The Role of Sirtuins in Cell Life and their Potential Therapeutic Uses

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Sirtuins (SIRTs) constitute a family of enzyme-type proteins dependent on nicotinamide adenine dinucleotide. These enzymes are considered cellular metabolic sensors since the cell's energy level can regulate their activity to compensate for energy fluctuations. They constitute an evolutionarily conserved family of deacetylases class III enzymes, with a recognized role in prolonging life expectancy. Sirtuins are related to the development of age-associated pathologies, such as cancer, diabetes, neurodegeneration, and metabolic disorders. This group of enzymes has become a possible therapeutic target due to their capacity for modulating cellular processes, such as genome repair and maintenance, and for regulating metabolic pathways, homeostasis, and cell proliferation. In addition, SIRTs are associated with pathologies such as cancer and COVID-19. There is a need for future studies that will clarify the relationship between these enzymes group and the prevention and development of diseases. [*P R Health Sci J 2023;42(4):269-275*]

Key words: Enzyme, NAD deacetylases, Oxidative stress, Metabolism, Sirtuins

Sirtuins (SIRTs) are enzymes that catalyze the hydrolysis of acetyl lysine in histones dependent on cofactor nicotinamide adenine dinucleotide (NAD+) (1) (Figure 1). These enzymes modulate essential molecular pathways in eubacteria, archaea, and eukaryotes (2). These enzymes exert their actions throughout the body, from nerve tissue to the liver, the pancreas, adipose tissue, muscle, the cardiovascular system, the mammary glands, the lungs, and the reproductive system (3). They are closely related to several biological processes: cell metabolism, cell proliferation, genome stability, aging in mammals, and age-related diseases, including cancer, metabolic disorders, and neurodegenerative diseases (4).

Additionally, sirtuins have been implicated in regulating genome integrity, metabolic homeostasis, the glucose and glutamine metabolic pathways, and lipid metabolism; they are known to have roles in modulating the activity of metabolic enzymes by post-translational modification and the maintenance of telomeres, as well as in caloric restriction, apoptosis, inflammation, energy deficiency, tissue fibrosis, and mitochondrial biogenesis (5). These enzymes play an essential role in gene transcription, cell cycle progression, DNA repair, and cell metabolism (6). Sirtuins are activated in response to decreased cellular energy stores and have been implicated in the control of many physiological processes, including senescence. Seven closely related members of the SIRT family have been identified, which are divided into four classes: class I comprises SIRT1, SIRT2, and SIRT3; class II includes SIRT4; class III consist of SIRT5; and class IV is made up of SIRT6 and SIRT7 (7).

At the mammalian genome level, each SIRT isoform has a position at the cell level, including in the nucleus, cytoplasm, and mitochondria; in the cell nucleus are usually located SIRT1, SIRT3, SIRT6, and SIRT7; in the mitochondria, SIRT3, SIRT4, and SIRT5; and in the cytoplasm, SIRT1 and SIRT2 (5). The importance of SIRTs in many physiological processes has led to research on the pathophysiological and therapeutic roles of these metabolic sensors in various conditions, such as cancer, type II diabetes, metabolic diseases associated with obesity, neurodegeneration, and heart disease; these diseases are associated with alterations in SIRT activity related to decreased cellular energy (8). Sirtuins are currently considered important in the maintenance of health and responses to stress, preventing the development of various diseases associated with age through several mechanisms related to the regulation of the stress response, apoptosis, and DNA repair (9). This review aims to show the activity of SIRTs (at the cellular level) and their close relationship in modulating several cells' metabolic processes (Figure 2).

Characteristics of the sirtuins

Sirtuin 1

The SIRT1 in the best-characterized; it comprises a 747 amino acid sequence that predicts a molecular weight of 81 kDa. In human vascular endothelial cells, SIRT1 is highly expressed,

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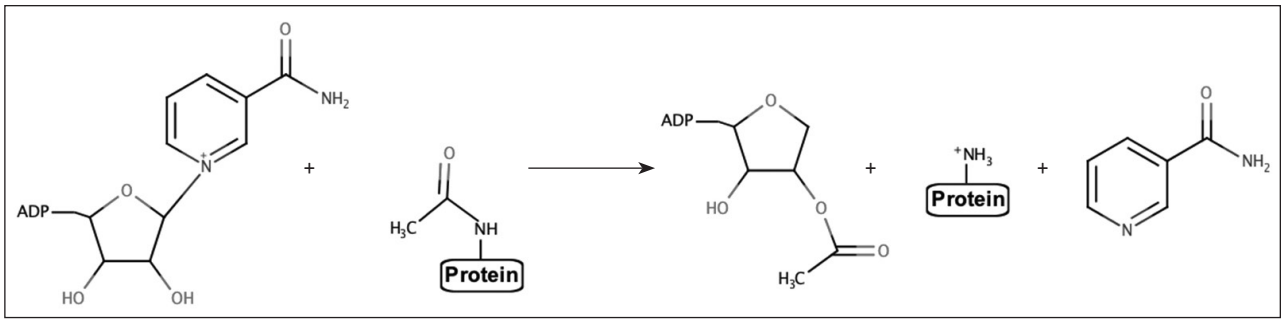


Figure 1. Deacetylation reaction catalyzed by sirtuins.

regulating many cellular biological processes, such as apoptosis, inflammation, stress resistance, cell growth, cell senescence, and metabolism (8). One of the most studied aspects of this SIRT has been its role in calorie restriction (CR), which last is known to increase life expectancy in several organisms, showing that CR can affect SIRT1 function through many NAD+-dependent redox pathways, which leads to the conclusion that CR could increase the levels of nicotinamide, a specific inhibitor of SIRTs (10). This SIRT can deacetylate more than 50 non-histone protein substrates, including the tumor suppressor p53 (11). This last inhibits the expression of pro-apoptotic genes by activating the apoptotic cascade and substrates such as signal transducer and activator of transcription, forkhead box O (FOXO) 1, FOXO3, and nuclear factor-κB, which are transcriptional factors that modulate apoptosis, cellular aging, and inflammation (12). This particular enzyme has an essential role in neurodegenerative and kidney diseases, both of which have been identified as being age related (13). In particular, the activation of SIRT1 provides protection against diseases associated with neurological compromise since such activation protects neurons against apoptosis, inflammation, and oxidative stress, which suggests that this enzyme could be a therapeutic target for the treatment of neurological disorders (14). Studies have demonstrated that SIRT1's regulation of several important metabolic factors plays a role in modulating gluconeogenesis and glycolysis. In addition, SIRT1 plays a protective role in cholesterol metabolism and has a neuroprotective function, which is to induce anti-inflammatory activity in different tissues (15). *In vivo* and *in vitro* studies show that SIRT1 is involved in cardiovascular disease pathogenesis and protects cardiomyocytes from hypoxic conditions and oxidant molecules (16). SIRT1 has an important role in aging, having shown a protective effect (in the form of caloric restriction) against neurodegenerative disease and improving the proliferative state of neural stem cells in the rat hippocampus, in addition to participating in the protection against cellular oxidative stress and DNA damage (8). This isoform has been reported to be involved in aging and longevity in animal models (2); SIRT1 promotes the transcription of genes related to cell survival, energy metabolism, and mitochondrial biogenesis (11). This SIRT has been shown to regulate insulin secretion, oxygen consumption, mitochondrial capacity, chromatin structure, and gene expression (17). Finally, SIRT 1 is an essential regulator of normal embryonic development and is highly expressed in the early stages of morula and blastocyst, and its expression decreases with embryonic development (18). As SIRT1 plays a dual role in the promotion and suppression of cancer, its overexpression has been associated with cancer progression and drug resistance in several types of cancers, including breast, colon, melanoma, skin, liver, and prostate cancers, as well as in chronic myeloid leukemia. Additionally, SIRT1 has been shown to regulate more than 50 different substrates associated with cancer proliferation and survival (12).

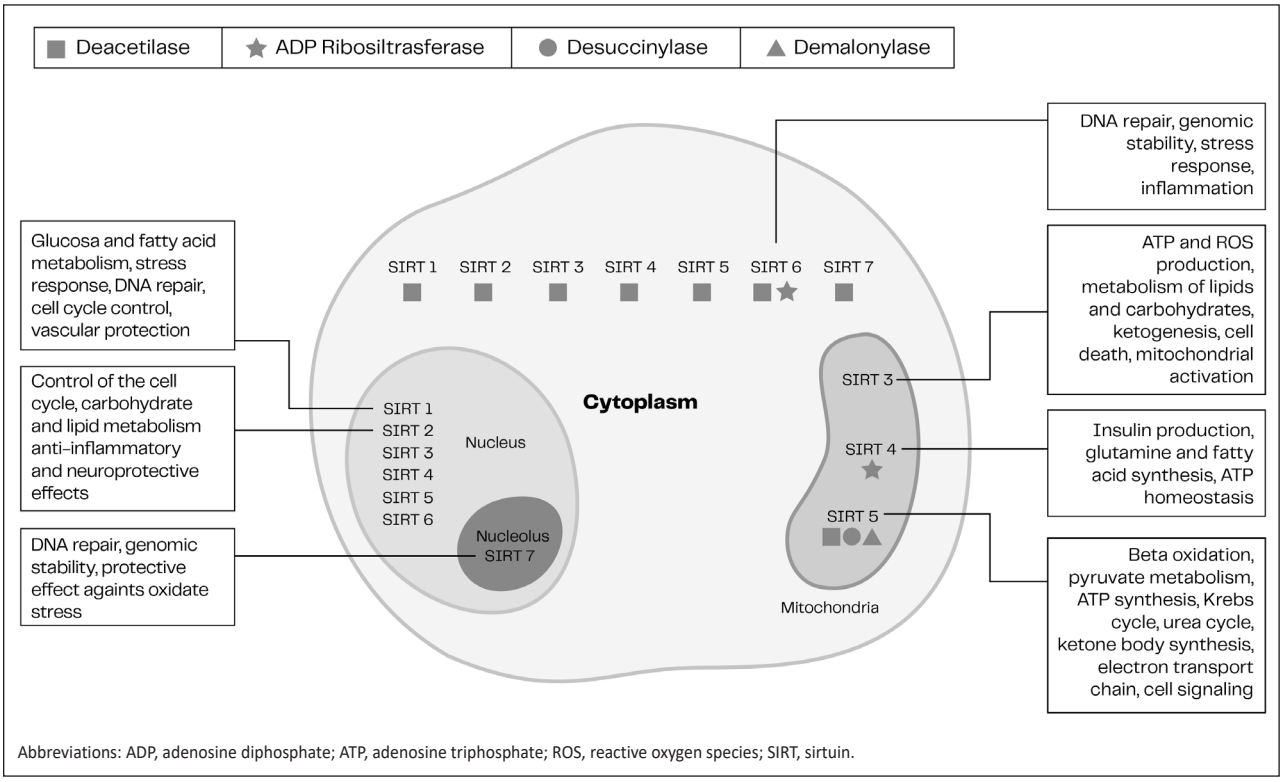
Sirtuin 2

Sirtuin 2 is an enzyme with NAD+-dependent acetyl-lysine deacetylase activity (19); it is found mainly in the cytoplasm (2). However, recent studies have documented SIRT2's presence in the nucleus, where it regulates the cell cycle (20); it is distributed mainly in the brain, specifically in the cytoplasm of neurons and oligodendrocytes (21). It is an α-tubulin protein with a type of deacetylase activity closely associated with oligodendrocyte differentiation (15) and contributing to myelin sheath formation and myelin–axon interaction (11). It is an important regulator of senescence, cell differentiation, stress tolerance, metabolism, and cancer (8). Recently, SIRT2 has been found to accumulate in the neurons of the central nervous system aging, and its microtubule deacetylase activity is linked to brain pathologies involving aging and neurodegenerative diseases (22). Sirtuin 2 is expressed in several tissues, with specific metabolic activity taking place in the brain, muscles, liver, testicles, pancreas, kidneys, and adipose tissue of mice (23). This SIRT is associated with mitotic structures, including the centrosome, which regulate the cell cycle; studies show that the deacetylation of SIRT2 tubulin could control microtubule stability in the mitotic spindle and, therefore, control, as well, the regular division of the chromosome during the cell cycle (24). The SIRT2 protein is involved in the suppression of tumorigenesis, preventing chromosome instability during mitosis (18). The levels of SIRT2 fluctuate during the cell cycle, with a marked increase in SIRT2 expression and phosphorylation during the mitotic G2/M transition phase, playing an essential role in mitotic exit from the cell cycle; in turn, SIRT2 deacetylates FOXO3A, which, in turn, promotes the expression of antioxidant and

pro-apoptotic molecules under cellular stress (25). Sirtuin 2 is involved in multiple cellular functions, including actin-binding ferrous ion transport, amino acid metabolism in the cell, transmembrane signaling, morphogenesis, and those associated with the trans face of the Golgi complex (26). In addition, SIRT2 has an important role in the regulation of lipid metabolism, adipogenesis, and gluconeogenesis and is involved in the maintenance of mitochondrial potential and adenosine triphosphate (ATP) levels (3). Some reports show that this isoform is upregulated in certain types of cancer, such as hepatocellular carcinoma, gastric cancer, melanoma, and leukemia, while other studies suggest that SIRT2 is downregulated in prostate and ovarian cancers and in gliomas. Concerning other types of cancer (such as lung, colorectal, and breast cancers), the results are controversial; for this reason, it is necessary to investigate the interaction between SIRT2 and cancer to understand the development of tumorigenesis associated with SIRT2 (23).

Sirtuin 3

This SIRT is mainly distributed in organs with a high content of mitochondria, such as the kidneys, heart, and liver; in the lungs, SIRT3 is found at relatively lower levels (15). It is the most studied and best characterized mitochondrial SIRT (27). It is the largest deacetylase protein located in the mitochondrial matrix, and its primary function is to protect the mitochondria from oxidative stress, regulating the citric acid (Krebs) cycle and the electron transport chain in complexes I, II, V, and, recently discovered, III (10). In these complexes, SIRT3 participates in deacetylation by activating its components, thus increasing mitochondrial oxidative phosphorylation (28). The first substrate identified for this SIRT was the enzyme acetyl-coenzyme A (CoA) synthetase, whose deacetylation leads to its activation, and which has an important role in the thermogenesis of brown adipose tissue (25). Sirtuin 3 prevents oxidative stress damage caused by the accumulation of ammonium groups as a result of protein catabolism. In mitochondria, SIRT3, together with SIRT5, regulates the urea cycle's metabolic reactions and acts on carbamoyl phosphate synthetase I and deacetylates ornithine transcarbamylase, which leads to the elimination of oxidative stress promoted by ammonium (29). Likewise, SIRT3 deacetylates many proteins that regulate mitochondrial function at the mitochondrial level, such as ATP production and the regulation of reactive oxygen species (ROS) production, β-oxidation, ketogenesis, and cell death, among others (12). In β-oxidation, SIRT3 promotes the oxidation of fatty acids in mitochondria by deacetylating acyl-CoA dehydrogenase, a key enzyme in the oxidization of long-chain substrates (25). Low levels of SIRT3 can cause increased oxidative stress and insulin resistance (30). In turn, SIRT3 participates in the glycolytic process by oxidizing the glucose molecule and regulating its enzymes (5,12). The previously mentioned deficiency of SIRT3 has been shown to produce glucose intolerance, decreased insulin signaling, and increased oxidative stress in skeletal muscle (7). Acting as a tumor suppressor, SIRT3 keeps the mitochondria in breast cancer intact (30), mainly



Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; ROS, reactive oxygen species; SIRT, sirtuin.

Figure 2. The roles of the various sirtuins in cellular metabolism. Graphic design: Arias.Montoya Juliana 2023.

by inhibiting ROS production through the deacetylation of superoxide dismutase (SOD) 2, isocitrate dehydrogenase (IDH) 2, and FOXO3A. This SIRT can have profound consequences on tumor cell growth (27); furthermore, it protects against oxidative stress by the deacetylation and activation of SOD2 and IDH2, with the higher activity of these redox enzymes preventing toxic ROS accumulation (25). It is also thought to be directly related to longevity in humans (it has been found to be highly expressed in long-lived individuals) (31), extending cell life by participating in the regulation of cellular metabolic energy and interacting with genes related to longevity, such as FOXO3a, and removing ROS, the proliferation of which can be a sign of aging (15). The levels of SIRT3 are increased in the synovial membrane of patients with rheumatoid arthritis and decreased in patients with osteoarthritis, suggesting it might have a role as therapy in multiple joint tissues (32). The beneficial effect of SIRT3 in the maintenance of energy metabolism and the antioxidant defense system's activation is evident (33).

Sirtuin 4

A hallmark of SIRT4 is weak deacetylase activity; however, it is a potent adenosine diphosphate (ADP)-ribosyl transferase that is dependent on NAD+ and is specifically located in mitochondrial compartments (15,27). In addition, it is known to be involved in lipoamidase activity by removing the lipoyl or biotinyl modifications from lysine residues (34), which inhibits the activity of pyruvate dehydrogenase, an enzyme that links the glycolysis pathway to the Krebs cycle (25). The overexpression of SIRT4 promotes ROS production induced by mitochondrial stress, reducing oxygen consumption, an indication of mitochondrial activity (35). The first identified substrate of SIRT4 was the mitochondrial enzyme glutamate dehydrogenase, an enzyme that allows the conversion of glutamate to α-ketoglutarate (27). The main function of SIRT4 involves the metabolism of glutamine in proliferative cells (21). In addition, SIRT4 regulates metabolic functions such as insulin secretion and the β-oxidation of fatty acids by the deacetylation of malonyl-CoA decarboxylase, an enzyme responsible for generating acetyl-CoA from malonyl-CoA, thus controlling β-oxidation (18). At the level of the liver, SIRT4 regulates glucose production and metabolic catabolism by controlling glutamine availability (7). Several studies have shown that the expression of SIRT4 is significantly insufficient in gastric cancer, in bladder, breast, colon, and thyroid tumors, and in leukemias (15). This SIRT has been shown to be involved in endothelial dysfunction associated with chronic obstructive pulmonary disease (26). In turn, it takes part in the regulation of the cell cycle and the prevention of tumorigenesis by inhibiting the metabolism of glutamine and promoting genomic stability (25).

Sirtuin 5

This SIRT has relatively weak deacetylase activity (15) and has recently been reported to have NAD+-dependent malonylase, desuccinylase, and deglutarylase activity (35). Sirtuin 5 regulates many cellular metabolic pathways, including ammonium metabolism, fatty acid oxidation, and glycolysis. It is a mitochondrial SIRT that is highly expressed in the human cerebral cortex (11) and can activate the mitochondrial isoform SOD (36). Recent studies have reported this SIRT has a crucial role in the desuccinylation of fatty acids (by oxidizing enzymes such as hydroxymethylglutaryl-CoA synthetase, and enoyl-CoA hydratase) and the demalonylation of malonyl-CoA decarboxylase, thus promoting the β-oxidation of fatty acids (37). As do SIRT3 and SIRT4, SIRT5 targets (in the main) mitochondrial substrates and decreases glycolysis by inducing oxidative phosphorylation and fatty acid oxidation (3). At the levels of glycolysis and the Krebs cycle, this SIRT controls the post-translational modifications of the succinate dehydrogenase, pyruvate dehydrogenase, and glyceraldehyde 3-phosphate dehydrogenase complexes; it also has been reported that, in response to oxidative stress, this SIRT desuccinylates SOD and isocitrate dehydrogenase, converts glucose-6-phosphate dehydrogenase, and maintains the redox balance of the cell (38).

Sirtuin 6

The deacetylase and ADP transferase activity of SIRT6 is weak (15); it is primarily a nuclear protein (33). Sirtuin 6 is involved in maintaining the integrity of the genome (39) and in regulating both gene expression and ribosomal DNA transcription (3). In addition, SIRT6 is related to metabolism, signaling, and damage repair mechanisms at the DNA level. Therefore, it is considered a promising therapeutic target in treating neurodegenerative diseases and metabolic disorders, such as diabetes and cancer (40). Its main function lies in maintaining genomic stability and repairing DNA damage by different mechanisms (25). This SIRT participates in glucose homeostasis through the cellular reduction of insulin signaling (by inhibiting gluconeogenesis) and is involved in lipid homeostasis (by negatively regulating lipogenic transcription factors) (12). It has been reported that SIRT6 regulates aging, stability, and genome repair, acts as a potent tumor suppressor, and protects vascular endothelial cells from premature senescence and telomere damage; studies have shown that SIRT6 promotes the secretion of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα) (15), through the deacylation of lysine from this cytokine, stimulating macrophages in its production (25). Sirtuin 6 regulates several metabolic pathways (e.g., glycolysis and gluconeogenesis), which activity can, in turn, affect cancer proliferation. Various types of cancer contain low levels of SIRT6, and the deficiency of the latter results in genetic instability and tumorigenesis (40). Similarly, cells deficient in this SIRT have shown both defects at the DNA level in the base excision repair system and high genomic instability (41). The oncogenic potential of this SIRT was demonstrated in human hepatocarcinoma and rectal colon cancer. It was demonstrated, as well, that this SIRT deacetylates and represses the transcription of genes related to tumor

suppression and maintenance in oncogenic transformation (25). Sirtuin 6 maintains telomeres and genomic stability, and its overexpression induces apoptosis in cancer cells (22).

Sirtuin 7

Acting as a weak NAD+-dependent deacetylase enzyme, SIRT7 clears acetyl-like groups present on the acetylated lysine residues of proteins of interest in a reaction that generates nicotinamide adenine mononucleotide, 2'-O-acetyl-ADP-ribose, and deacetylated substrates (26). The least studied enzyme of the enzyme family under discussion, SIRT7 is mainly located in the nucleolus, and only half of the deacetylated substrates have been identified as being expressed in certain tissues (the liver, spleen, and heart); genetic deletion of this gene leads to a 50% reduction in life expectancy and the development of cardiac pathological changes such as fibrosis, cardiac hypertrophy, and inflammatory cardiomyopathy (42). This SIRT interacts with RNA polymerase I and histones and positively regulates the transcription and expression of ribosomal RNA genes (25); SIRT7 has important roles in the DNA damage response, tumorigenesis, and metabolism (4). It is associated with the condensation of the chromosome and nucleus and has recently been implicated in protein synthesis, chromatin remodeling, and cell survival (39). This enzyme protects cells from oxidative stress, genotoxic stress, and endoplasmic reticulum stress caused by unfolded proteins. Moreover, SIRT7 promotes the genetic stability of cells by regulating the repair of damaged non-homologous DNA, which is essential for prolonging life (32); additionally, it decreases the oxidative stress evidenced in the attenuation of cell proliferation (11). This form of SIRT can control myocardial development and prevent dysfunction associated with stress and aging through the deacetylation of P53 and FOXO1 (26). Reduced levels of SIRT7 inhibit tumor growth due to reduced polymerase I activity and disturbances in ribosomal biogenesis (43). Together with SIRT1 and SIRT6, SIRT7 exerts its activity by regulating DNA stability and gene expression and maintaining chromatin structure and cell cycle progression; however, the relationship between SIRT7 expression and cancer progression is still unclear (44).

The 7 SIRT proteins have been identified in several animals, and many homologs of these have been found in widely diverse hosts, from bacteria to humans. The first identified species was the yeast *Saccharomyces cerevisiae*. However, SIRTs have been found in the nematode *Caenorhabditis elegans*, in *Drosophila melanogaster*, and in mammals (22). These protein structures are highly conserved and correlated. In addition, all the SIRTs have essential functions in the cell cycle of life and survival, either activating or inhibiting different functions.

Diseases and sirtuins

Sirtuins have an essential role in the development of diseases. Sirtuins 1 and 6 are implicated in type 2 diabetes mellitus, obesity, insulin resistance, fatty liver disease, and cardiovascular disease (6), and SIRT2 is associated with neurodegenerative diseases (its inhibition could delay the progression of both Parkinson's and Huntington's diseases) (15). Next, SIRT3 is involved in atherogenesis, inflammation, and endothelial function (7), while SIRT4 is associated with aging and is upregulated during senescence; this particular SIRT can cause damage to mitochondrial function and health, in that it does not allow the adequate clearance of dysfunctional mitochondria (35). When overexpressed, SIRT5 can lead to various diseases such as Alzheimer's, Parkinson's, and cancer (15); some genes are involved with the risk of developing carotid plaques, which may be helpful in the detection of asymptomatic individuals who are at increased risk for vascular disease (26). Aside from the specific associations mentioned earlier, SIRT6 maintains vascular hemostasis, limits atherosclerosis, and is linked to the prevention and delay of cardiovascular diseases (26). Finally, SIRT7 contributes to skeletal homeostasis, and its deletion, to decreased bone formation and increased bone resorption (32). This SIRT has important roles in stress resistance and cardiac health as well as in regulating hepatic lipid metabolism. It has been found to be upregulated in several cancer types, including thyroid cancer, node-positive breast cancer, bladder cancer, hepatocellular carcinoma, and colorectal cancer (39).

Covid-19 and sirtuins

The SIRT family has been described as a primary defense (by modulating the host's immune response and viral gene expression) against DNA- and RNA-based viral pathogens (45). Recent studies show that these enzymes control the production of pro-inflammatory cytokines at the level of innate immune cells. Involved in viral immune responses (similar to those of macrophages), SIRTs are, in turn, also involved in the differentiation of CD8+ T lymphocytes, which are responsible for killing cells infected with intracellular pathogens such as viruses (46). For example, increases of SIRT1 decrease viral replication by inhibiting the activation of ADM17 (A disintegrin and metalloproteinase domain 17) and decreasing the levels of cytokines such as TNFα, interleukin (IL) 1b, and IL-6. Contrarily, decreases in the levels of SIRT1 favor viral replication with no effect on ADM17, leading to uncontrolled increases in TNFα, IL-1b, and IL-6 (47). Sirtuin activity decreases with age, reducing NAD+ levels, decreasing deacetylase activity (which leads to a dysregulated immune response in patients with severe COVID19) (48), and inducing hyperactivity of the nucleotide-binding oligomerization domain–like receptor protein 3 inflammasome, which produces the storm of cytokines in COVID19 patients (49). In patients with type 2 diabetes mellitus: 1) NAD+ levels are altered; and 2) dysfunction in cellular energy metabolism together with COVID-19 increases the risk of severe disease, and of course, mortality is increased (50).

As of the writing of this article, the enzymes in this group have become possible therapeutic target due to their capacity for modulating cellular processes, such as maintaining and repairing the genome, regulating metabolic pathways, maintaining homeostasis, and regulating cell proliferation—as

well as their association with pathologies such as cancer and even COVID-19. There is a need for future studies that will clarify the relationship between these enzymes and the prevention and development of diseases.

Resumen

Las sirtuinas constituyen una familia de proteínas tipo enzimas dependientes de nicotinamida adenina dinucleótido. Estas enzimas con consideradas sensores metabólicos celulares, dado que su actividad puede ser regulada por la energía de la célula como mecanismo para compensar las fluctuaciones energéticas. Constituyen una familia evolutivamente conservadas de enzimas de clase III de tipo deacetilasas, con un papel reconocido en prolongar la expectativa de vida. Las sirtuinas están relacionadas en la modulación de procesos celulares relacionados al desarrollo de patologías asociados con la edad como cáncer, diabetes, neurodegeneración y desordenes metabólicos. En la actualidad este grupo de enzimas se ha convertido en posible blanco terapéutico debido a su capacidad de modular procesos celulares como mantener y reparar el genoma, regular vías metabólicas, mantener el equilibrio en el organismo, proliferación celular, así como la relación que guarda en patologías como el cáncer e incluso COVID-19, continuamos con la necesidad de futuros estudios que permitan conocer la relación entre estas enzimas y la prevención o desarrollo de enfermedades.

References

1. Carafa V, Altucci L, Nebbioso A. Dual Tumor Suppressor and Tumor Promoter Action of Sirtuins in Determining Malignant Phenotype. Front Pharmacol. 2019;10:38. Published 2019 Jan 30. doi:10.3389/fphar.2019.00038
2. Rizzi L, Roriz-Cruz M. Sirtuin 1 and Alzheimer's disease: An up-to-date review. Neuropeptides. 2018;71:54-60. doi:10.1016/j.npep.2018.07.001
3. Zullo A, Simone E, Grimaldi M, et al. Effect of nutrient deprivation on the expression and the epigenetic signature of sirtuin genes. Nutr Metab Cardiovasc Dis. 2018;28(4):418-424. doi:10.1016/j.numecd.2018.02.004
4. Islam MS, Wei F-Y, Ohta K, Shigematsu N, Fukuda T, Tomizawa K, et al. Sirtuin 7 is involved in the consolidation of fear memory in mice. Biochem Biophys Res Commun. 2018;495(1):261–6. https://doi.org/10.1016/j.bbrc.2017.10.159
5. Zhu S, Dong Z, Ke X, et al. The roles of sirtuins family in cell metabolism during tumor development. Semin Cancer Biol. 2019;57:59-71. doi:10.1016/j.semcancer.2018.11.003
6. Zhou S, Tang X, Chen HZ. Sirtuins and Insulin Resistance. Front Endocrinol (Lausanne). 2018;9:748. Published 2018 Dec 6. doi:10.3389/fendo.2018.00748. Sosnowska B, Mazidi M, Penson P, Gluba-Brzózka A, Rysz J, Banach M. The sirtuin family members SIRT1, SIRT3 and SIRT6: Their role in vascular biology and atherogenesis. Atherosclerosis. 2017;265:275-282. doi:10.1016/j.atherosclerosis.2017.08.027
8. Mimura T, Kaji Y, Noma H, Funatsu H, Okamoto S. The role of SIRT1 in ocular aging. Exp Eye Res. 2013;116:17–26. https://doi.org/10.1016/j.exer.2013.07.017
9. Grabowska W, Sikora E, Bielak-Zmijewska A. Sirtuins, a promising target in slowing down the ageing process. Biogerontology. 2017;18(4):447-476. doi:10.1007/s10522-017-9685-9
10. Webster BR, Lu Z, Sack MN, Scott I. The role of sirtuins in modulating redox stressors. Free Radic Biol Med. 2012;52(2):281-290. doi:10.1016/j.freeradbiomed.2011.10.484
11. Zhang F, Wang S, Gan L, et al. Protective effects and mechanisms of sirtuins in the nervous system. Prog Neurobiol. 2011;95(3):373-395. doi:10.1016/j.pneurobio.2011.09.001
12. Giblin W, Skinner ME, Lombard DB. Sirtuins: guardians of mammalian healthspan. Trends Genet. 2014;30(7):271-286. doi:10.1016/j.tig.2014.04.007
13. Wakino S, Hasegawa K, Itoh H. Sirtuin and metabolic kidney disease. Kidney Int. 2015;88(4):691-698. doi:10.1038/ki.2015.157
14. Bastianetto S, Ménard C, Quirion R. Neuroprotective action of resveratrol. Biochim Biophys Acta. 2015;1852(6):1195-1201. doi:10.1016/j.bbadis.2014.09.011
15. Wang Y, He J, Liao M, Hu M, Li W, Ouyang H, et al. An overview of Sirtuins as potential therapeutic target: structure, function and modulators. Eur J Med Chem. 2019;161:48–77. https://doi.org/10.1016/j.ejmech.2018.10.028
16. Donniacuo M, Urbanek K, Nebbioso A, et al. Cardioprotective effect of a moderate and prolonged exercise training involves sirtuin pathway. Life Sci. 2019;222:140-147. doi:10.1016/j.lfs.2019.03.001
17. Iside C, Scafuro M, Nebbioso A, Altucci L. SIRT1 Activation by Natural Phytochemicals: An Overview. Front Pharmacol. 2020;11:1225. Published 2020 Aug 7. doi:10.3389/fphar.2020.01225
18. Correia M, Perestrelo T, Rodrigues AS, et al. Sirtuins in metabolism, stemness and differentiation. Biochim Biophys Acta Gen Subj. 2017;1861(1 Pt A):3444-3455. doi:10.1016/j.bbagen.2016.09.008
19. Chen Z, Lin J, Feng S, et al. SIRT4 inhibits the proliferation, migration, and invasion abilities of thyroid cancer cells by inhibiting glutamine metabolism. Onco Targets Ther. 2019;12:2397-2408. Published 2019 Mar 28. doi:10.2147/OTT.S189536
20. Eldridge MJG, Pereira JM, Impens F, Hamon MA. Active nuclear import of the deacetylase Sirtuin-2 is controlled by its C-terminus and importins. Sci Rep. 2020;10(1):2034. Published 2020 Feb 10. doi:10.1038/s41598-020-58397-6
21. Chen X, Wales P, Quinti L, et al. The sirtuin-2 inhibitor AK7 is neuroprotective in models of Parkinson's disease but not amyotrophic lateral sclerosis and cerebral ischemia. PLoS One. 2015;10(1):e0116919. Published 2015 Jan 21. doi:10.1371/journal.pone.0116919
22. Dang W. The controversial world of sirtuins. Drug Discov Today Technol. 2014;12:e9-e17. doi:10.1016/j.ddtec.2012.08.003
23. Wang Y, Yang J, Hong T, Chen X, Cui L. SIRT2: Controversy and multiple roles in disease and physiology. Ageing Res Rev. 2019;55:100961. doi:10.1016/j.arr.2019.100961
24. Bergmann L, Lang A, Bross C, et al. Subcellular Localization and Mitotic Interactome Analyses Identify SIRT4 as a Centrosomally Localized and Microtubule Associated Protein. Cells. 2020;9(9):1950. Published 2020 Aug 24. doi:10.3390/cells9091950
25. Poulose N, Raju R. Sirtuin regulation in aging and injury. Biochim Biophys Acta. 2015;1852(11):2442-2455. doi:10.1016/j.bbadis.2015.08.017
26. D'Onofrio N, Vitiello M, Casale R, Servillo L, Giovane A, Balestrieri ML. Sirtuins in vascular diseases: Emerging roles and therapeutic potential. Biochim Biophys Acta. 2015;1852(7):1311-1322. doi:10.1016/j.bbadis.2015.03.001
27. Sebastián C, Mostoslavsky R. The role of mammalian sirtuins in cancer metabolism. Semin Cell Dev Biol. 2015;43:33-42. doi:10.1016/j.semcdb.2015.07.008
28. Bagul PK, Katare PB, Bugga P, Dinda AK, Banerjee SK. SIRT-3 Modulation by Resveratrol Improves Mitochondrial Oxidative Phosphorylation in Diabetic Heart through Deacetylation of TFAM. Cells. 2018;7(12):235. Published 2018 Nov 28. doi:10.3390/cells7120235
29. Pop RM, Popolo A, Trifa AP, Stanciu LA. Phytochemicals in Cardiovascular and Respiratory Diseases: Evidence in Oxidative Stress and Inflammation. Oxid Med Cell Longev. 2018;2018:1603872. Published 2018 Aug 9. doi:10.1155/2018/1603872
30. Choi JE, Mostoslavsky R. Sirtuins, metabolism, and DNA repair. Curr Opin Genet Dev. 2014;26:24-32. doi:10.1016/j.gde.2014.05.005
31. Zhang J, Fang L, Lu Z, Xiong J, Wu M, Shi L, et al. Are sirtuins markers of ovarian aging? Gene. 2016;575(2):680–6. https://doi.org/10.1016/j.gene.2015.09.043

32. Almeida M, Porter RM. Sirtuins and FoxOs in osteoporosis and osteoarthritis. Bone. 2019;121:284-292. doi:10.1016/j.bone.2019.01.018
33. Naia L, Rego AC. Sirtuins: double players in Huntington's disease. Biochim Biophys Acta. 2015;1852(10 Pt A):2183-2194. doi:10.1016/j.bbadis.2015.07.003
34. German NJ, Haigis MC. Sirtuins and the Metabolic Hurdles in Cancer. Curr Biol. 2015;25(13):R569-R583. doi:10.1016/j.cub.2015.05.012
35. Lin S, Xing H, Zang T, Ruan X, Wo L, He M. Sirtuins in mitochondrial stress: Indispensable helpers behind the scenes. Ageing Res Rev. 2018;44:22-32. doi:10.1016/j.arr.2018.03.006
36. Wątroba M, Dudek I, Skoda M, Stangret A, Rzodkiewicz P, Szukiewicz D. Sirtuins, epigenetics and longevity. Ageing Res Rev. 2017;40:11-19. doi:10.1016/j.arr.2017.08.001
37. Yang X, Wang Z, Li X, et al. SHMT2 Desuccinylation by SIRT5 Drives Cancer Cell Proliferation. Cancer Res. 2018;78(2):372-386. doi:10.1158/0008-5472.CAN-17-1912
38. Nishida Y, Rardin MJ, Carrico C, et al. SIRT5 Regulates both Cytosolic and Mitochondrial Protein Malonylation with Glycolysis as a Major Target. Mol Cell. 2015;59(2):321-332. doi:10.1016/j.molcel.2015.05.022
39. Kiran S, Anwar T, Kiran M, Ramakrishna G. Sirtuin 7 in cell proliferation, stress and disease: Rise of the Seventh Sirtuin!. Cell Signal. 2015;27(3):673-682. doi:10.1016/j.cellsig.2014.11.026
40. Heger V, Tyni J, Hunyadi A, Horáková L, Lahtela-Kakkonen M, Rahnasto-Rilla M. Quercetin based derivatives as sirtuin inhibitors. Biomed Pharmacother. 2019;111:1326-1333. doi:10.1016/j.biopha.2019.01.035
41. Chang AR, Ferrer CM, Mostoslavsky R. SIRT6, a Mammalian Deacylase with Multitasking Abilities. Physiol Rev. 2020;100(1):145-169. doi:10.1152/physrev.00030.2018
42. Zhao L, Cao J, Hu K, et al. Sirtuins and their Biological Relevance in Aging and Age-Related Diseases. Aging Dis. 2020;11(4):927-945. Published 2020 Jul 23. doi:10.14336/AD.2019.0820
43. Tsai YC, Greco TM, Cristea IM. Sirtuin 7 plays a role in ribosome biogenesis and protein synthesis. Mol Cell Proteomics. 2014;13(1):73-83. doi:10.1074/mcp.M113.031377
44. Sacconnay L, Carrupt PA, Nurisso A. Human sirtuins: Structures and flexibility. J Struct Biol. 2016;196(3):534-542. doi:10.1016/j.jsb.2016.10.008
45. Budayeva HG, Rowland EA, Cristea IM. Intricate Roles of Mammalian Sirtuins in Defense against Viral Pathogens. J Virol. 2015;90(1):5-8. Published 2015 Oct 21. doi:10.1128/JVI.03220-14
46. Amatriain-Fernández S, Gronwald T, Murillo-Rodríguez E, et al. Physical Exercise Potentials Against Viral Diseases Like COVID-19 in the Elderly. Front Med (Lausanne). 2020;7:379. Published 2020 Jul 3. doi:10.3389/fmed.2020.00379
47. Miller R, Wentzel AR, Richards GA. COVID-19: NAD+ deficiency may predispose the aged, obese and type2 diabetics to mortality through its effect on SIRT1 activity. Med Hypotheses. 2020;144:110044. doi:10.1016/j.mehy.2020.110044
48. Yao C, Bora SA, Parimon T, et al. Cell-Type-Specific Immune Dysregulation in Severely Ill COVID-19 Patients [published correction appears in Cell Rep. 2021 Mar 30;34(13):108943]. Cell Rep. 2021;34(1):108590. doi:10.1016/j.celrep.2020.108590
49. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people?. Aging (Albany NY). 2020;12(10):9959-9981. doi:10.18632/aging.103344
50. Wyk AF van, Verwey T. Case Report 1: NAD+ Oscillation Therapy (NOT) to treat Covid-19 aggravated by poorly controlled Diabetes Melitus Type 2. Preprint. Posted online December 11, 2020. Research Square. Accessed April 3, 2022. https://doi.org/10.21203/rs.3.rs-123044/v1