protein denaturation, infiltration of leukocyte, induce apoptosis, and finally thromboembolism (Wettschureck et al., 2019). Some researchers believe that flexible advancement, where arteries' flexibility increases before becoming maladaptive and decompensated, may be linked to vascular remodeling, which in turn causes circulatory difficulties and target organ failure (Lacolley et al., 2017). Consequently, VSMCs and ECs play critical roles in vascular remodeling, atherosclerotic foam cell formation, angioplasty, arterial catheter, blood vessel injury response, and restenosis progression (Saiyang et al., 2021). Ang II increased vascular

endothelial cell antioxidant release and nuclear factor erythroid 2-related factor 2 (NRF2) upregulation when SIRT6 was overexpressed. Ang II induced apoptosis and reactive oxygen species generation were both prevented by SIRT6, whereas the advantages of SIRT6 were greatly attenuated in the absence of NRF2 (Saiyang et al., 2021; Y. Yang et al., 2019). Other studies found that SIRT6/ROS signaling regulates vascular inflammation by suppressing inflammatory interleukin IL-6, IL-1, and monocyte chemotactic protein-1 (MCP-1). Further, Sirt6 maintains the level of Nrf2 in cardiomyocytes by binding to Nrf2 and preventing Keap1 from interacting with it. Meanwhile, Keap1, a negative regulator of Nrf2, has its expression lowered by Sirt6 (Kanwal et al., 2019; Saiyang et al., 2021). Vascular endothelium malfunction and cardiovascular senescence were observed in response to elevated sugar and H_2O_2 concentrations, NF-kB signaling and SIRT6 regulate both of them. SIRT6 excision led to elevated expression of p21Cip1/Waf1, plasminogen activator inhibitor 1 (PAI-1), and intercellular adhesion molecule 1 (ICAM-1). According to these findings, SIRT6 has a functional role in shielding ECs from DNA and telomere degradation and avoiding early senescence. The endothelial-type oxidation also inhibited the nitrogen synthase (eNOS) activity of HUVECs (Cardus et al., 2013).

In contrast, internal thickening of extracellular matrix characterizes cardiac fibrosis. Associated with cardiac remodeling, systolic and diastolic dysfunction, and arrhythmias, it's the hallmark of the pathophysiology underlying the majority of cardiovascular illnesses (Schelbert et al., 2019). Cardiac fibrosis can manifest as either replacement fibrosis or widespread fibrosis. The latter can be reversed and is evaluated with T1 mapping technique for cardiac magnetic resonance, but the former is irreversible and is detected with late gadolinium enhancement (Bing et al., 2019). Studies show that SIRT6 is highly upregulated in response to cardiac fibrosis caused by angiotensin II, while inhibition of SIRT6 increases cardiac fibroblast expansion and ECM production via upregulation of -SMA expression and stimulation of the

NF-B signaling pathway (Tian et al., 2015). It has been hypothesized that miR-21, a type of microRNA, targets TGF-2, a type of growth factor (Schelbert et al., 2019). According to Fan et al., SIRT6 was found to boost miR-21 synthesis, and this reduced TGF-2 level and IL-1 as well as decreased Col I synthesis along with fibroblast multiplication (Fan et al., 2016). In order to suppress TGF- signaling, SIRT6 was found to deacetylate SMAD3 at H3K9 along with H3K56, respectively. Furthermore, SIRT6 and TGF- promoter selectivity significantly decreased and SMAD3 expression significantly increased with senescence (Maity et al., 2020). By stimulating AMPKACE2 signaling and inhibiting the CTGF-FKN pathway, SIRT6 has also been shown to protect against fibrosis, myocardial injury, and pathological remodeling (Morigi et al., 2018; Z. Z. Zhang et al., 2017). Recent research found that in TAC-induced cardiac fibrosis, wild-type SIRT6 overexpression blocked the TGF-1/SMAD2 signaling pathway and prevented the production of NF-B downstream regulators such IL-1 and 6, and MMP-9, each of which encouraged fibroblast proliferation. These results revealed that SIRT6 averted cardiac fibroblast occur by TGF-1 developed via suppressing Smad2 and NF-B activation (Q. Zhang et al., 2019).

3.3 SIRT6 and Vascular Inflammation

Inflammation is a biophysically complicated response to pathogen infection and tissue injury (X. Li et al., 2021). A considerable proportion of the elderly population had activated inflammatory bodies and raised IL-1b levels, both of which are associated with a greater likelihood of suffering severe aging illnesses (Furman et al., 2017). The danger of cardiovascular diseases, and especially atherosclerotic visceral disorders, is raised (X. Li et al., 2021; Song et al., 2012). Modifying inflammation is a promising technique for postponing age-related health deterioration and warding off CVD (Ferrucci & Fabbri, 2018). Quite a few studies have found that SIRT6 can lessen inflammation in a wide range of tissues (G. Liu et al., 2021; N. Zhang et al., 2016). SIRT6 increased microRNA-21 activity, which in turn

reduced type I collagen production and fibroblast multiplication by blocking TGF-b2 and IL-1α appearance (Fan et al., 2016). Having a deficiency in SIRT6 is enough to boost myofibroblast formation, which in turn causes age-related heart failure and multiple organ stiffness (Maity et al., 2020). SIRT6 gene deletion increased pro-inflammatory cytokines IL-1b, IL-6, and TNF-α and decreased anti-inflammatory IL-10, causing persistent liver fibrosis and inflammation (Kim et al., 2019). Inflammatory cytokine synthesis and release are also aided by SIRT6 resulting in persistent inflammation, the underlying cause of neurotoxicity in Parkinson's diseases (Nicholatos et al., 2018). Colitis causes a drop in intestine SIRT6 levels, which is linked to gut inflammation. By maintaining the activity of R-spondin 1 (Rspo1), a critical epithelial cell growth factor in the intestines development, SIRT6 may serve a protective function (F. Liu et al., 2017). Epigenetic modulation by SIRT6 in renal podocytes diminishes the prevalence of chronic proteinuric nephropathy by inhibiting the release of inflammatory cytokines such as IL-1b, IL-6, and TNF-α (M. Liu et al., 2017). The activity of toll-like receptor (TLR4) can be downregulated, and phosphorylation of nuclear factor (NF)-B component (p65) can be suppressed, both of which reduce the inflammation caused by Propionibacterium acnes (R. Zhang et al., 2018). Based on these findings, stimulating SIRT6 could be a practical strategy for reducing inflammation. Reduced inflammation can be achieved with the use of sitagliptin, a medication that has received relatively little attention. For instance, sitagliptin has been shown to drastically reduce MCP-1, IL-6, and IL-1 secretion in TNF-α stimulated ECs while considerably increasing SIRT6 activity (Y. He et al., 2019; G. Liu et al., 2021).

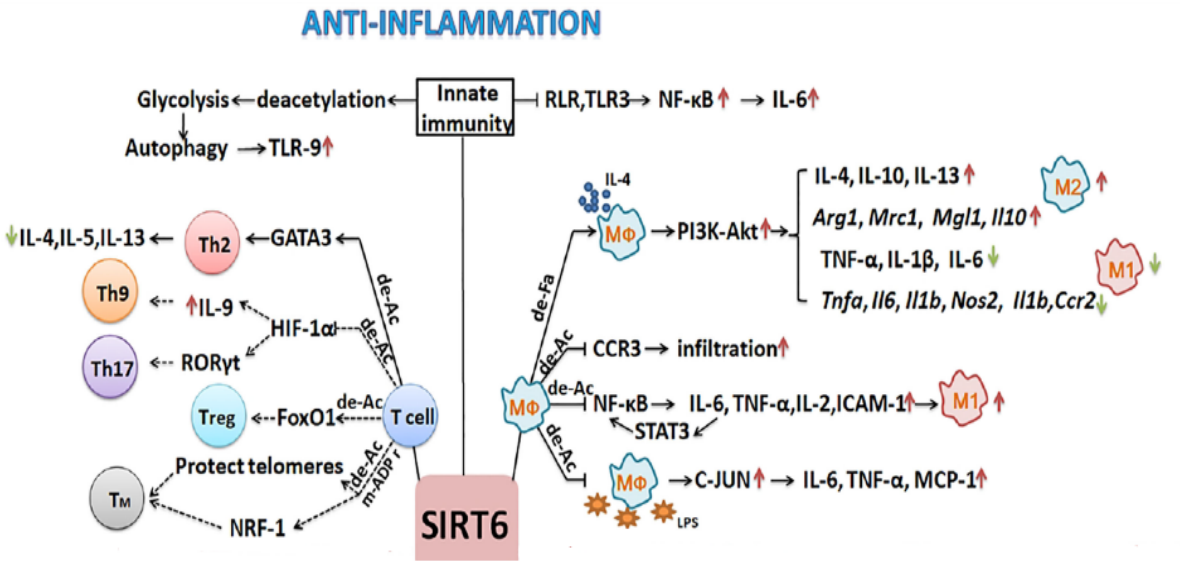

Figure 3: Anti-inflammatory effects of SIRT6 (Y. Li et al., 2022).

Chapter 4: SIRT6 in Cardiovascular Diseases Suppression

4.1 SIRT6 Suppresses NFATc4 Expression in Cardiomyocyte Hypertrophy

In the progression of cardiac hypertrophy, NFATc4 is a key player. The role it plays in several illnesses, like heart enlargement, has been extensively studied (Z. Li et al., 2019; Sharma et al., 2018). Hyper-activity of SIRT6 reduced NFATc4 protein and mRNA levels, elevated degree of phosphorylation, limited its nuclear buildup, the decrease in its gene transcription, and reduced expression of the gene which was supposed to affect brain natriuretic polypeptide (BNP) in phenylephrine (PE)-induced hypertrophic cardiomyocytes (Z. Li et al., 2019). Calcineurin dephosphorylates and alters NFATc4 from the cytoplasm to the nucleus, where it controls genes for BNP and other hypertrophic proteins (Z. Li et al., 2019). Dephosphorylated NFATc4 is nuclear translocated controlling the levels at which hypertrophy-related genes by attaching to the specific DNA (S. Li et al., 2017). More hypertrophic biochemical routes that NFATc4 engages with include GATA-4, MAPK, GSK3, p38, and JNK. The CaN-NFAT signaling pathway is thus hypothesized to represent an important mechanism in the development of cardiac enlargement (Z. Li et al., 2019; Pharmacology et al., 2016). The transcriptional event of nuclear factor kappa B (NF-kB) enzymatic constituent p65 is suppressed by SIRT6, which does so by the suppression of acetylase p300 expression and encouragement of its breakdown. This in turn reduces the levels of STAT3 (Z. Li et al., 2019; Pharmacology et al., 2016; Shen et al., 2016). During PE-induced cardiomyocyte enlargement, CaN dephosphorylation causes NFATc4 to be translocated to the nucleus, where it can activate transcriptional factor. BNP protein synthesis was significantly reduced after infection with Ad-SIRT6 (recombinant adenovirus vectors expressing green fluorescent protein tagged SIRT6), suggesting that the cardiomyocytes may be shielded by SIRT6 from the growth-promoting effects of PE. The p-NFATc4/NFATc4 ratio and NFATc4 phosphorylation were both reduced,

whereas Ad-SIRT6 restored both that had resulted from PE therapy, and both mRNA and protein synthesis of NFATc4 were inhibited (Z. Li et al., 2019). Heart enlargement may result from diminished SIRT6 deacetylase activity (Lu et al., 2016). The anti-hypertrophic effect of SIRT6 has been shown to originate from its ability to dampen the CaN-NFATc4 biochemical route. Txnip, PDK4, and NF-kB target genes are all involved in insulin-like growth factor signaling, and there is mounting evidence that SIRT6 deacetylates H3K9 and H3K56 within their individual gene promoters. So, SIRT6 might restrict NFATc4 transcription by deacetylating putative histones in the promoter area (Khan et al., 2018; Z. Li et al., 2019; K. Qin et al., 2018). In addition to RNAi, microRNAs including miR-133a and miR-29a-3p are involved in downregulating NFATc4 activity (M. Li et al., 2016). SIRT6 has a pivotal role in microRNA regulation (Fan et al., 2016). The phosphorylation and decreased nuclear aggregation of NFATc4 are two additional mechanisms by which its stimulation is suppressed by SIRT6 (Z. Li et al., 2019). CaN, a type-2B phosphatase also known as PP2B, and other potential kinases work together to phosphorylate NFATc4. Mitogen-activated protein kinases (MAPK) are hypothesized to play a significant role as NFAT family co-regulators (Coleman et al., 2015). Three major offshoots of MAPK biochemical routes are the extracellular signal-regulated kinases (ERKs), p38, and c-Jun N-terminal kinases (JNKs) (Kasuya et al., 2018). In contrast to NFATc4, others protein such as, NFATc1, NFATc2, and NFATc3 can all be phosphorylated by JNK. Direct phosphorylation of NFATc1, NFATc2, and NFATc4 by p38 has been shown to occur, although NFATc3 is not one of them. p38 suppression initiates CaN-NFAT signaling, which induces hypertrophic cardiomyopathy (Porter et al., 2000; T. T. C. Yang et al., 2002). Phosphorylation of NFATc4 is regulated by SIRT6, which does so by triggering p38. SIRT6's deacetylase expression allows it to suppress NFATc4 activity, therefore avoiding nuclear aggregation and dephosphorylation (Z. Li et al., 2019).

4.2 By Increasing Macrophage Autophagy and Decreasing Endothelial Cell Contact, SIRT6 Maintains Atherosclerosis Plaques

The chronic inflammatory condition known as atherosclerosis is characterized by the accumulation of lipids in the arterial walls. The most common cause of ACS and other acute cardiovascular events is occluding thrombosis, which occurs when atherosclerotic layers are damaged (De Vries & Quax, 2016; T. Wang et al., 2020). Stroke and chest-pain are the two main outcomes of atherosclerosis. Atherosclerosis risk factors include autophagy and inflammation, both of which SIRT6 may affect. Suppressing Sirt6 lead to an increase in macrophages and lipid vacuoles and a decrease in -smooth actin and collagen, directly increasing the enlargement and instability of atherosclerotic plaque (T. Wang et al., 2020).

Experimental research has shown that plaque angiogenesis has a vital role in the cause of cardiovascular diseases including strokes and cardiac arrests (De Vries & Quax, 2016; T. Wang et al., 2020). There is some speculation that the elevated concentrations of TLR-4 and HIF-1 expression in the plaques lead to angiogenesis, which in turn causes bleeding and weakens the plaques. Atherosclerotic plaque inflammation is triggered by TLRs (Toll-like receptors), such as TLR-3 and TLR-4, being stimulated by free cholesterol in macrophage membranes (J. He et al., 2017). Macrophage autophagy protects against advanced atherosclerosis by lowering the death rate of macrophages and the oxidative stress induced by NADPH oxidase (Liao et al., 2012). Recently, sirt6 suppression has been identified as a significant promoter of vulnerable plaque but also its thickness. Sirt6, which functions in an IGF-AKT-mediated apoptosis signaling cascade, has been demonstrated to be crucial for melanoma progression (L. Wang et al., 2018). When monocytes are stimulated, they increase TLR-4, which then promotes the production of inflammatory cytokines including IL-6 and TNF (Jaipersad et al., 2014). Infiltration of macrophages and the subsequent generation of interleukin-6 both increase plaque susceptibility (T. Wang et al., 2016). Sirt6 may reduce the levels of HIF-1 and TLR-4 via an

autophagy-mediated mechanism, hence decreasing angiogenesis and increasing plaque durability. Macrophage apoptosis is similarly avoided by sirt6 hyper-activation, and autophagic flux is risen dramatically. Platelet selectin, ICAM-1, and VCAM-1 production are all downregulated in response to SIRT6 overexpression, which in turn inhibited macrophage and foam cell invasion (T. Wang et al., 2020).

4.3 SIRT6 Promotes the Activation of Nrf2/ARE Signaling

Hypertension is caused by the release of the vasoactive peptide angiotensin II. Endothelial dysfunction has been linked to Ang II, which has been shown to cause apoptotic cell death and oxidative stress in vascular endothelium. In recent years, Sirtuin6 (SIRT6) has been recognized as a key modulator in protecting against Ang II-induced cardiovascular damage (Y. Yang et al., 2019). By preventing monocyte adherence to the aortic endothelial cells, SIRT6 overexpression reduces threat of atherosclerosis and endothelial malfunction (Z. Liu et al., 2016; Xu et al., 2016). Importantly, endothelial cells that have activated Nrf2 redox signaling are safeguarded against Angiotensin II-induced apoptotic cell death and oxidative damage (M. Li et al., 2017; Priestley et al., 2016). By enhancing the engagement of Nrf2 and RNA polymerase II to ARE key targets and encouraging the transactivation of Nrf2-regulated antioxidant genes, SIRT6 shields HMSCs from oxidative stress (Pan et al., 2016). In addition, SIRT6 encourages Nrf2 signaling stimulation by suppressing Bach1, an Nrf2 Nuclear antagonist (Ka et al., 2017). Inhibition of Angiotensin II-induced oxidative damage through SIRT6 hyper-activity was accompanied by an increase in Nrf2/ARE signaling (Y. Yang et al., 2019). Transactivation of Nrf2-regulated antioxidant genes is facilitated by SIRT6, which improves the ARE binding sites, where Nrf2 and RNA polymerase II are recruited (Pan et al., 2016). In addition, SIRT6 is said to improve Nrf2/ARE signaling activity by deacetylation of Nrf2 (W. Zhang et al., 2017). However, these results provide credence to the theory that SIRT6 has a favorable role in regulating Nrf2.

Chapter 5: SIRT6 as a Target to Treat Cardiovascular Diseases

5.1 Therapeutic Activation of SIRT6 to Treat Cardiovascular Diseases

There is pharmacological promise for SIRT6 modulators because of SIRT6's anti-senescence effects in vascular tissues. Cardiovascular senescence and illness can be suppressed by SIRT6 in all cell types, making SIRT6 a promising therapeutic target for treating age-related cardiovascular disorders (Fiorentino et al., 2021; Korotkov et al., 2021; G. Liu et al., 2021). Three SIRT6 activators, MDL-801, MDL-811, and MDL-800, were discovered in 2018 by Huang et al., which attach to an allosteric location and boost SIRT6 deacetylase function by up to 22-fold (Huang et al., 2018; Ren et al., 2022). The enzymatic effectiveness of SIRT6 deacetylation is greatly improved by MDL-800 and MDL-801. Since the MDL components' enhanced actions on SIRT6 are in line with their strong affinity for the protein, it is likely that the MDL substances work by specific binding to SIRT6 to stimulate its deacetylation. Compounds containing MDLs do not need to attach to an aromatic group or fluorophore on the substrate before activating SIRT6 deacetylation; instead, they do it rapidly. Reports indicate that in addition to its deacetylase function, SIRT6 also substantially accelerates the fatty-acid deacylation and ADPribosyltransferase actions on targets (Feldman et al., 2013; Huang et al., 2018; Jiang et al., 2013). MDL-811, a SIRT6 stimulator, reduces cerebral ischemia reperfusion damage and cerebro-inflammation via the EZH2/FOXC1 pathway. This treatment dramatically boosted neuronal restoration (T. He et al., 2021; Ren et al., 2022). When considered as a whole, the already known SIRT6 stimulator MDL-800/811 have profound importance as prospective medications for treating senescence and age-associated cardiovascular disorders such atherosclerosis, hypertension, and stroke in mammals (Ren et al., 2022).

Table 2: Identified SIRT6 activators.

Compound	Substrate	Mechanism of action	References

Cyanidin	H3K9ac	Increased FOXO3α and dose-dependent SIRT6 induction in Caco-2 cells. Diminished Twist1 and GLUT1 activity.	(Rahnasto-Rilla et al., 2018)
UBCS039	H3K9ac	SIRT6 amplification in fibrosarcoma, epithelial cervix cancer, and NSCLC. Drop in H3K9 and H3K56 acetylation and cell death linked to autophagy.	(Iachettini et al., 2018; You et al., 2017)
MDL-800	H3K9ac	H3K9ac and H3K56Ac levels in HCC and NSCLC drop dose-dependently, inducing cell cycle arrest. Also, in mice xenograft studies, HCC tumor development was inhibited.	(Huang et al., 2018; Shang et al., 2021)
MDL-811	H3K9ac, H3K18ac and H3K56ac	H3K9ac, H3K18ac, and H3K56ac levels in several CRC cell lines were reduced dose-dependently, and there were antiproliferative effects linked to pronounced G0/G1 cell cycle arrest. Moreover, CRC development was inhibited in patient-derived organoids, and patient and cell line-derived xenografts both exhibited antitumor effectiveness.	(Shang et al., 2020)
CL5D	H3K9ac	Implies that the aromatic rings' electron-withdrawing groups are essential for SIRT6 activation. Whole length histones isolated from HEK293T cells exhibit increased SIRT6 deacetylase activity with time.	(Klein & Denu, 2020)

Nicotinamide is a byproduct of sirtuin-mediated deacylation, which has the potential to block the deacylation of SIRT6. Three chemicals, BHJH-TM4, BHJH-TM1, and BH-TM3, in particular, inhibit SIRT6 at micromolar concentrations (J. Liu & Zheng, 2016). SIRT6 selective antagonist initially identified via in silico screening was the salicylates molecule OSS-128167, which has a modest level of micromolar potency (G. Liu et al., 2021). Additionally, this substance has the ability to lessen TNF-α secretion. Recent research has revealed that the hydroxamate analogue trichostatin A, renowned for nanomolar antagonistic activity due to zinc-chelating characteristics, suppresses SIRT6 (Wood et al., 2018). Derivatives of quinazolinediones function as SIRT6 blockers. Such precursor substances have been shown in physiological function tests to decrease TNF-α synthesis in BxPC-3 cells.

Table 3: Identified SIRT6 Inhibitors.

Compound	Substrate	Mechanism of action	References
BHJH-TM3	H3K9ac	Increased fatty acylation of TNFα in HEK293T cells with SIRT6 depletion.	(J. Liu & Zheng, 2016)
OSS_128167	H3K9ac	Boosts glucose absorption in L6 rat myoblasts and BxPC3 cells via an increase in H3K9 acetylation and induction of GLUT1 overexpression. Improves glucose tolerance and insulin, triglyceride, and cholesterol plasma levels were all decreased in a mouse model diabetes with type 2. Decreased viability and proliferation inhibition of DLBCL cells.	(Cea et al., 2016; Parenti et al., 2014; Sociali et al., 2017)

5-(4-methylpiperazin-1-yl)-2-nitroaniline	H3K9ac and H3K18ac	Dose-dependent increase of H3K9 and H3K18 acetylation levels in BxPC-3 cells. Heightened levels of GLUT-1 activity. Lowering of blood sugar levels of type 2 diabetes.	(Sun et al., 2020)
A127-(CONHPr)-B178	H3K9ac	Foci were seen in HUVECs with elevated DNA damage indicators and telomere disruption. TNFα levels decreased.	(Yuen et al., 2019)

5.2 SIRT6 Modulators in Cardiovascular Diseases

Since SIRT6 plays crucial roles in various human illness, controlling SIRT6 activity with small modulators may be therapeutically advantageous for preventing the onset and advancement of such illnesses (Klein & Denu, 2020; Mautone et al., 2020). Sitagliptin, a DPP-4 antagonist that lowers systemic inflammation by elevating SIRT6 activity (Y. He et al., 2019). Due to SIRT6's intricate participation in several chemical cascades, it might be argued that controlling SIRT6 straightforwardly by small molecule binding provides a more focused and effective strategy for treating relevant disorders. The active site and the allosteric region are two distinct regions in the SIRT6 protein where tiny substances can interact (Bolívar & Welch, 2017; G. Liu et al., 2021; You et al., 2017; You & Steegborn, 2018). It has been reported that tiny molecule modulators, including both antagonists and agonist that attach with the active site, perform at SIRT6 via attaching to the pocket located on trailing edge of SIRT6's prolonged acyl channel for binding close towards the N-terminal sequence. When compared to its near counterpart, catechin gallate (CG), quercetin is shown to enhance SIRT6 deacetylation activity by binding to the elongated SIRT6 acyl pathway. In contrast, CG shows antagonist expression by binding to the site as quercetin. According to the co-structure study, CG differs from quercetin by providing a slanted position because of the saturated chroman ring, which directs the chroman

ring and its trihydroxybenzoate derivative towards the both N-terminal and V154/G155 (Fiorentino et al., 2021; You et al., 2019). Recently, it is demonstrated that SIRT6 triggered by CR and prevents NF-kB activity and retards senescence (Kitada et al., 2019; N. Zhang et al., 2016). Although lutein and quercetin limit SIRT6 activity, N-acylethanolamine has been shown to interact with SIRT6 and boost SIRT6 function (G. Liu et al., 2021; Rahnasto-Rilla et al., 2016). It was hypothesized that Icariin, a substance found in Herba Epimedii, might activate SIRT6 and decrease NF-B signaling, suggesting that it would have a protective impact against CVDs (Y. Chen et al., 2015; Y. Li et al., 2018).

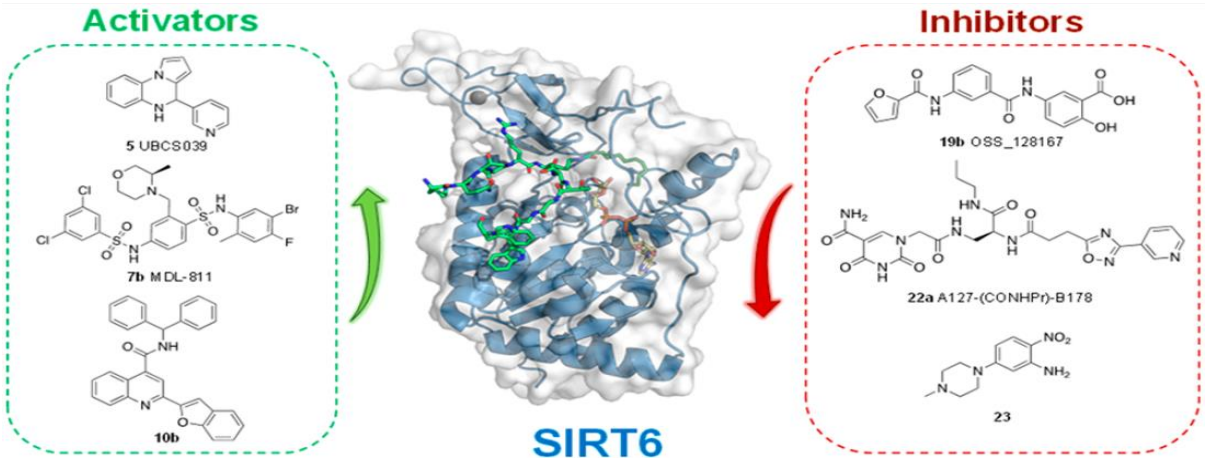

Figure 4: SIRT6 modulators (Activators and Inhibitors)(Fiorentino et al., 2021).

Chapter 6: Conclusion and Future Directions

The anti-aging benefits of SIRT6 extend to the cellular, tissue, organ, and organism levels. SIRT6 modulates cardiac dysfunction, inflammation, that promote to the pathophysiology of cardiac disorders include CHD, cardiac problems, vascular remodeling along with stiffness. By downregulating AKT and upregulating AMPK and its associated casecade including p300, NFATc4, and ACE2, SIRT6 safeguards against heart enlargement, myocardial fibrosis, and mortality of people with heart diseases. Additionally, via inhibiting the NF-B and c-Jun pathway, SIRT6 prevents the development of pathological cardiac enlargement, cardiac remodeling, and sudden cardiac death. Overall, SIRT6 modulation presents a unique approach to the management of CVDs. New research has shown that SIRT6 offers CVD resistance. A complex network of new targets has been discovered as a result of extensive study about roles of SIRT6 in heart failure, atherosclerosis, cardiac remodeling, and cancer treatment (Saiyang et al., 2021). Regardless of their lower effectiveness, small-molecule modulators like the phenylpiperazines and UBCS039 should not be overlooked since they may provide a large chemical landscape for further structural analysis through fragment-based drug design, leading to novel chemical entities with improved therapeutic profiles and biophysical features as SIRT6 modulators (H. Chen et al., 2013, 2015; Hajduk & Greer, 2007). Researchers might considerably increase the effectiveness of the creation or stimulation of SIRT6 chemicals by constructing the amino acid chains with the SIRT6-specialized acetyl group attaching domain H3K9 or H3K56 and then integrated with simulation software of virtual screening of compounds. This would lead to new possibilities in the study and treatment of CVDs (Saiyang et al., 2021).

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