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Overview

Sirtuins in tumorigenesis

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Abstract

Sirtuins (SIRT) are group of enzymes that require nicotinamide adenine dinucleotide (NAD+) to catalyze their reactions. These chemical compounds have mono (ADP-ribosyl) transferase or deacetylases activities, and they can be found in nearly all species. The mammalian sirtuin family is described by seven proteins, namely. Every group of sirtuins can be found in the different regions of the cells; SIRT1 is predominantly nuclear, SIRT2 is located mainly in the cytoplasm (but it can shuttle between the nucleus and the cytoplasm), SIRT3, SIRT4, and SIRT5 are mitochondrial proteins, (SIRT3 can move from the nucleus to mitochondria during cellular stress), SIRT6 and SIRT7 are nuclear sirtuins. Sirtuins have a lot of functions in different physiological processes such as gene repression, metabolic control, apoptosis and cell survival, DNA repair, development, inflammation, neuroprotection, and healthy aging. Because of so many roles in physiological processes there is a huge interest not just in their functions but also in the different compounds which can modify their functions. In this article we will focus on the role of sirtuins in tumorigenesis.

Abbreviatians:
SIRT – sirtuins
NAD – nicotinamide
ADP – adenosine diphosphate
SNPs – single nucleotide polymorphisms
HDACs – histone deacetylases
BMI – body mass index
IDH2 – isocitrate dehydrogenase 2
GDH – glutamate dehydrogenase
MnSOD – manganese superoxide dismutase
VNTR – variable number tandem repeat
TNF-α – tumor necrosis factor – alfa
HIC1 – hypermethylated in cancer 1
FOXO 1 – Forkhead Box 1
FOXO 3 – Forkhead Box 3
Cdh1 – cadherin-1
Cdc20 – cell-division cycle protein 20
NEDD4 – neural precursor cell expressed developmentally down-regulated protein 4
AML – acute myeloid leukemia
ROS – reactive oxygen species
SOD2 – superoxide dismutase
ETC – electron transport chain
Skp2-S – phase kinase associated protein 2

INTRODUCTION

Each sirtuin is characterized by approximately 275 amino acid conserved catalytic core region and by unique additional N-terminal and/or C-terminal sequences of variable length *(1)*. Sirtuins are also known as class III histone deacetylases (HDACs), but their NAD+-dependency distinguishes them from other HDACs classes *(2, 3)*.

The main sirtuin structure is characterized by a large Rossman-fold domain (small part of compounds that is typical for NAD+ binding proteins), a small zinc-binding domain, and a number of flexible loops *(4)*. The large Rossmann-fold domain is characterized by six parallel β-strands and a different number of β-helices, depending on the type of sirtuin. Zinc-binding domain is characterized by the three antiparallel β-sheets, a variable β-helical region and a Zn^{2+}cation *(5)*. One of the most flexible regions of sirtuins is cofactor binding loop that connects the large and the small domain of enzyme *(6, 7)*. This loop conformation is dependent of the NAD+ or other reaction intermediates presence (the most important is 2-O-acetyl-ADP-ribose) *(8)*.

OVERVIEW OF SIRTUINS FUNCTIONS

Different roles of sirtuins have been described in a great number of physiological or pathological conditions. Some of them are metabolism, aging, circadian clock regulation, pathophysiology of cancer, different inflammatory conditions, nutritional behavior and obesity *(5, 9)*. However, different types of sirtuins have different physiological function in the human body (Figure 1).

A recent study has reported associations of SIRT1 single nucleotide polymorphisms (SNPs) to the both obesity and body mass index (BMI) *(10)*. SIRT1 is linked to the mitochondrial biogenesis in some tissues. It also stimulates fat and cholesterol catabolism in liver, skeletal muscle, and adipose tissue.

Some recent studies have shown impaired regulation of SIRT2 in glioma. SIRT2 deletion can cause tumor occurrence; to the contrary its repletion may be used as a tumor suppressive therapy *(11)*. SIRT2-deficient mice develop gender-specific tumorigenesis; mammary tumor in females and hepatocellular carcinoma in males *(12)*. SIRT3 is presented in both mitochondria and nucleus. It has main role in cellular energy metabolism and redox regulation by deacetylating some mitochondrial proteins such as acetyl-coenzyme A synthetase 2, isocitrate dehydrogenase 2 (IDH2), glutamate dehydrogenase (GDH), manganese superoxide dismutase (MnSOD*) (13)*. This sirtuin is the only one for which the correlation between a polymorphism and prolonged human life has been proven (*12*).

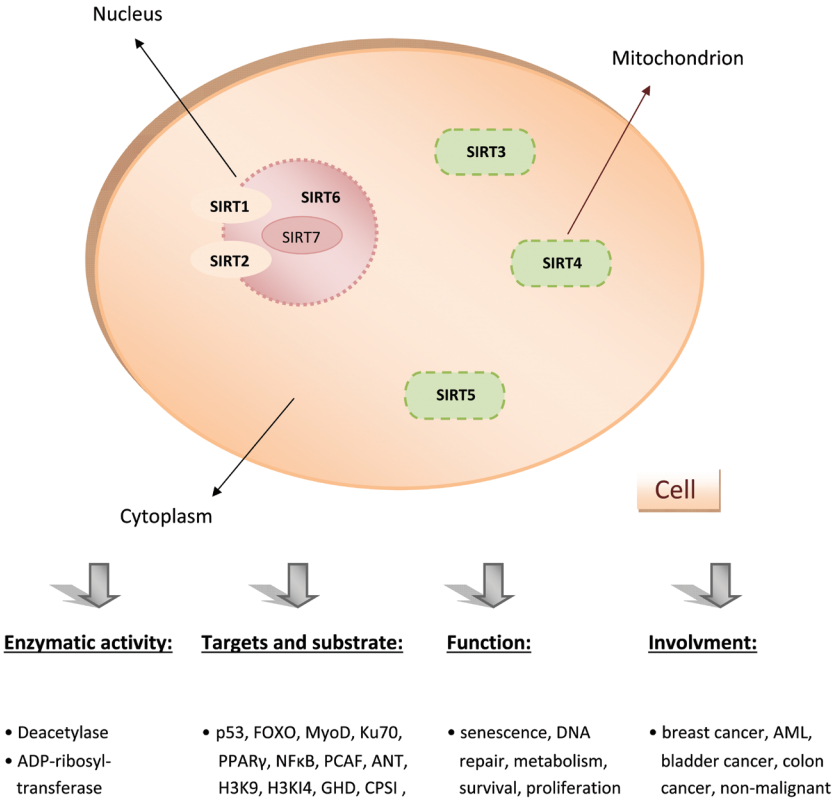

Figure 1. *Location of the sirtuins in the cell. Their enzymatic activity, targets and substrates, function and involvment in various tumors are listed.*

It is known that a VNTR polymorphism in intron 5 of the SIRT3 gene has an allele-specific enhancer activity. The allele which has not enhancer activity is almost absent in males older than 90 years *(14)*.

SIRT4 is localized in mitochondria and has a role in the regulation of cellular metabolic functions like insulin secretion and fatty acid oxidation *(15, 16)*. Some research has shown that SIRT4-depleted mice develop hyperinsulinemia and lung carcinoma *(15, 17)*. SIRT5 is also mitochondrial sirtuin just like SIRT3 and SIRT 4.

Study of Nakagawa et al has shown that SIRT5-null mice can develop urea cycle defect and hyperammonemia after fasting *(18)*.

SIRT6 is localized to the nucleus and has both deacetylase and ADP-ribosyltransferase activity. SIRT6 has been shown to have a function in the regulation of transcription, genome stability, TNF-α secretion, metabolism and life expectancy *(19)*. SIRT6 deficient mice die around 1 month after birth, showing premature aging phenotypes, hypoglycemia, cardiac hypertrophy, hypersensitivity to DNA damage, and genomic instability *(19)*.

SIRT7 is the only sirtuin localized to the nucleolus and it is linked to the ribosome biogenesis by the regulation of transcription by positive regulation of RNA polymerase I transcription *(20)*. SIRT7 deficiency induces apoptosis in human cells what indicates SIRT7 importance in cell survival. The results of some recent studies have shown that SIRT7-deficient mice die around 1 year after birth, and develop inflammatory cardiomyopathy *(21)*.

SIRTUINS AND TUMORIGENESIS

Sirtuins require special attention in cancer research because of their biological role in metabolism, cell death, regulation of genomic stability, inflammation and cellular proliferation. Various studies have shown that studying sirtuins can contribute to answering the question about the connection between tumor development and aging.

SIRTUIN 1 AND TUMORIGENESIS

Sirtuin 1 (SIRT1) has a dual role in the development of tumors as a tumor suppressor or promoter depending on the type of tumor and the spatial distribution of SIRT1 upstream and downstream factors (Figure 1).

SIRT1 participates in the development and progression of tumors through deacetylation causing inhibition of the function of the tumor suppressor p53, p73, and gene hypermethylated in cancer 1 (HIC1) *(17-19)*. During aging reduction of HIC1 promoter hypermethylation occurs as well as an increase of SIRT1 content. Both processes increase cell survival and tumor development *(19)*. SIRT1 promotes cell migration by direct interaction with cortactin *(22)* and promotes the expression of multidrug resistance – associated protein 2*(23)*. Additionally, SIRT1 promotes chemoresistance of tamoxifen – resistant breast cancer cells by deacetylating FOXO1 *(23)*. Increased expression of SIRT1 in advanced prostate cancer promotes cell invasion, migration and metastasis through matrix metalloproteinase -2 *(24)*. A study of SIRT 1 in colorectal cancer showed a correlation with increased expression of c – Myc *(25)*. SIRT1 is increased in breast carcinoma *(26)*, colon cancer *(27)*, lung cancer *(28)*, prostate cancer *(29)*, thyroid cancer *(30)*, gastric cancer *(31)*, liver cancer *(32)*, pancreatic cancer *(33)*, ovarian and cervical cancers *(34)*.

On the other hand SIRT1 can prevent tumor growth through mechanisms of genomic protection by enabling protection from stress, DNA reparation mechanism and regulation of metabolism. In addition, tumor cells themselves can prevent and control innate and adaptive immune responses through inactivation of NF – ϰB transcription factor and reduction of surviving *(35, 36)*. SIRT1 expression is reduced in human head and neck squamous cell carcinoma and is associated with poor prognosis in patients with this type of carcinoma *(37)*. It has been shown that inhibition of SIRT1 blocks p53-dependent apoptosis and DNA damage signaling which favors the growth of tumors. Further studies are needed in order to clarify the different roles of SIRT1 in tumor development.

SIRTUIN 2 AND TUMORIGENESIS

In tumorigenesis, sirtuin 2 (SIRT2) can have the function of a promoter or a suppressor according to the type of tumor. SIRT2 functions as a tumor suppressor through the deacetylation of its substrates, such as FOXO1 (Forkhead Box 1)*(38)*, FOXO 3a (Forkhead Box 3) *(39)*, Cdh1 *(12)*, Cdc20 *(12)*, H3K56 *(40)*, or H4K16 *(41)*. These are important molecules that maintain cell cycles, replication, and DNA damage response. Several studies have shown that SIRT2 may function as a tumor suppressor by maintaining mitotic integrity in a cell *(11)*. It was shown that the expression of SIRT2 is down-regulated in breast cancer *(41)*, head and neck squamous cell carcinoma*(37)*, gliomas *(11)* and esophageal adenocarcinoma. The deficiency of SIRT2 increases the levels of mitotic regulators such as Aurora A and Aurora B *(12)*.

There are also some opposite data suggesting that SIRT2 may have tumor-promoter characteristics. It was observed that the expression of SIRT2 was increased in acute myeloid leukemia *(42)*, neuroblastoma cells, pancreatic cancer cells *(43)*, and hepatocellular carcinoma *(44)*. It is upregulated in pancreatic cancer cells by c-MYC and in neuroblastoma cells by N-MYC. SIRT2 stabilizes N-MYC and c-MYC protein by downregulation of ubiquitin-protein ligase NEDD4 expression. In AML cells SIRT2 and NAD+ salvage enzyme nicotinamide phosphoribosyl transferase are upregulated and included in the abnormal proliferation and survival of leukemic cells.

SIRTUIN 3 AND TUMORIGENESIS

Metabolic transformation is one of the major characteristics of tumor.

It has been shown that knock-out mitochondrial-derived Sirtuin 3 (SIRT3) increases spontaneous tumorigenesis in mammary glands, indicating a role of SIRT3 as a tumor suppressor *(45)*. SIRT3 participates in mitochondrial metabolism, counteracts oxidative stress, defends cells against apoptosis and prevents cell ageing and tumor formation.

Several studies have shown that under conditions of stress SIRT3 regulates ROS homeostasis through deacetylating and activating superoxide dismutase (SOD2) *(46, 47)*. Reduced expression of SIRT3 leads to increased production of ROS by reducing activity of SOD2 or increasing leakage of electrons in the electron transport chain (ETC), which promotes genomic instability and the development of tumors *(45)*. Some studies have shown that lack of SIRT3 increased glycolytic metabolism by enhancing the stability of HIF1α *(48)*.

Moreover SIRT3 inhibits tumorigenesis by deacetylating and inactivating S – phase kinase associated protein 2 (Skp2), a subunit of the E3 ubiquitin kinases that are important in the S phase of the cell cycle *(49)*. Accordingly SIRT3 is reduced in human breast cancers, hepatocellular carcinoma, and head and neck squamous cell carcinoma *(50)*. Further studies are needed in order to explain the possible role of SIRT3 in therapeutic procedures.

SIRUINT 4 AND TUMORIGENESIS

The role of Sirtuin 4 (SIRT4) has not yet been elucidated, but recent studies have shown that it may have a role as a tumor suppressor *(17, 51)*.

Expression of protein SIRT4 is decreased in human gastric, ovarian, bladder, and breast carcinoma compared to normal tissue. Increased content of SIRT4 reduces transformation and cell proliferation *(51)*. Some other studies have shown that a lack of SIRT4 leads to increased glutamine – dependent cell proliferation and genome instability caused by the stress resulting in tumorigenesis *(17)*. SIRT4 knock-out mice were shown to have increased spontaneous lung tumors compared to wild-type mice *(17)*. Future research should show the significance of SIRT4 expression in various cancers, and the significance of its interaction with glutamine.

SIRTUIN 5 AND TUMORIGENESIS

The role of Sirtuin 5 (SIRT5) in the development of cancer is not known.

SIRTUIN 6 AND TUMORIGENESIS

Some studies have shown that Sirtuin 6 (SIRT6) may have a tumor suppressor function through reduction of Myc and HIF1α transcriptional activity *(52)*.

Expression of SIRT6 is reduced in human pancreatic cancer and colon carcinoma. Some studies have shown that SIRT6 can suppress the initiation of liver cancer through reduction of survivin expression by deacetylation of H3K9 *(52)*.

Additionally, SIRT 6 reduces the activity of NF–kB *(53)*. SIRT6 also participates as a tumor suppressor in breast cancer by regulating DNA repair and metabolism.

Some studies have shown that SIRT6 can increase the secretion of cytokines in cancer and produce an increase in angiogenesis through regulation of Ca^{2+} responses or deacetylation of TNFα *(54)*.

Increased expression of SIRT6 can increase resistance to chemotherapy such as paclitaxel and epirubicin by inhibiting FOXO 3a activity *(55)*.

These data suggest multiple mechanisms by which SIRT6 exerts its effects in cancer cells. Future studies should investigate the biological effects and molecular mechanisms of SIRT6 in individual tumors.

SIRTUIN 7 AND TUMORIGENESIS

Biological role of Sirtuin 7 (SIRT7) in tumors is not fully explained.

Previous results have shown that SIRT7 can be oncogene, activating oncogenes capacity of cancer cells such as loss of contact inhibition and anchorage -independent growth. Lack of SIRT 7 reduces tumor potential of cancer cells *(56)*. Recent research has shown an increase of SIRT7 in hepatocellular carcinoma and that deletion of SIRT7 may cause suppression of cell growth *(57)*.

Further studies should investigate the molecular mechanisms of SIRT7 activities in cancer.

CONCLUSIONS

Sirtuins play a significant role in inflammation, metabolism, cellular proliferation, regulation of genomic stability, and cell death. Based on their involvement in these processes sirtuins are involved in cancer pathophysiology. It became clear that sirtuins can help to address the question on the molecular relationship between the tumor and aging. Future research is needed in order to determine the molecular mechanism of action of each sirtuin in cancer and the possible role of sirtuins in cancer therapy.

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