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Sirtuins and the Twelve Hallmarks of Ageing: A Framework for Understanding Ageing Processes and Targeted Intervention

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Abstract:- Ageing is an innate phenomenon that has not been fully elucidated, despite increasing research on ageing in response to the worsening global ageing population. This demographic shift leads to profound ethical and social implications for human health, delineated by the twelve hallmarks of ageing. Sirtuins, a family of NAD^+- dependent enzymes, are key in the ageing process, thus have been more extensively studied in recent years. This review summarises the mechanisms and molecular pathways through which sirtuins modulate each hallmark of ageing and therefore influence ageing and the incidence of age-related illnesses. The mounting evidence of the close interaction between sirtuins and longevity pathways indicates sirtuins' function as therapeutic targets for extending health span and life span. We further summarise interventions which target sirtuins to modulate age-related changes on the molecular, cellular, and systemic levels.

Keywords:- *Sirtuins, Ageing, Senescence, Age-Related Diseases, Hallmarks of Ageing, Longevity Pathways.*

I. INTRODUCTION

Ageing is a broadly defined term used to describe the progressive physiological changes [1] in organisms when molecular and cellular damage accumulate [2]. The changes that organisms experience are exacerbated as aged organisms become more sensitive to internal and external stimuli [3]. Compounding oxidative stress and inflammation [3] declines physiological and biological functions, increasing the incidence of degenerative diseases including dementia, cardiovascular and neurodegenerative diseases [4].

The global ageing population has spurred scientists to find means of extending health span and lifespan. Initially classified as an incurable and natural process, extensive research has revealed that biological age can be reversed [5]. As biological age reflects an individual's physiological health, it is often considered a more accurate measure of health span than chronological age [6]. Recently, composite indices consisting of different biological clocks like telomere length have been developed to calculate an individual's biological age [7].

The identification of nine hallmarks of ageing in 2013 [8], recently expanded in 2023 to include three new hallmarks [9], has facilitated the study of biochemical changes occurring within aged organisms. Each hallmark is responsible for undesirable changes in molecular and physiological functions [10], and they have since been used extensively to target ageing. Dietary and pharmacological interventions are continually being tested to discover effective methods to slow ageing through the regulation of longevity pathways, which modulate other signalling pathways and genes associated with cellular processes vital for the promotion of a healthy lifespan. The four main longevity pathways include mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), insulin-like growth factor-1 (IGF-1) and sirtuin pathways [11].

II. OVERVIEW OF SIRTUINS

Sirtuins are an NAD^+-dependent protein family present in all domains of life [12]. In 1979, the first sirtuin, *Sir2* (silent information regulator 2) was discovered in yeast and identified as a gene that controls mating [13]. *Sir2*'s lifespan extending properties were eventually discovered in the 1990s, turning researchers' focus to mammalian sirtuins with the aim of extending human health span. The seven mammalian sirtuins (SIRTs 1-7) are orthologs of yeast *Sir2* [14] and activate DNA repair, gene silencing, insulin secretion, lipid metabolism, fatty acid oxidation, mitochondrial biogenesis, chromosomal stability, apoptosis, and ageing [12], [15]. SIRT reliance on NAD^+ allows them to act as metabolic sensors of stress to activate oxidative metabolism and stress resistance [16], [17]. Similarly, poly (ADP-ribose) polymerases (PARPs) also compete for NAD^+. The dynamic interplay between PARPs and SIRTs influences a variety of cell functions, with broader implications for brain ageing [18].

Despite being structurally and functionally different, SIRTs 1-7 share some similarities. Each sirtuin consists of a catalytic core domain with 275 amino acids and an N-terminal or C-terminal sequence of variable length [12]. They also have common molecular mechanisms, including deacetylation, deacylation, ADP-ribosylation [14]. Notably, sirtuins modify proteins by catalysing the removal of acetyl groups from lysine residues of target proteins, a process known as lysine deacetylation [19]. This allows sirtuins to regulate essential biological processes [20] and metabolic reactions, including glycolysis, gluconeogenesis,

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mitochondrial fatty acid oxidation [17]. Although not fully elucidated, growing evidence indicates that sirtuin-targeting interventions have the potential to treat human diseases and interventions like resveratrol, metformin and rapamycin are currently in the clinical-trial phase of drug development [21], [22].

The subcellular location of each sirtuin can change conditionally [19] and may vary between different cell types because of different environmental conditions [16]. SIRTs 3, 4 and 5 are mitochondrial sirtuins, playing a key role in metabolic regulation, antioxidative defence [23]. SIRTs 1 and 6 are found in the nucleus (with SIRT7 specifically in the nucleolus) while SIRT2 is localised in the cytosol. The ability of sirtuins to modify many proteins in a range of cellular locations leads to its wide-ranging impacts on the twelve hallmarks of ageing [8].

Table 1: A Summary of the Location, Target Substrates and Functions of SIRTs 1-7

Mammalian SIRT	Location	Target Substrates	Functions
1	Nucleus	SUV39H1 on H3K16 [24], [25], FOXOs [26], Ku70 [27], p53 [27], [28]	Protects chromatin in response to oxidative stress [29]; Promotes DNA damage response [27]; Activates production of pro-inflammatory cytokines [28]; Improves stress-resistance [28]
2	Cytosol	H4K20 [30], PCK1 [31], FOXO1, NRF2 [28], H4K16 [28], α-tubulin [32]	Compacts chromatin to promote genomic stability via epigenetic modulation [30]; Regulates blood glucose homeostasis [31]; Protection against oxidative stress and regulation of autophagy[1]; Regulates cellular differentiation [32]18/06/2024 08:41:00
3	Mitochondrion	HMGCS2 [33], FOXO3 [34]	Regulates oxidative stress response [33]; Promotes genomic stability [33]; Decreases fatty acid oxidation [33], [34], [35]; Reduces inflammation [36]; Prevents insulin resistance in nutrient-rich environments [34]; Maintains lipid homeostasis [34]
4	Mitochondrion	MCD [37], GDH [28], AKT/mTOR [28]	SIRT4 knockout induces apoptosis, fatty acid oxidation and improves insulin resistance [34], thus regulating lipid metabolism and reducing risk of obesity [37]; Protects against oxidative stress induced by respiration [28]; Protects against genomic instability via cell cycle arrest [28]; Represses release of IL-1β, TNF-α and IL-6, which are pro-inflammatory cytokines [28]
5	Mitochondrion	CPS1 [38], E2F1 [14], SOD1 [39]	Regulates blood ammonia concentrations [38]; Increases cell proliferation [14]; Controls mitochondrial metabolic pathways like the Krebs cycle [28]; Decreases ROS [39]
6	Nucleus	H3K9 [40], H3K56 [41], PARP1 [42]	Regulates telomeric chromatin and stabilises association with WRN [40]; Promotes DNA double-strand break repair [43], [44]; Increases efficiency of reprogramming old somatic cells into induced pluripotent stem cells [45]; Improves self-renewal capacity of HSCs [46]; Regulates embryonic stem cell differentiation [47]
7	Nucleolus	DNA methyltransferase 1 [48], H3K18 [49]	Contributes to formation of heterochromatin [48]; Promotes genomic stability via increased stress tolerance [48]; SIRT7 depletion decreases tumorigenesis [49]

Abbreviations: SUV39H1: Suppressor of variegation 3-9 homolog 1; H3K16: Histone H3 Lysine 16; H4K20: Histone H4 Lysine 20; PCK1: Phosphoenolpyruvate carboxykinase 1; FOXO1: Forkhead Box Protein O1; NRF2: Nuclear factor erythroid 2-related factor 2; H3K9: Histone H3 Lysine 9; H3K56: Histone H3 Lysine 56; WRN: Werner syndrome gene product; HMGCS2: Hydroxymethylglutaryl CoA synthase 2; FOXO3: Forkhead Box Protein O3; MCD: malonyl CoA decarboxylase; GDH: glutamate dehydrogenase; CPS1: carbamoyl phosphate synthetase 1; SOD1: Superoxide dismutase 1; H3K9: Histone H3 Lysine 9; H3K18: Histone H3 Lysine 18

III. PATHOPHYSIOLOGY OF AGEING & AGE-RELATED DISEASES

NAD^+ can be synthesised from nicotinamide (NAM) via the salvage pathway, nicotinic acid via the Preiss-Handler pathway or *de novo* from tryptophan [17]. Under stress conditions, these mechanisms cannot maintain the NAD^+ concentration [50]. In humans, NAD^+ levels in skin cells decline by approximately 50% over the course of adult ageing [50]. NAD^+ deficiency accompanying ageing reduces SIRT activity [51]. As sirtuins protect against age-related pathologies and the functional decline of tissues and organs [52], declining NAD^+ levels lead to a range of diseases [53] like cardiovascular and metabolic diseases [34].

Sirtuins are closely related to immunometabolism, the interaction between immunity and metabolism [51] which is vital for immune system responses including secreting cytokines and chemokines, along with immune system cell differentiation and proliferation [16]. The immune system

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removes infectious organisms and agents maintain tissue homeostasis. When the immune system becomes defective, immune-mediated diseases arise [16]. As metabolic regulators, sirtuins regulate and target dysfunctional immunometabolism crosstalk during ageing to slow the onset of age-related illnesses.

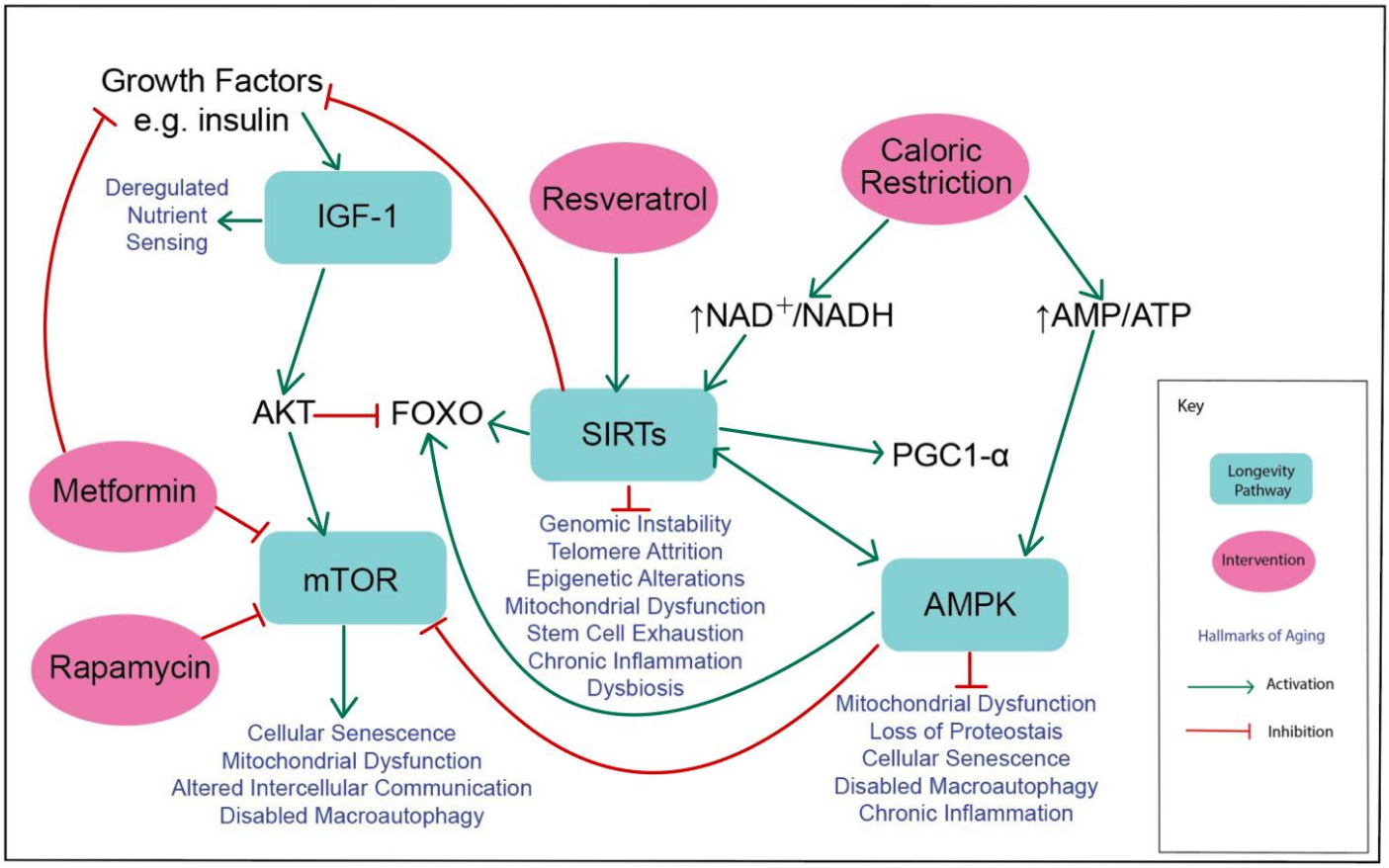

Fig 1: Interplay between SIRTs and other longevity pathway influences various hallmarks of ageing, regulating health span. The activation of protein kinase B (AKT) by Insulin-like Growth Factor 1 (IGF-1) allows growth factors like insulin to be detected by the mammalian target of rapamycin (mTOR) pathway. Suppression of mTOR by AMP-activated protein kinase (AMPK) extends lifespan by modulating different hallmarks. AMP-activated protein kinase (AMPK) is activated when AMP/ATP ratio increases while SIRT activity increases as NAD+/NADH ratios increase (both of which may result from caloric restriction, a natural intervention known to extend lifespan). AMPK and SIRTs engage in a positive feedback loop with FOXO (Forkhead Box Proteins) and peroxisome proliferator-activated receptor gamma coactivator-1α (PGC1-α), phosphorylating and deacetylating them respectively to enhance beneficial gene expression and extend health span. Besides caloric restriction, resveratrol, rapamycin, and metformin directly act on longevity pathways to extend lifespan by inhibiting the hallmarks of ageing.

IV. SIRTUINS AND THE HALLMARKS OF AGEING

A. Epigenetic Alterations

Epigenetics refers to the alterations in one's phenotype resulting from variations in gene expression and involves the preservation of the underlying DNA sequence. Epigenetic alterations encompass shifts in patterns of DNA methylation, noncoding RNA, chromatin remodelling and post-translational modifications of histones [8], [54], occurring over most of the genome [55].

As individuals age, there is an overall deterioration of epigenetic marks [54]. The transformation of the epigenetic landscape is known as "epigenetic drift." This state is characterised by a departure from the normal epigenetic state cells [55], hindering cell function [54]. Epigenetic landmarks are crucial in gene regulation, and the plasticity of gene expression in response to intra and extracellular conditions but are disrupted by changes in the environment [54].

Epigenetic drift highlights the insufficient maintenance and repair of epigenetic drift-induced alterations in epigenetic marks, contributing to impaired cellular and molecular functions in cells [54]. DNA methylation undergoes changes with chronological age [56]. Age-associated hypomethylation and hypermethylation have been reported to promote tumour progression [57] as they often occur upstream of crucial genes for development [55]. Increasing evidence suggests that epigenetic changes are not only associated with ageing, but also caused by it, indicating a close interplay between the epigenome and other hallmarks of ageing [58].

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SIRTs play a crucial role in mediating these epigenetic alterations. As histone deacetylases, SIRTs modify histones to regulate key metabolic pathways [59] intricately linked to the epigenome [58]. Notably, SIRTs 1, 2, 6 and 7 have been reported to modify histones, transcription factors, and epigenetic enzymes [60]. SIRT1, for instance, deacetylates lysine residues of histones, exerting control over chromatin organisation and structure [60]. It is recruited by chromatin-associated factors like B-cell leukaemia 11 (BCL11) to deacetylate histones 1, 3 and 4 [61]. SIRT6 overexpression has also been shown to prolong life span [58].

Through its histone deacetylase activity, SIRTs 1 and 2 target suppressor of variegation 3-9 homologue 1 (SUV39H1) at lysine 16 on histone H4 (H4K16) [24]. SUV39H1 interferes with chromatin organisation in humans, establishing constitutive heterochromatin [25]. Heterochromatin formation promotes cellular response to stress [60] by facilitating chromatin integrity in migrating cells [62]. A key heterochromatin region regulated by SUV39H1 is at telomere regions, stabilising these regions to slow telomere attrition [25] and regulate telomere length, playing an essential role in preventing genomic instability.

B. Genomic Instability

The stability of the genome is crucial for the maintenance of cellular function, but faces constant threats from exogenous agents like carcinogens, X-rays, UV light and internal factors like DNA replication errors and hydrolytic DNA damage [63]. Additionally, reactive species like reactive oxygen species (ROS), reactive nitrogen species and lipid peroxidation, which are produced during metabolic reactions, can also damage DNA [64]. The cumulative effect of genetic mutations and DNA damage over time challenges the integrity and stability of DNA [8], resulting in cellular senescence [65]. Without efficient cell replacement systems, these factors drive mutagenesis [66], leading to cancer and compromising the lifespan of organisms.

In response to single-base or two-base alterations, chain breaks and cross-linkages [64], [67], cells activate various DNA repair pathways, including base excision repair, mismatch repair, nucleotide excision repair, homologous recombination and nonhomologous end joining [68]. Unfortunately, these DNA repair pathways are often disrupted and deregulated by both extrinsic and intrinsic factors [69]. Damaged DNA cannot be replaced [69], so dysfunctional DNA repair mechanisms contribute to accumulating mutations and chromosomal abnormalities, culminating in genomic instability.

SIRTs 1, 2, 4, 6 and 7 all play essential roles in maintaining genomic stability. Under oxidative stress, SIRT1 localises to sites which repair DNA [60]. SIRT2 deacetylates FOXO3a, increasing binding of FOXO to DNA, increasing $p27^{Kip1}$ expression. $p27^{Kip1}$ is a cyclin-dependent kinase inhibitor and tumour suppressor gene [70] which activates a DNA damage response [71] to arrest the cell cycle and protect the cell against oxidative stress. Genome protection is also regulated via cell cycle arrest by mitochondrial SIRT4, which inhibits the conversion of glutamate to alpha-ketoglutarate (αKG) by glutamate dehydrogenase (GDH). This in turn prevents the anaplerotic replenishment of intermediates in the Krebs cycle, indirectly resulting in DNA repair [28], [72].

SIRTs 1, 6 and 7 regulate DNA repair by activating PARP1, another NAD^+-dependent protein crucial for DNA single-strand and double-strand break repair [42], [43], [73]. PARPs and SIRTs activate genomic damage-signalling kinases like DNA-PK, ATM, FOXOs, p53 and CIRBP to accelerate DNA repair [17]. Furthermore, SIRTs 1, 6 and 7 deacetylate H3K18Ac, recruiting the damage response factor 53BP1 to DNA double-strand breaks [43], protecting against mitotic errors. This supports chromosomal structures like telomeres and reduces both telomere attrition and genomic instability.

In the human genome, there are approximately 350 copies of highly transcribed ribosomal DNA (rDNA) genes. However, rDNA is very susceptible to recombination and external stress, contributing significantly to genomic instability with age [74]. SIRT7, concentrated in the nucleoli where rDNA genes are located [74], recruits DNA methyltransferase 1 and SIRT1 to moderate the heterochromatin rRNA formation, improving genomic stability [75]. Moreover, SIRT7 deacetylates H3K36ac in rDNA sequences, silencing and stabilising rDNA heterochromatin [76].

C. Telomere Attrition

Telomeres are noncoding regions at the ends of DNA which are made of TTAGGG repetitive base sequence [77]. Like the ends of a shoelace, they prevent ‘fraying’ of chromosomes, protecting them against damage like degradation and interchromosomal fusion [78], thus contributing to genomic stability.

Telomerase, an RNA-directed DNA polymerase, is made of telomerase reverse transcriptase (TERT) and telomerase RNA (TERC). TERT adds DNA tandem repeats to the ends of chromosomes [77] while the TERC gene provides instructions for telomere replication by telomerase [77]. While stem cells have telomerase activity, telomerase is rarely expressed in somatic cells [78], rendering telomeres susceptible to age-related degradation. In humans, cell division leads to a similar rate of base pair shortening across all tissues [79]. Once telomeres reach a critical length, cells exhibit senescence-associated secretory phenotype (SASP), inducing cell cycle arrest [80] as a DNA damage response [74]. Telomere attrition is intricately linked with premature senescence, indicating the loss of telomeric repeat binding factor 2 protein [81] and contributing to cellular senescence. Without a mechanism to lengthen telomeres in somatic cells leads to telomere attrition, increasing the risk of tissue fibrosis and premature ageing [8].

Sirtuins localise to telomeres to regulate its length [82], but the exact mechanism with which sirtuins achieve this remains unclear. Notably, SIRT1 is a positive regulator of telomere length [83]. SIRT1 overexpression in mice was reported to increase telomere length, indicating that SIRT1 plays a key role in telomere maintenance [83]. The age-

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accompanied attrition of telomeres induces the repression of SIRTs in liver tissue, leading to the hyper-acetylation of FOXO1, PGC-1α, p53 and histones [82]. The compromised deacetylase activity of sirtuins then affects other sirtuin targets and exacerbates age-related decline [82]. SIRT6 also contributes to telomere homeostasis. By deacetylating histones H3K0, H3K56 and H3K18, SIRT6 inhibits the transcription of senescence-related transcription factors, thereby preserving telomeres [84].

D. Loss of Proteostasis

Protein homeostasis (proteostasis), is the regulation of intracellular protein synthesis, folding, and degradation by the proteostasis network (PN). PN is indispensable for the maintenance of a healthy proteome. However, due to the extensive range of conformations of a polypeptide chain, the folding process of polypeptide chains is susceptible to errors [85]. The proteasome regulates proteostasis by degrading proteins via the ubiquitin-proteasome system (UPS) or by the lysosome through autophagy, but both mechanisms have been proven to decline with age [8].

Molecular chaperones are key players in PN as they refold proteins which are misfolded or damaged during times of cellular stress [86], whilst ensuring that cells have their necessary proteins [85]. When PN is disrupted, destabilised proteins escape the folding and degradation mechanisms of molecular chaperones [86], leading to a build-up of misfolded proteins, which is associated with Parkinson's disease and Alzheimer's disease. Heat-shock proteins are the main classes of molecular chaperones which respond to cellular stress, for example high temperature conditions. The SIRT1-modulated deacetylation of heat shock factor-1 (HSF-1) regulates heat shock proteins [87], extending lifespan.

Autophagy is a cytoprotective mechanism [88] that degrades soluble misfolded or oligomeric proteins and removes bulk protein aggregates [89]. When autophagy is deficient, protein aggregates accumulate and lead to progressive neurodegeneration [90]. Expression of ATG5, ATG7 and BECN1 (autophagy-related) genes decreases with age [90]. Consequently, PN becomes dysfunctional during ageing. Protein aggregates accumulate and distract chaperones from folding the proteins required for the healthy functioning of a cell [91].

For instance, β-amyloid peptides deposit outside neurons and abnormal forms of tau proteins accumulates [92] during the onset of Alzheimer's disease. Thus, the loss of proteostasis leads to an increased risk of chronic neurodegenerative disorders, along with malignant phenotypes in cancer. SIRT1 deacetylates FOXO3a, resulting in increased expression of the pro-autophagy protein Bnip3 [93]. SIRT2 dissociation from FOXO stimulates the autophagy gene ATG7 and induces autophagy [94], protecting against such disorders.

E. Disabled Macroautophagy

Macroautophagy is the main type of autophagic process, involving sequestering parts of the cytoplasm in vesicles to be delivered for degradation in lysosomes [9]. This is vital in both proteostasis and the clearing of other dysfunctional macromolecules or organelles [9], which has been reported to maintain cellular and tissue homeostasis [89]. Furthermore, macroautophagy aids in maintaining levels of energy in cells during periods of starvation [95] by improving mitochondrial function [96]. SIRT3 expression promotes macroautophagy by activating AMPK. AMPK regulates cellular energy homeostasis and stimulates proteins required for macroautophagy. The SIRT3-activated formation of lysosome-associated membrane protein 2A-heat shock cognate 71kDA protein-perilipin-2 complex suggests an interconnected relationship between SIRTs, proteostasis and macroautophagy [97]. Besides clearing proteins, macroautophagy also involves the degradation of lipid droplets. SIRT3-stimulated macroautophagy in mice with high-fat diets was shown to inhibit lipotoxicity [97].

F. Deregulated Nutrient-Sensing

Nutrient sensing is essential for maintaining proper cellular function [98] as these signals sense the availability of nutrients and in response, activate or deactivate cell signalling pathways. Several crucial signalling pathways are involved in nutrient sensing and metabolic regulation to facilitate anabolism and nutrient storage [99]. One of the central players in this process is Insulin-like Growth Factor 1 (IGF-1), which senses glucose levels and activates the protein kinase B (Akt/PKB) pathway, known to promote muscle hypertrophy [100]. Akt/PKB then initiates a phosphorylation cascade targeting the FOXO family of transcription factors [101], regulating metabolism and cellular responses to nutrient deprivation and stress. Lack of IGF-1 induces the translocation of FOXO factors to the nucleus, triggering resistance to oxidative stress and other cellular responses associated with increased lifespan [101].

Activation of the IGF-1/AKT pathway allows the increase in growth factors to be detected by mTOR [102], establishing mTOR as another key player in nutrient sensing. Thus, mTOR is vital for the Akt/PKB signalling cascade [103]. mTOR is a serine/threonine protein kinase from the phosphoinositide 3-kinase (PI3K) family [104], consisting of mTOR complexes 1 and 2 (mTORC1 and mTORC2 respectively). mTORC1 is activated by growth factors like insulin via the IGF-1/AKT pathway [105], promoting cell proliferation [103]. mTOR regulates cellular processes involved in energy metabolism [106]. However, this suppressed autophagy and enhanced anabolism is tumorigenic [103]. Studies of replicative ageing models, such as Drosophila melanogaster and yeast, have shown that suppressing mTOR can lead to an increase in lifespan, underlining its role in the regulation of ageing [104].

In contrast, 5' AMPK operates opposite to the insulin and IGF-1 signalling pathway and mTOR [8]. AMPK serves as an energy sensor that signals nutrient scarcity and negatively regulates enzymes involved in lipid anabolism [107]. Low ATP levels associated with ageing [108] activate

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AMPK, inhibiting mTORC1 [104] and inducing autophagy [99],[107]. This process is critical for the maintenance of cellular function maintenance and cell survival [109], as well as preventing the damaged mitochondria accumulation and mitochondria-generated ROS. AMPK also directly phosphorylates FOXO transcription factors to increase the gene expression to promote stress resistance [101], promoting longevity [98].

SIRT1 and AMPK engage in a positive feedback loop [8], where SIRT1's upregulation of AMPK leads to the activation of PGC1-α to promote fatty acid mobilisation [36], [60]. These pathways orchestrate mitochondriogenesis, enhanced antioxidant defences and improved fatty acid oxidation [110]. By regulating insulin secretion from pancreatic β cells and targeting AMPK, SIRT1 may overturn the development of diabetes [36].

SIRT2 functions in the cytoplasm, deacetylating FOXO1 and the rate-limiting enzyme phosphoenolpyruvate carboxykinase (PEPCK) in the gluconeogenesis pathway to increase glucose synthesis whilst deterring lipid synthesis when nutrients are low [36], [111]. SIRT4 inhibits the fatty acid oxidation in fat and muscle cells, providing cellular energy during fasting. Malonyl CoA, a metabolite that inhibits fat catabolism, is deacetylated by SIRT4, which activates malonyl-CoA decarboxylase, promoting fat synthesis [23]. Additionally, SIRT4 inhibits pancreatic β cell insulin secretion via the ADP-ribosylation of GDH [23], increasing the glutamate and glutamine metabolism to generate ATP, and repressing leucine-mediated insulin secretion [54], which might maintain insulin sensitivity to protect metabolic health and slow ageing.

G. Mitochondrial Dysfunction

Mitochondria, often termed 'the powerhouse of the cell', play a significant role in oxidative metabolism [112] and metabolic homeostasis. Their key functions rely on a delicate balance between mitochondrial fission and fusion, autophagy, and biogenesis [64]. Any disruption to this equilibrium can cause mitochondrial dysfunction, resulting in reduced energy generation and increased ROS. Mitochondria are the main sites of ROS production, responsible for almost 90% of all cellular ROS [113]. Elevated ROS levels cause oxidative damage to genomes, lipids and proteins [112], contributing to genomic instability [64].

Furthermore, heightened oxidative stress can induce the release of mitochondrial DNA (mtDNA) into the cytoplasm, which bind to cyclic guanosine monophosphate-adenosine monophosphate synthase and activates the stimulator of interferon genes, regulating SASP [114]. SIRTs 1, 3 and 4 have been reported to protect the cell from ROS [115] and subsequently protect aged organisms from neurodegenerative disorders [116]. SIRT3 influences most mitochondrial functions by controlling the expression of different mitochondrial proteins [117]. SIRT3 loss increases ROS, activating hypoxia-inducible factor 1α (HIF1α), which enhances the expression of HIF1 target genes and increases the risk of tumour growth [73].

mtDNA encodes 37 genes crucial to produce functional products for the electron transport chain (ETC) and oxidative phosphorylation [64]. However, mtDNA is more prone to mutations than nuclear DNA since mtDNA lacks protection by histones and a gene repair system [65]. Aged organisms often exhibit fewer mtDNA copies and an accumulation of mtDNA mutations [118], exacerbating mitochondrial dysfunction. The supplementation of NAD^+ in telomerase knockout mice increased SIRT activity, improved mitochondrial biogenesis, and increased the activity of ETC complex I and IV by increasing mtDNA copy numbers [82].

As mitochondria become dysfunctional during ageing, misfolded proteins accumulate, leading to a loss of proteostasis. SIRT7 increases the expression of mitochondrial unfolded protein response (mtUPR) genes to clear misfolded proteins and increase mitochondrial mass, aiding in proteostasis [46] and mitochondrial regulation. SIRT2 has also been linked to the preservation of mitochondrial integrity, particularly in aged hematopoietic stem cells (HSCs) [46].

The efficacy of the ETC also decreases during ageing due to increased electron leakage, reducing ATP production. The reduction in MCLK1, a mitochondrial enzyme responsible for producing the electron carrier ubiquinone, reduces electron transport and causes a decline in the activity of Krebs cycle [112], altering apoptotic signalling and triggering inflammation. The downregulation of PGC-1α, responsible for mitochondrial biogenesis, contributes to these age-related changes.

H. Stem Cell Exhaustion

Adult stem cells are the primary mechanism by which dying cells are replenished in many different tissues [119], ensuring tissue maintenance and the production of somatic cell lineages. Stem cell susceptibility to changes in the microenvironment [119] contributes to the age-related decline in their regenerative potential [8], [119]. Stem cell exhaustion is considered a key driver of ageing [120] as it exacerbates the accumulation of DNA damage and genomic instability [8].

HSCs, a multipotent subset of adult stem cells, are essential to produce blood cell lineages [121]. Other hallmarks of ageing, such as telomere attrition and genomic instability, have been implicated in the DNA mutation accumulation in HSCs and abnormal haematopoiesis [121]. As HSCs differentiate into a range of cell types, any alterations to the genetic material will be inherited by daughter cells, which might significantly amplify the consequences of the genotoxic damage [122].

The decline in the regenerative capacity of hematopoietic stem cells, often exacerbated by persistent inflammation [46], results in reduced immunosenescence and haematopoiesis, where fewer adaptive immune cells are produced [8], [120]. This has been intricately linked to a decline in tissue integrity and overall health [123]. SIRTs safeguard the stemness of hematopoietic stem cells and prevent cellular exhaustion [46] through ROS elimination,

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FOXO activation and p53 inhibition [124]. SIRT6, recruited by the Wnt transcription factor LEF, deacetylates and suppresses H3K56ac, aiding in the maintenance of HSC quiescence and self-renewal capacity [46].

In aged HSCs, the downregulation of SIRTs 1, 2 and 7 leads to reduced deacetylation of targets like H4K16ac [46], [125]. Hence, a potential avenue for rejuvenating stem cells and mitigating the impacts of stem cell exhaustion is the activation of SIRTs through SIRT-activating compounds (STACs).

SIRTs extend their protective role beyond HSCs, influencing the regenerative potential of other stem cells like mesenchymal stem cells (MSCs), which are also vital for tissue repair and regeneration [126]. SIRTs 1 and 3 protect MSCs from age-associated DNA damage [126], [127] by inducing TERT and increasing telomerase activity [126]. By protecting against genomic instability and telomere attrition, SIRTs reduce stem cell exhaustion [126]. Furthermore, SIRT2 also exhibits upregulation during embryonic stem cell (ESC) differentiation [124]**.** When SIRT2 was depleted in mouse embryonic fibroblasts, reduced reprogramming efficiency was observed [128].

I. Chronic Inflammation

The inflammatory response depends on cells like macrophages, lymphocytes and monocytes [36], [129]. SIRTs have also been identified as activators and differentiators of these cells [36]. SIRT1 regulates p53 to suppress inflammation [36]. While inflammation can be beneficial in increasing the chances of survival during injury or infection [36] by eliminating pathogens [130], the age-accompanied inflammation of the signalling environment of chemical messages, known as inflammaging [131], is damaging. This innate state may result from accumulated pro-inflammatory tissue damage, the immune system's inability to clear pathogens and invaded host cells, or the pro- and anti-inflammatory cytokines that spread via extracellular vesicles [131]. This chronic state leads to stem cell and lymphocyte exhaustion, which hinder immunity [46].

Hyperinflammation, a condition where severe inflammation leads to the release of excessive levels of cytokines [132], [133], results from imbalances in pro- and anti-inflammatory cytokines. By exacerbating tissue damage [130], hyperinflammation contributes to age-related changes like bone fragility and muscle weakness [8] or tumorigenesis. Hyperinflammation increases NAD^+ demand by the inflammatory response, inhibiting SIRT1 [130]. As SIRT1 activity decreases, pro-inflammatory cytokines like C-reactive protein 1β, interleukin 6 and tumour necrosis factor alpha increase [131], reducing survival and cognitive ability [134], [135]. As age decreases the effectiveness of immune responses against pathogens and cancer cells [46], SIRT activation can reduce altered intercellular communication and mediate inflammation to improve the immune response.

J. Altered Intercellular Communication

Intercellular Communication refers to how cells transmit messages between each other [136] at the endocrine [137], neuroendocrine, and neuronal levels, and may vary depending on physiological and pathological factors [136]. The communication between cells in multicellular organisms coordinates development, adaptation and function [138]. As chronic inflammation significantly compromises intercellular communication [131], the SIRT-mediated reduction in inflammation can indirectly inhibit altered intercellular communication.

SIRT activation is vital in preventing altered intercellular communication, as they regulate the crosstalk between epigenetic regulation in response to oxidative stress and mitochondrial metabolism [46]. Immunometabolism, the close interaction between metabolic processes and immunity [51], is controlled by various signalling pathways that intersect with SIRT-regulated pathways [16]. Notably, Nuclear Factor-κB (NF-κB) signalling plays a key role in immune response and inflammation [139]. SIRTs 1, 2 and 6 inhibits the acetylation of NF-κB's p65 subunit, suppressing NF-κB activation [14] and stimulating the differentiation of T cells, thereby promoting immune reactivity [46]. However, conditions like Alzheimer's disease inhibit SIRT1, increasing the acetylation of NF-κB and increasing the activation of this pathway, leading to elevated pro-inflammatory signalling [18].

K. Dysbiosis

Dysbiosis, characterised by an imbalanced gut microbiome, is intricately linked with altered intercellular communication and its resultant chronic inflammation. This disruption might stem from dietary changes and age-related alterations in the host environment [9]. The bi-directional communication between the host and gut bacteria is vital for metabolism and nutrient absorption, yet the age-related occurrence of dysbiosis disrupts this communication, increasing pro-inflammatory bacteria while simultaneously decreasing beneficial microbes, worsening insulin resistance and resulting in genomic instability and chronic inflammation [140]. Furthermore, by increasing β-amyloid peptides formation and accumulation in the brain, dysbiosis can also contribute to the loss of proteostasis [140].

SIRTs expressed in the gut are crucial for maintaining and renewing the intestinal epithelium, promoting gut health, reducing inflammation, and modulating antimicrobial protein levels [141]. Notably, SIRT1 has been shown to alter intestinal microbiota, reducing dysbiosis-associated inflammation [142]. Modifying SIRT levels via interventions can potentially correct dysbiosis and slow age-related conditions like neurological disorders, obesity, and cancer [9].

L. Cellular Senescence

Cellular senescence is a permanent phenotype exhibited [74] by cells when they lose their proliferative and differentiation abilities [65]. In young organisms, senescence serves a beneficial purpose by allowing efficient cell replacement systems to clear senescent cells, preventing the

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proliferation of damaged cells to protect against cancer [81]. When senescence was induced prematurely in oncogenic cells *in vivo*, tumour progression was prevented, providing cancer protection [136].

However, in aged organisms, these cell replacement systems become inefficient and senescent cells accumulate, increasing the secretion of cytokines, chemokines and inflammatory mediators [143]. Besides altering intercellular communication, inflammation is also a key driver of age-related diseases and may exacerbate premature ageing [144]. Increased senescence has been associated with increased DNA double strand breaks, ROS and inflammation [81], hindering tissue homeostasis [8].

Several hallmarks of ageing, including epigenetic alterations, genomic instability, telomere attrition and mitochondrial dysfunction, can trigger senescence [145]. Different stress stimuli lead to various phenotypes exhibited by senescent cells. Under high stress from DNA damage, activated oncogenes, ROS, cytokines and nucleotide depletion, cells may undergo stress-induced premature senescence, a form of senescence that occurs independently of the programmed shortening of telomeres over time [81]. SIRT1 has been reported to deacetylate FOXO3 and FOXO4, suppressing stress-induced cellular senescence [146], though its exact mechanism against specific phenotypes is unknown.

Senescent cells share common characteristics, such as prolonged growth arrest, altered metabolism and the presence of a specific SASP [147]. Senescent cells exhibit decreased levels of Lamin B1, impairing the structure of the nuclear lamina [147]. SIRTs mediate cellular senescence by delaying age-associated telomere attrition and genomic instability by stimulating DNA damage repair [146]. The senescence response depends on the p53, which controls genes controlling cell-cycle arrest [148]. When DNA is damaged, p53 activation arrests cell growth so that DNA repair or apoptosis can occur, hence maintaining genome integrity [148]. SIRT1 deacetylates p53 to maintain tissue homeostasis and protect against oncogenesis [149].

Senescence-associated beta-galactosidase is commonly used as a senescent marker as it is secreted during lysosomal stress response. This response involves the accumulation of dysfunctional substrates within lysosomes [150]. Senescent cells secrete inflammatory cytokines and permanently arrest growth to prevent neoplastic transformation [151]. SIRTs suppress cellular senescence by inhibiting telomere attrition, stimulating DNA damage repair, and mediating inflammation [146]. SIRT3 overexpression in macrophages alleviates inflammation [36]. Moreover, inactivation of NF-κB by SIRTs 1, 2 and 6 also inhibits inflammation [14]. By reducing proinflammatory mediators, SIRTs can prevent neuroinflammation [92] and other diseases like cancer, Alzheimer's diseases, chronic obstructive pulmonary disease [136].

V. INTERVENTIONS THAT ALTER SIRTUIN LEVELS TO EXTEND LIFESPAN

Sirtuins are becoming an increasingly attractive therapeutic target due to its interconnected relationship with the twelve hallmarks of ageing. The discovery of sirtuin-activating compounds (STACs), as well as other interventions to enhance SIRT activity, holds promise for the prevention of obesity, Type 2 diabetes, and neurodegenerative diseases [152].

A. Caloric Restriction

Caloric restriction (CR) is a dietary intervention that involves providing an organism with 60-90% of the calories in a balanced diet, whilst preventing malnutrition [153]. Alongside intermittent fasting and exercise, CR is thought to be the one of the only effective natural interventions which can extend lifespan and health span without genetic or pharmacological intervention [143]. Studies have shown that CR can slow the development of metabolic diseases like insulin resistance and type 2 diabetes [154], as well as age-related diseases like cancer and neurodegeneration [153].

CR ameliorates telomere attrition, mitochondrial dysfunction, genomic instability, loss of proteostasis, deregulated nutrient sensing and altered intercellular communication [153] through its interconnected relationship with sirtuin pathways. CR increases the level of all SIRTs [148], indicating its broad influence on SIRT activity.

One mechanism by which CR slows age-related deterioration is the induction of autophagy [3]. Autophagy is activated under conditions of stress like nutrient deficiency or mitochondrial damage [94], [155] and has been reported to maintain cell function and stimulate cell survival [109], reducing age-associated mortality [156]. By decreasing nutrients or growth factors and inducing autophagy, CR increases levels of SIRT1 and AMPK, and decrease mTOR and IGF-1 signalling, reducing oxidative damage [157], [158].

CR also plays a role in the modification of epigenetic marks that contribute to stem cell rejuvenation. This leads to increased regenerative capacity of stem cells, allowing for the replacement of damaged cells [124]. SIRT1 has been identified as a vital component for CR to induce greater numbers of intestinal stem cells (ISCs) [124]. Additionally, CR activates AMPK, increasing the NAD^+/NADH ratio and SIRT activity, thus reducing ROS production and the induction of SASP [14]. CR further reduces oxidative stress by increasing SIRT1-mediated deacetylation of FOXO [159] to upregulate free radical scavenger genes [160].

The induction of NAMPT, a biosynthetic enzyme crucial for the regulation of NAD biosynthesis [161], is another effect of CR in humans. Since the circadian transcription factors mediate the transcription of the NAMPT gene, CR drives the activities of all SIRTs, making it a promising intervention for extending lifespan.

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B. Resveratrol

Resveratrol is a polyphenol found in grapes, peanuts, apples, blueberries, mulberries and red wine [3], [162]. It has gained attention from the scientific community as it is a very promising intervention to improve health and achieve longevity. Though other plant polyphenols like quercetin have been shown to increase SIRT1 activity [163], resveratrol stands out as a polyphenol that is comparatively cheaper, less toxic and more potent [158].

Notably, resveratrol was the first molecule which highlighted the possibility of allosteric activation of SIRTs [158], which can potentially allow SIRT activity to be tightly controlled. When resveratrol was administered to obese septic mice, SIRT1 activation decreased microvascular inflammation by reducing cell adhesion [164]. Additionally, 0.2mM resveratrol showed a significant 2.5-fold increase in SIRT5 deacetylase activity [163].

Studies have indicated that resveratrol promotes lifespan by modulating inflammation, oxidative stress, cell senescence, telomere attrition and mitochondrial dysfunction [144]. Akin to CR, resveratrol acts by upregulating sirtuins, protecting against cancer, diabetes and cardiovascular disease [158]. Resveratrol modulates NF-κB, p53, PARP1 [158], AMPK, mTOR pathways, which overlap with SIRT1 signalling [117], regulating cell survival and inflammation.

Resveratrol's influence on various signalling pathways [117] induces autophagy, modulates the immune system and attenuates inflammation [165]. Post absorption, resveratrol is metabolised into resveratrol-3- and -4'-O-glucuronide/sulphate, which possess anti-inflammatory, antioxidant and cytotoxic effects [117]

C. Metformin

Metformin is a well-established first-line drug [10] which is considered a safe and effective antihyperglycemic agent [10] and has been used to treat type 2 diabetes for over 60 years [166]. Besides improving insulin-resistance [80] and inhibiting hepatic glucose production [167], metformin has also been found to exhibit a range of effects closely related to the hallmarks of ageing, namely cellular senescence [10], deregulated nutrient-sensing [8].

Metformin's antioxidant properties mitigate ultraviolet radiation-induced ROS by upregulating antioxidant enzymes like catalase, superoxide dismutase and glutathione peroxidase [10] and inhibiting mitochondrial respiratory chain Complex I [168], thus preventing genomic instability, telomere attrition and cellular senescence. Additionally, Metformin delays cellular senescence and inhibits telomere attrition by increasing the expression of TERT and enhancing the clearance of senescent cells, reducing the expression of proinflammatory cytokines [10].

Studies have shown metformin's effects on deregulated nutrient sensing: it downregulates IGF-1 and mTOR pathways whilst activating AMPK [80], like the physiological effects observed with resveratrol [158]. The activation of AMPK by metformin via the increase in AMP/ATP ratio [19] enhances resistance to nutrient deprivation and stress, increasing lifespan [158]. As AMPK and SIRTs are interconnected longevity pathways, metformin also activates SIRTs 1 and 3, which contribute to the delay of cellular senescence and the promotion of mitochondrial biogenesis [80].

D. Rapamycin

In 1972, scientists discovered Rapamycin, a compound produced by Streptomyces hygroscopicus on the soil of Easter Island [169]. Initially recognised for inhibiting the growth of the yeast Candida albicans [170], this serendipitous discovery has paved the way for research into ageing by extending life span in a wide range of species [171].

Rapamycin has been shown to have antifungal, immunosuppressive, and anticancer properties [172]. Its versatility in multiple fields of research, including anticancer and anti-ageing research highlights its potential as an intervention. Rapamycin has demonstrated its efficacy as a pharmacological inducer of autophagy, a key cytoprotective mechanism [88]. Moreover, rapamycin also suppresses cellular senescence [171] by suppressing the Stat3 pathway [173], which reduces age-related inflammation in immunosuppressive cells [174], to decrease SASP [173].

In human cells, the age-related inhibition of SIRT1 increases the vulnerability of human cells to metabolic stress. Rapamycin treatment has been shown to protect cells against metabolic stress [88]. One of the main molecular mechanisms behind this is the inhibition of mTORC1 by rapamycin, through its binding to FKBP12 [175]. mTOR activation in response to high oxidative stress can lead to a reduction in SIRTs 1 and 6, thereby accelerating ageing. Thus, rapamycin's inhibition of mTOR can protect against senescence [176]. SIRT1 has also been suggested to be required for the protective effects of rapamycin against glucose-induced [177] and oxidative stress-induced premature senescence [176].

VI. CONCLUSION

In this review, we have delineated the main mechanisms through which sirtuins modulate the hallmarks of ageing. The mounting evidence emphasising sirtuins as pivotal regulators of longevity pathways suggests their promise as therapeutic targets. Interventions that modulate the hallmarks of ageing by controlling sirtuin activity holds significant promise in extending health span and life span. While our understanding of sirtuin modulation remains incomplete, it provides a solid foundation for advancing interventions to extend life span and enhance the quality of life. Looking forward, interventions addressing age-associated changes across multiple levels should be further developed to target ageing through its twelve hallmarks.

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