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Review

A Review of the Recent Advances Made with SIRT6 and Its Implications on Aging Related Processes, Major Human Diseases and Possible Therapeutic Targets

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Abstract: SIRT6 is a NAD^+ dependent enzyme and stress response protein that has sparked the curiosity of a plethora of researchers in different branches of the biomedical sciences. A unique member of the known Sirtuin family, SIRT6 has several different functions in several different molecular pathways related to DNA repair, glycolysis, gluconeogenesis, tumorigenesis, neurodegeneration, cardiac hypertrophic responses and so on. Only in recent times however did the potential usefulness of SIRT6 come to light as we learned more about its biochemical activity, regulation, biological roles and structure [1]. Even until very recently, SIRT6 was known more for chromatin signaling but being a nascent topic of study, more information has been ascertained and its potential involvement in major human diseases namely, diabetes, cancer, neurodegenerative diseases and heart disease has been demonstrated. It is pivotal to explore the mechanistic workings of SIRT6 since future research may hold the key to engendering strategies, involving SIRT6, that may have significant implications for human health and expand upon possible treatment options. In this review, we are primarily concerned with exploring the latest understanding of SIRT6 and how it can alter the course of several life-threatening diseases that cripple today's society such as processes related to aging, cancer, neurodegenerative diseases, heart disease and diabetes. In addition, SIRT6 has shown to be involved in liver disease, inflammation and bone related issues but more emphasis is given to the former. Lastly, any recent promising pharmacological investigations and study of potential therapeutic targets are also delineated in this review.

Keywords: SIRT6, Diabetes, Gluconeogenesis, Cancer, Aging, Heart Disease, Pharmacological SIRT6 Inhibitor, Cardiac Hypertrophy, Tumorigenesis, Neurodegeneration, Neurodegenerative Diseases, AD

1. Introduction

Sirtuins are a family of enzymes, which are NAD+ dependent and highly conserved in various systems. They are also the principal regulators in lower life organisms [1]. Silencing information regulator 2 or Sir2 was the original member of this family which was first observed in Saccharomyces cerevisiae [2-6]. In a given life form, Sir2 prolongs life by the suppression of formation of extra-chromosomal ribosomal DNA circles which are toxic in yeast [7-11]. In mammals, there are seven different sirtuins; these are SIRT1 through SIRT7. These have a broad range of functions in the cell with respect to energy balance, stress resistance to the cells, genomic stability, and aging etc. [12-15]. However, not all sirtuin family members are found in the same place. SIRT1 and SIRT2 are found in the nucleus as well as the cytosol, SIRT3, SIRT4 and SIRT5 in the mitochondria and SIRT6 and SIRT7 in the nucleus [16-19]. This review is primarily concerned with SIRT6. SIRT6 is a protein involved in the regulation of chromatin and has been shown to have a number of roles in metabolism, aging and disease and could potentially be a useful target in the treatment of several human diseases [20-24].

SIRT6 being tightly bound to chromatin and can be described as a NAD+ dependent deacetylase concerned with H3K9 and H3K56 (Histone H3 lysine 9 and H3 lysine 56, respectively) [25,26]. The initial uncovering of this histone deacetylation lead to the discovery of roles of these enzymes in variegated processes such as telomere maintenance, DNA repair, and gene expression [27]. The reasoning behind this is that this process is related to a less accessible chromatin that also has a conformation which is closed and therefore was less pellucid [28-32].

Structure of SIRT6 and its activity: The catalytic core region of the sirtuin family of proteins include approximately 275 amino acids. Their length and sequence fluctuate due to the variable N-terminal extensions (NTE) and C-terminal extensions (CTE) they possess. Further catalysis and regulation of sirtuins is promoted by the presence of large and structurally homologous Rossmann-fold domain for NAD+ binding. In addition, a more structurally assorted, zinc-binding domain is also existent within the catalytic core region [33-38]. The structural monomer of SIRT6 is shown below in Figure 1 [39]. The human SIRT6 can be best distinguished as a NAD+ -dependent histone deacetylase that contains 355 amino acids. Lysine is deacetylated through the coupling of SIRT6 with NAD+ hydrolysis yielding O-acetyl-ADP (adenosine 5'-diphosphoribose), nicotinamide, and a deacetylated substrate. Contrary to all other sirtuins, SIRT6 can bind NAD+ in the absence of an acetylated substrate. This enables SIRT6 to act as an NAD+ sensor, while the nicotinamide produced inhibits SIRT6 activity. SIRT6 occupies an open conformation where the zinc-binding motif is separated from the Rossman-fold domain. The presence of hydrogen bonds between the Rossman-fold and the zinc-binding motif stabilizes the structural conformation of SIRT6 [39-43]. Recently, it has been discovered that the free fatty acids (FFAs) endogenously activates SIRT6 deacetylase in vitro however, it still remains to be seen how it impacts the deacetylase activity in vivo [44-48]. It is noteworthy that the deacetylase activity of purified protein in vitro is 1000-fold lower for SIRT6 when compared to SIRT1. SIRT6 has also been known to remove long-chain fatty acyl groups from lysine residues in addition to removing the single acetyl groups. In addition to the deacetylation reaction, SIRT6 also used NAD+ to produce O-myristoyl-ADP, the deacetylated substrate and nicotinamide. This demyristoylation activity is about 300 times higher than the SIRT6 in vitro deacetylation activity [49]. Furthermore, SIRT6 can use NAD+ as a substrate with poly-(ADP-ribose) polymerase 1 (PARP1) and itself, thereby depicting a very weak ADP-ribosylation activity [50]. A thorough characterization of the CTE and NTE of SIRT6 unravels further important functional roles they play in biological systems. In order to facilitate proper sub-cellular targeting, the CTE of SIRT6 contains the nuclear localization signal 345 PKRVKAK 351 that is expendable for enzymatic activity. In contrast, the NTE of SIRT6 is climacteric to the intrinsic H3K9 and H3K56 deacetylase activity in cells and also in chromatin association. Absence of the NTE significantly decreases the deacetylase activity of SIRT6 through defective enzymatic activity. Furthermore, the NTE and CTE of SIRT6 are of significance for nucleosome binding in addition to its diverse enzymatic activities [51].

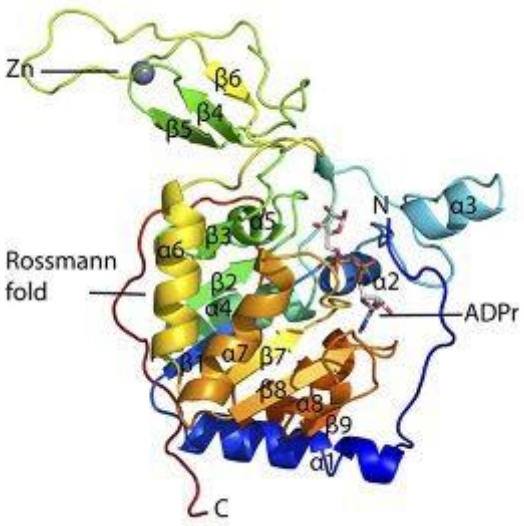


Figure 1. Structure of a SIRT6 monomer [adapted from reference 21].

Observed implications of SIRT6: In the cellular domain, a deficiency in SIRT6 may lead to several alterations in glucose metabolism, genomic stability, sensitivity to radiation, hydrogen peroxide etc. [29]. Few rather practical evidences manifest in mouse models. For example, when mice are deprived of SIRT6 they exhibit phenotypes along the lines of shortened life expectancy, cancer and metabolic disorders. In direct contrast, mice that have an overexpression of SIRT6 are seen to have an increase in life expectancy. For example, mice that are put on a specific diet regimen which is calorie restricted are observed to overexpress SIRT6 that may offer protection against many aging associated illnesses [20-24]. SIRT6 deficient mice have also shown signs of hypoglycemia, loss of subcutaneous fat, curved spines, diminished levels of insulin growth factor-1 (IGF-1) etc. [28].

The focus of this review will be on the advances made in the understanding of SIRT6 and its implications on aging and several major human diseases. Lastly we will relate recent findings to possible future avenues of research that could be explored by researchers in order to make advances with regards to SIRT6 and potential therapy benefits it may offer.

2. Role of SIRT6 in DNA repair and aging related processes

Even though aging related physiologic decline and increased human mortality is very poorly understood in biology, genomic stability related studies on SIRT6 may offer some useful insight into the arena. The cycle that aging has with genomic instability and DNA damage presents a very critical problem shown in Figure 2. Since DNA is a critical target for aging related issues, the involvement of SIRT6 in DNA repair requires some attention. Especially, in processes such as maintenance of telomeres, repairing of double-strand breaks and break excision repair [52-56].

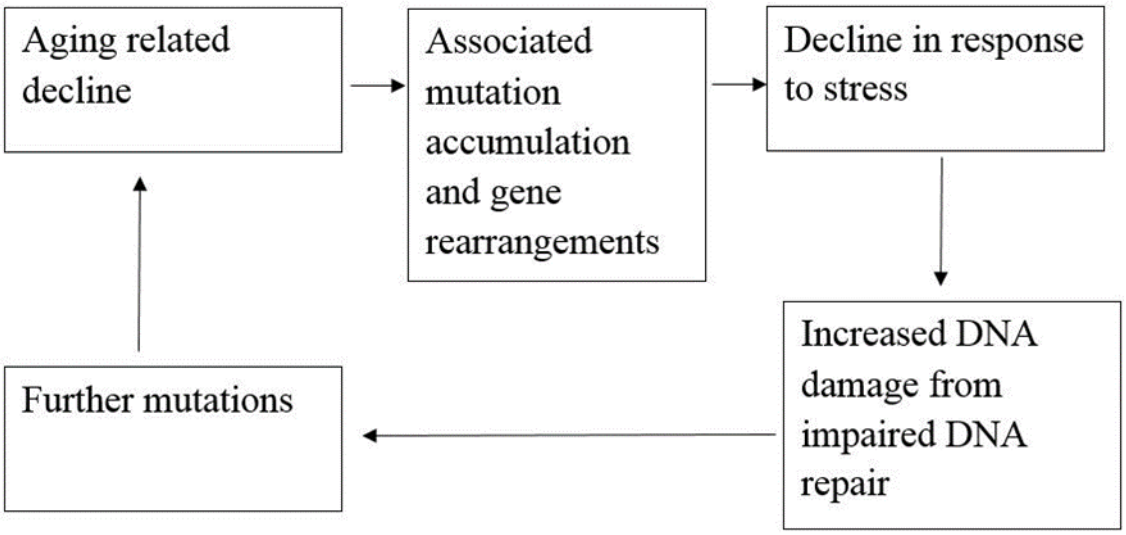


Figure 2. The cycle of aging related decline and genetic instability [adapted from reference 56]

Maintenance of telomeres: SIRT6 deficiency leads to several problems such as random telomere sequence loss that is replication associated, accumulation of DNA damage and chromosomal end to end fusion. These lead to genomic instability and may cause early death of cells. In the case of telomere maintenance, the deacetylation of H3K9 and H3K56 during the S-phase is a key process that is required for the association of Werner Syndrome Protein (WRN) and telomeric chromatin [57-62]. WRN is a major player in the genome stability in general; it is crucial in processes such as DNA replication, telomere metabolism etc. This protein may have a part to play in the replicating of lagging telomeric DNA as well as the correct capping of telomeres. The importance of the deacetylation process in this case indicates the genomic instability associated with SIRT6 deficiency may be explained by the association between chromatin and WRN [63,64].

Base excision repair: SIRT6 may also have a role to play in base excision repair. After a number of studies done on knockout mouse models, researchers have hypothesized that SIRT6 may be fostering base excision repair. Even though more experimental evidence is still required before one could make more definitive conclusions but a few likely explanations of the mechanisms have been posited. One possibility is that SIRT6 may be regulating chromatin in a way to increase DNA accessibility to factors that lead to base excision repair. Another possibility is that increased levels of SIRT6 may be associated with decreased oxidative stress. This may be due to the role SIRT6 holds in the activation of PARP1 [29].

Double strand DNA break repair: There is also some evidence that limns the role of SIRT6 in Double strand DNA break repair. Increased levels of SIRT6 has been associated with improved homologous recombination and non-homologous end joining. In addition, some SIRT6 activities such as deacetylation and mono-ADP-ribosylation are required in the DNA repair process. The interaction that SIRT6 has with PARP1 not only plays a role in base excision repair but double strand repair as well. Evidence suggests that this interaction is only significant when there is oxidative stress involved in the case of double strand repair [50]. Studies involving SIRT6 substrate CtIP [C-terminal binding protein (CtBP) interacting protein] have revealed that SIRT6 loss is associated with accumulation of DNA damage, reduced rates of homologous recombination and increased cell exposure to agents that induce double strand breaks [65,66]. Moreover, SIRT6 has been observed to interact with SNF2H (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin) in order to facilitate the expression of SNF2H in double strand DNA damage sites. Both in vitro and in vivo evidence suggests

that SIRT6 histone deacetylation and the interaction with SNF2H both play a crucial role in DNA damage repair mechanisms [67]. A list of identified substrates of SIRT6 is shown on Table 1.

Table 1. A few substrates of SIRT6 and their linked functions in cell related to aging (adapted from reference 68)

Substrate	Linked functions in cell
H3K9ac	Regulation of transcription, stability of telomeres, response to DNA damage
H3K56ac	Regulation of transcription, stability of telomeres, response to DNA damage
H3K18ac	Silencing of heterochromatin
NPM1	Cellular Senescence
PARP1	DNA double-strand break repair and base-excision repair
KAP1	DNA double-strand break repair

Aging and Life expectancy: Only very recently, studies involving transgenic mice revealed the role the SIRT6 plays in life expectancy [69-75]. Particularly in male transgenic mice, an overexpression of SIRT6 was correlated with a 15% increase in life expectancy. A potential explanation for this phenomena was the reduction in insulin-like growth factor signaling in adipose tissue [69]. Stress granules (SGs), which are RNA/protein complexes that are formed in response to stress on the cell, are important in prolonging life and are usually impaired with age and aging related processes. Studies have shown that SIRT6 may localize to SGs in the cytoplasm in response to stress and aid in recovery from said stress that may arise from oxidative damage, heat shock or deprivation of nutrients [76,77]. Therefore a loss of SIRT6 may be associated with the disruption of these SGs and the acceleration of aging related processes. In addition to its role as a histone deacetylase, it would not be entirely implausible for SIRT6 to be a cytoplasmic regulator of SGs thereby affecting life expectancy. This, is conjunction with its linked roles in metabolism, heart disease, genetic stability and cancer may make SIRT6 crucial player in human aging [78-81].

3. SIRT6 in glucose metabolism and diabetes

Diabetes is a major human disease that is characterized by irregularities in glucose regulation and SIRT6 has been demonstrated to be a principal regulator of glucose homeostasis. Diabetes is often caused by β-cell dysfunction and recent studies have shown that SIRT6 may be important in glucose stimulated insulin secretion from these pancreatic β cells and SIRT6 may help in improving insulin secretion in diabetics [82]. In knockout mouse models, mice that are deficient in SIRT6 tend to show extreme hypoglycemia, which causes premature death [16]. When inspecting the cause of this phenotype, the primordial causes such as intestinal glucose uptake or increased secretion in the kidneys were overshadowed by an increase in uptake in adipose and muscle tissue. Moreover, in vitro and in vivo studies with multiple cell models have revealed that this increase in uptake of glucose may specifically be related to SIRT6 deficiency [83].

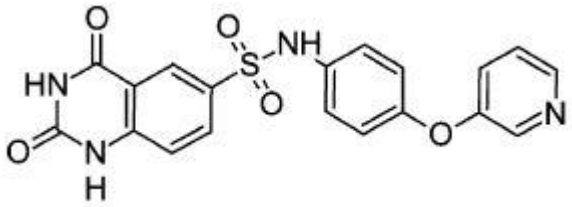
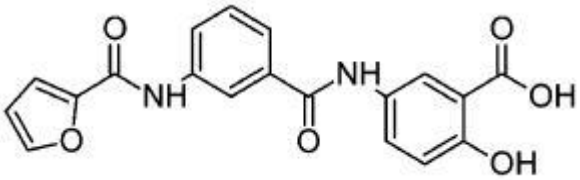
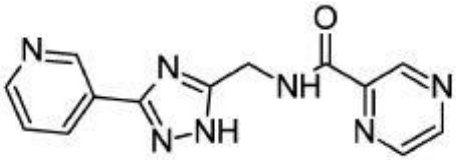
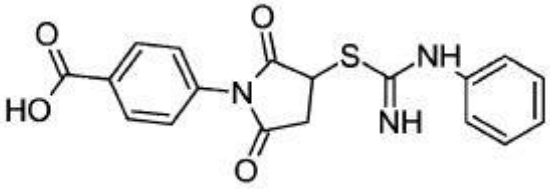
SIRT6 in glycolysis and the suppression of glucose-metabolic genes: Since this type of glucose uptake falls on the domain of irregularity, it is necessary to inspect why this is so. To be specific, SIRT6 is responsible for suppressing a few genes that can be characterized as glucose-metabolic by interacting with HIF1α (hypoxia inducible factor-1α) target genes. These glucose-metabolic genes were lactate dehydrogenase (LDH), pyruvate dehydrogenase kinase 1 (PDK1), and glucose transporter-1 (GLUT-1). HIF1α has a key role in this suppression process since it is known to coordinate several genes that activate processes such as glycolysis [83]. Under nutrient stressed conditions or hypoxia, glycolysis plays an important part by taking over the metabolic role.

Therefore, researchers have concluded reasonably that SIRT6, a negative regulator of enhanced glycolysis, is responsible for the repression of HIF1α and eventually leads to a decrease in cellular glucose uptake [84].

SIRT6 in gluconeogenesis: Researchers have also limned the role SIRT6 plays with regards to expression of gluconeogenesis genes. Studies show that these expressions were higher in livers that were deficient in SIRT6. This posits the theory that the liver may be trying to compensate for the onset of hypoglycemia that results from this lower expression of SIRT6 [85]. Peroxisome proliferator-activated receptor-α coactivator 1α (PGC-1α), is a principal regulator that is responsible for stimulating gluconeogenesis in the liver. It does so by increasing the level of gluconeogenesis enzymes that leads to more glucose uptake in the cells. The interaction between SIRT6, PGC-1α and a protein named general control non-repressed protein 5 (GCN5) leads SIRT6 to reduce the amount of glucose production. Conversely, a lower expression of SIRT6 leads to higher amount of glucose production [86]. In another study, wild type mice were compared to liver specified Forkhead box O1 (FOXO1) knockout mice with respect to SIRT6 and it was observed that the overexpression of SIRT6 reduced gluconeogenesis expression in the wild type but not in the FOXO1 mice. Hence, researchers posited the theory that SIRT6 is responsible for regulating gluconeogenesis in the liver by modulating both PGC-1α and FOXO1 even though more research has to be done to further clarify the issue [87].

Pharmacological intervention with small molecule SIRT6 inhibitors: Since the involvement of SIRT6 holds such promise, researchers are in the process of identifying SIRT6 targeted therapeutic agents that may have a wide range of uses in diabetes as well as several other diseases. Table 2 shows a few relatively new SIRT6 inhibitors and their corresponding Asinex IDs that have shown some marked inhibition of SIRT6 [88]. In 2017, Sociali et al. studied the pharmacological effects of one of these compounds namely, 2,4-dioxo-N-(4-(pyridin-3-yloxy)phenyl)-1,2,3,4- tetrahydroquinazoline-6-sulfonamide (Asinex ID SYN17739303 in Table 2) on a mouse model for type 2 diabetes mellitus. The mice were 6-weeks old and were fed a high-fat diet. This compound was administered for 10 days and results indicated an improvement in glucose regulation via oral glucose tolerance test (OGTT) leading the researchers to conclude that small molecule inhibitors of SIRT6 may be a functional strategy in the improvement of glycemic control for type 2 diabetics. In addition to these positive findings, there was also a notable increase in glucose transporters as well as reduced levels of insulin, triglycerides and cholesterol observed in the same study possibly paving way for small molecule inhibition of SIRT6 for other diseases as well [89].

Table 2. Small molecule SIRT6 inhibitors (as reported by Parenti et al.)

Asinex ID	Compound Structure	Percentage inhibition of SIRT6 at 200 μM concentration of the compound
SYN17739303		100±4
BAS13555470		62±7
SYN10366754		12±3
BAS00417531		66±6

4. SIRT6 in heart disease

Researchers have also identified results that limn the importance of SIRT6 in cardiac failure and hypertrophy. Nicotinamide adenine dinucleotide (NAD) dependent deacetylases are critical in case of hypertrophy in cardiomyocytes [90]. In 2012, Cai *et al.* discovered that Nicotinamide mononucleotide adenylyltransferase 2 (Nmnat2) is a key enzyme in NAD biosynthetic pathway and its activity and protein expression were reduced in the case of cardiac hypertrophy. Thus, angiotensin II (Ang II) induced cardiac hypertrophy was seen to be reduced when Nmnat2 was overexpressed in mouse models. There was a positive correlation observed when the relative SIRT6 activity (protein expression and enzyme activity) was measured with regards to cardiomyocytes that were transfected with Nmnat2 over time. Therefore, it becomes reasonable to conclude that the activation of SIRT6 in Ang-II induced hypertrophy may have been related to Nmnat2 expression and SIRT6 in this case acts as a negative regulator in the case of cardiac hypertrophy. The fact that SIRT6 is a negative regulator of cardiac hypertrophy is further demonstrated in another study where SIRT6 deficient mice were compared to SIRT6 transgenic mice and the latter showed attenuated cardiac hypertrophy. In this

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particular study, it is shown that SIRT6 directly inhibits IGF signaling and inhibition of IGF signaling leads to a reduced rate of cardiac hypertrophy and vice versa [91]. This is illustrated below in Figure 3.

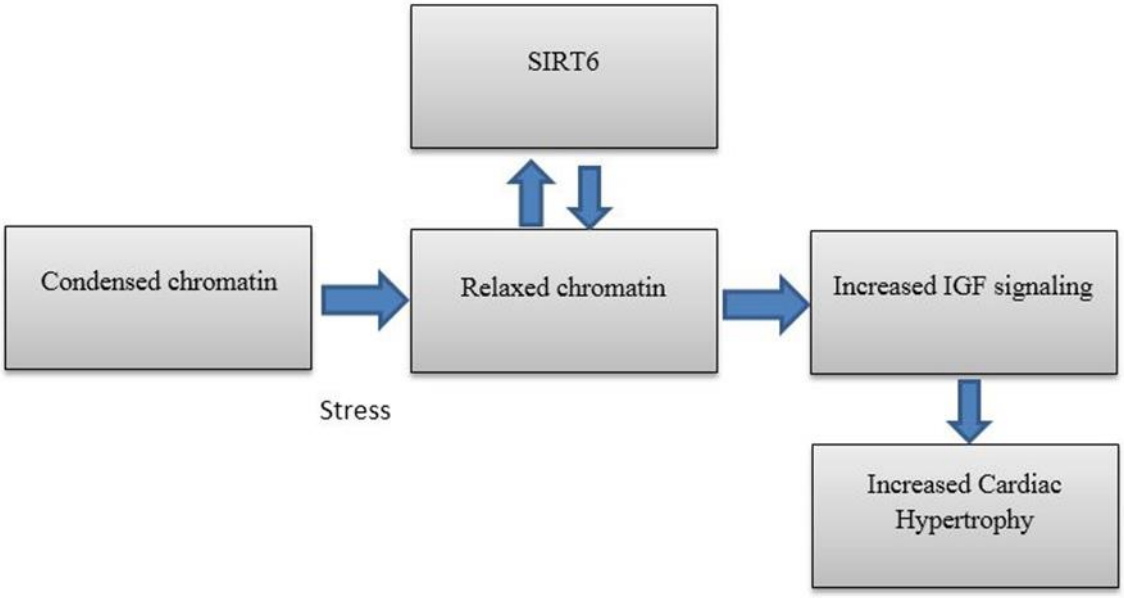

Figure 3. During normal function, SIRT6 is responsible for inhibiting the expression of IGF signaling genes. Under stressed conditions however, SIRT6 in cardiac tissue is reduced leading to an increase in IGF signaling and an increase in cardiac hypertrophy and multiple complications [adapted from reference 91]

More recently, in 2016, Lu *et al.* demonstrated the importance of SIRT6 in case of cardiac hypertrophy when they tested the autophagy activity of cardiomyocytes under isoproterenol treatment. Since reduced autophagy is been seen to contribute towards the pathogenesis of cardiac hypertrophy, it was demonstrated in this study that the increase in levels of SIRT6 lead to an enhanced autophagy of cardiomyocytes. SIRT6 was shown to have protective effects against cardiac hypertrophy with the onset of autophagy possibly by promoting the transcription factor FOXO1 (also plays a role in gluconeogenesis, as mentioned before) [92]. From the data currently available, it would seem that Nmnat2 manipulation, IGF signaling modulation and cellular autophagy targeting may be useful in targeting SIRT6 for future drugs in order to treat cardiac hypertrophy.

5. SIRT6 and cancer

Considering the wide range of processes that SIRT6 seems to be potentially involved in, it comes as no surprise that it may also be linked to cancer progression and tumor growth.

Tumor growth resulting from altered glycolysis: In terms of cell proliferation, tumor cells have specific and often exceptional metabolic requirements that are necessary for cell division and growth. In order to proliferate, nutrient uptake of these cells in a cell-autonomous fashion and re-organization of certain pathways (specifically, metabolic pathways) may be necessary to engender the biosynthesis of macromolecules that are required for this process [93]. One of the best possible explanations of this re-organization of metabolic pathways was given by Otto Warburg in 1927 by positing the Warburg effect [94]. Warburg observed that the enhancement of glycolysis under the presence of excess oxygen (aerobic condition) was responsible for this reprogramming of cancer cells. At this point it is worthwhile to come back to the modulation of HIF1α by SIRT6; as mentioned earlier, the activation of HIF1α (that corresponds to a deficiency in SIRT6), a transcription factor, may lead to enhanced

glycolysis and an increase in the uptake of glucose in the cell [83]. This phenomena is analogous to that of enhanced glycolysis that takes place in tumor cells. The study of this phenomena in mouse embryonic fibroblast cell lines showed that tumor growth was possible without the activation of oncogenes and only under enhanced glycolysis [84]. *In vivo* studies further corroborated this fact when genetic analysis and fluorodeoxyglucose positron emission tomography (FDG-PET) with SIRT6 deficient knockout mouse models revealed that the mice were three times as prone to acquire adenomas compared to wild-type mice When comparing mouse models for colorectal carcinomas and pancreatic ductal adenocarcinomas with wild type mice, it was seen that the HIF1α target genes i.e. LDH, GLUT1, and Phosphofructokinase-1 (PFK1) were noticeably unregulated. Consistent inferences were made when studying the survival rates of colorectal cancer as well. SIRT6 deficient mice were three times more likely to relapse in cancer progression compared to mice that showed high levels of SIRT6. All of these results taken together demonstrate the importance of SIRT6 in tumor progression [84, 95-99]. An important avenue for treatment was explored when the administration of dichloroacetate (DCA) was seen to slow down tumor formation of these SIRT6 deficient mice by inhibiting PDK1 which is also a key target gene for HIF1α [84].

SIRT6 and the initiation of hepatic cancer: *In vivo* studies have also revealed the importance of up-regulation of SIRT6 at the early stages of hepatic cancer. In this case the primary focus was c-JUN and c-FOS, which are the components of the transcription factor AP-1 [100,101]. From a mechanistic standpoint, c-JUN and c-FOS are responsible for increasing levels of SIRT6 expression and then SIRT6 in turn represses the activity of BIRC5 (also known as survivin). In other words, SIRT6 is a negative regulator of BIRC5. Targeting BIRC5's anti-apoptotic activity may be used to slow down cancer development at the early stages of hepatic cancer. A very interesting development in this case was the identification of the regulation pattern between c-JUN, c-FOS, SIRT6 and BIRC5 in dysplastic liver nodules. Even though further studies may be warranted in this case, this pivotal knowledge about SIRT6 up-regulation may prove to be very useful when combating tumorigenesis in the liver or premalignant liver lesions at the early stages of cancer development. However, unfortunately, this pathway does not function at advanced stages of hepato-cellular carcinoma [100].

Aberrant behavior of SIRT6 in other forms of cancer: In the aforementioned cancers, a trend was seen that the up-regulation of SIRT6 was associated with generally beneficial effects. However, this is not the case for all forms of cancers across the board. In the case of squamous cell carcinoma, *in vitro* and *in vivo* studies have demonstrated that high levels of SIRT6 are expressed because of the down-regulation of RNA-34a (miR-34a) [101]. In another study, with chronic lymphocytic leukemia (CLL) patients, it was discovered that the patients exhibited four times as high levels of SIRT6 compared to control groups leading the researchers to conclude that the overexpression of SIRT6 may be associated with poor prognosis for CLL patients [102].

The study of SIRT6 in relation to cancer raises more questions than actual answers; questions that researchers have to work diligently to attempt to answer in the future. Unfortunately at this stage, it is difficult to make definitive conclusions about the extent of insolvent of SIRT6 on cancer progression and tumor growth. It is especially interesting that overexpression of SIRT6 may offer benefits by protecting against genomic instability in some cases but also may act as an oncogene in some other cases or it may be doing both in all of the cases. Regardless, the role of SIRT6 in caner still remains highly nebulous.

6. SIRT6 in neurodegenerative diseases and brain aging

More recently, SIRT6 has also been shown to have implications in brain aging and major neurodegenerative diseases such as Alzheimer's disease (AD). In a recent study, cellular localizations were studied in the cerebral cortex and hippocampus of 24 month old mice and 3 month old mice and it was observed that SIRT6 expression was lower in the older mice [103,104]. In 2016, Jung *et al.* reported two critical observations that demonstrated its role in AD patients. The group observed

these findings in three different *in vitro* and *in vivo* models namely, HT22 mouse hippocampal neurons, brains of AD patients and brains of 5XFAD AD mice. The first critical observation was that Aβ42, which is a significant component of aged plaques, were inducing DNA damage that would otherwise be prevented in the HT22 mice by an overexpression of SIRT6. The second observation was that Aβ42 decreased SIRT6 expression overall in all of the three models [105]. In 2017, Kaluski *et al*. showed that severely reduced levels of SIRT6 may incite neurodegeneration of Alzheimer's patients by promoting DNA damage, cell death and hyper phosphorylation of tau proteins which are abundant in the central nervous system and neurons [106]. All of this put together shows that there may be a strong link between SIRT6 and neurodegenerative diseases. In a study published as recently as 2017 in *Neuroscience,* studies on SIRT6 showed that it may be responsible for protecting the brain from cerebrovascular ischemia and may be identified as a potential therapeutic target for ischemic stroke [107]. It is obvious that more research in this area is warranted for now it may be reasonable to infer that SIRT6 may be of paramount interest in neuroscience in the near future.

7. Advances made with SIRT6 in other areas

In addition to glucose metabolism, cancer, and aging related processes, SIRT6 has also been shown to be a negative regulator of triglyceride synthesis and affect liver disease. Its deficiency has resulted in the accumulation of triglycerides that may lead to fatty liver [108]. Recent studies have also demonstrated the importance of SIRT6 in cholesterol homeostasis by studying its regulation patterns with respect to the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene. In this case, knockout mouse models have shown that PCSK9 deficient mice exhibited lower levels of LDL that correspond to an overexpression of SIRT6 [109]. SIRT6 has also been shown to have pro-inflammatory and anti-inflammatory roles depending on the type of cell that is involved [110,111]. Sugatani et al. in Bone demonstrated that SIRT6 deficient mice also showed characteristics of osteopenia leading the researchers to conclude that molecular mechanisms of SIRT6 in the case of bones could lead to potential therapeutic targets that could reverse age related bone loss [112]. These are just a few examples of the numerous roles SIRT6 may play in different processes and it would seem that there is still significant work to be done in this area.

8. Conclusions

It is clear that with the emergence of all of these new studies on SIRT6, it has managed to pique the curiosity of a number of researchers in the biomedical sciences. The role of SIRT6 as a regulator or even a nutrient detector in cells has diversified its impact on aging related processes and major human diseases such as cancer, diabetes, neurodegenerative diseases and heart disease. SIRT6 has been shown to be involved in gene expression in the nucleus with regards to chromatin and more recently has also been shown to take part SG formation in the cytosol. For now, it would seem that the pleiotropic effects of SIRT6 is clear, however, the extent of involvement in each individual process still remains hazy. The variegated roles of SIRT6 may expand even further beyond that which is currently known but only time will reveal its true effects on human biology and various diseases. Even its implications in neuroscience could lead to potential solutions to long-standing problems such as Alzheimer's disease. Evidently, SIRT6 needs to be studied further; more time and resources are mandated in order to understand and identify potential therapeutic targets in processes such as glycolysis, glycolysis, tumorigenesis, osteoblastogenesis and so on. More studies on SIRT6 may possibly eventuate strong therapeutic targets and it may be possible to use rational drug design in order to alleviate or possibly even cure some primordial diseases that have proven hard to eliminate.

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