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Gene Section
Review

SIRT1 (sirtuin (silent mating type information regulation 2 homolog) 1 (S. cerevisiae))

WenYong Chen

Department of Cancer Biology, Beckman Research Institute, City of Hope, Duarte, CA 91010, USA

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Abstract

SIRT1 is a member of the mammalian sirtuin genes that encode for seven protein lysine modifiers with deacetylase, ADP-ribosyltransferase and other deacylase activities. SIRT1 plays diverse roles in regulating cell proliferation, differentiation, stress response, metabolism, energy homeostasis, aging and cancer. Besides deacetylating histone substrates, SIRT1 regulates functions of an array of non-histone proteins including transcriptional factors for gene regulation, DNA repair machinery elements for reducing catastrophic genome lesions, epigenetic factors for chromatin and gene regulation, nuclear receptors and circadian clock as well as related factors for metabolism, and other cell signaling molecules. SIRT1 is involved in many types of human cancer.

Identity

Other names: EC 3.5.1, hSIR2, hSIRT1, SIR2alpha, SIR2L1

HGNC (Hugo): SIRT1

Location: 10q21.3

DNA/RNA

Description

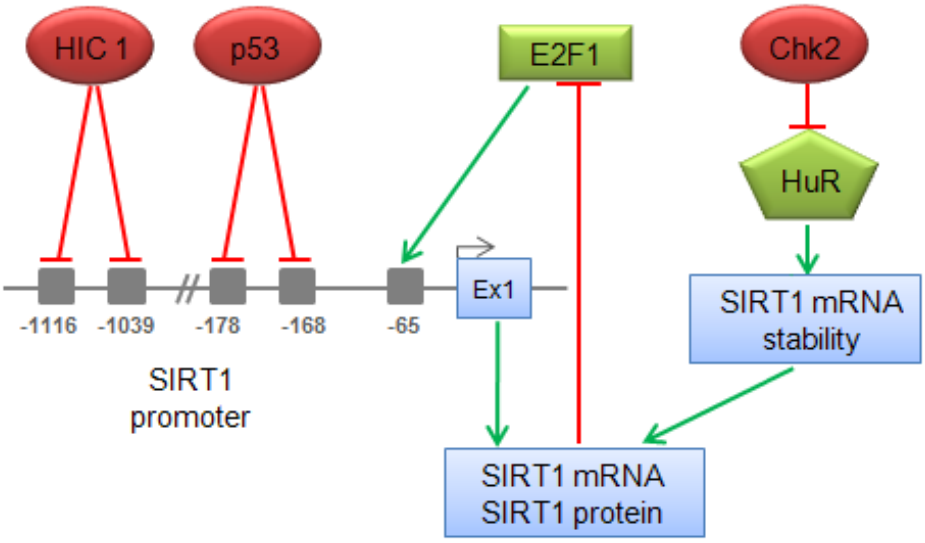
The SIRT1 gene spans about 34 kb including nine exons. The SIRT1 promoter contains a CCAAT box and a number of NF-kappaB and GATA transcription factor binding sites in addition to a small 350-bp CpG island in the 5' flanking genomic region.

The gene encodes a 747 amino acids protein with a predictive molecular weight of 81.7 kDa and an isoelectric point of 4.55 (Alcaín and Villalba, 2009).

Transcription

SIRT1 transcription is under the control of at least two negative feedback loops that keep its induction tightly regulated under conditions of oxidative stress.

SIRT1 promoter can be regulated by E2F1 and HIC1 during cellular stress. E2F1 directly binds to the SIRT1 promoter at a consensus site located at bp position -65 and appears to regulate the basal expression level of SIRT1. Such high levels of SIRT1 lead to a negative feedback loop where E2F1 activity is inhibited by SIRT1-mediated deacetylation. By contrast, the tumor suppressor HIC1 and SIRT1 form a transcriptional repression complex that directly binds SIRT1 promoter and represses SIRT1 transcription thereby inhibiting SIRT1-mediated p53 deacetylation and inactivation. Two HIC1 binding sites have been assigned to base pair positions -1116 and -1039 within the SIRT1 promoter (Chen et al., 2005). In addition, two functional p53 binding sites (-178 bp and -168 bp), which normally repress SIRT1 expression, have been identified.



SIRT1 gene expression is modulated at both transcriptional and posttranscriptional levels.

Furthermore, SIRT1 transcription is upregulated by MYC that binds at SIRT1 promoter position -80 and by STAT5 that binds at positions -2235 and -1838 in response to BCR-ABL oncogenic stress (Yuan et al., 2012).
SIRT1 expression is also regulated at the posttranscriptional level by HuR. It has been demonstrated that HuR, a ubiquitously expressed RNA binding protein, associates with the 3' UTR of the SIRT1 mRNA under physiological conditions and helps to stabilize the transcript. This interaction results in increased SIRT1 mRNA stability and thus in elevated protein levels. Conversely, the HuR-SIRT1 mRNA complex is being disrupted upon oxidative stress, which finally leads to decreased mRNA stability and therefore decreased SIRT protein levels. In addition, several microRNA (miR) species negatively regulate SIRT1 mRNA by targeting its 3' UTR, including miR-34a and miR-200a (reviewed in Roth and Chen, 2014).

Pseudogene

None identified.

Protein

Description

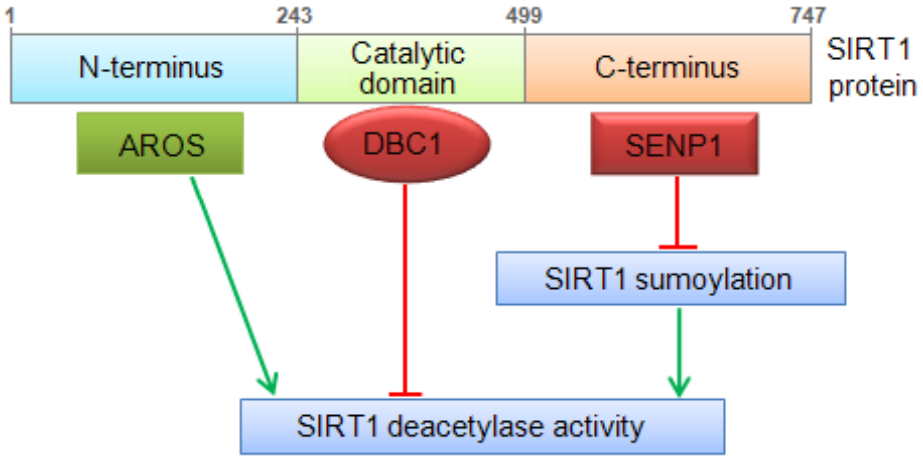
Human SIRT1 encodes 747 amino acids protein with a nuclear localization signal (NLS) at the N-terminus (aa 41-46) and a sirtuin homology domain at the center (aa 261-447); this domain is a conserved catalytic domain for deacetylation. The catalytic activity of SIRT1 is dependent on the cofactor nicotinamide adenine dinucleotide (NAD^+).

Expression

Expression appears to be ubiquitous in adult tissues

(although at different levels).

Two proteins have been identified to regulate the SIRT1 activity both positively and negatively through complex formation in the context of the cellular stress response.
The first identified direct regulator of SIRT1 was the active regulator of SIRT1 (AROS).
The AROS protein is known to significantly enhance the activity of SIRT1 on acetylated p53 both in vitro and in cell lines thereby promoting the inhibitory effect of SIRT1 on p53-mediated transcriptional activity of pro-apoptotic genes (e.g. Bax and p21Waf-1) under conditions of DNA-damage. A negative regulator of SIRT1, DBC-1 (deleted in breast cancer-1), has recently been identified. DBC1 binds directly to the catalytic domain of SIRT1, preventing substrate binding to SIRT1 and inhibiting SIRT1 activity.
Reduction of DBC1 inhibits p53-mediated apoptosis after induction of double-stranded DNA breaks owing to SIRT1-mediated p53 deacetylation. Both factors represent the first endogenous, direct regulators of SIRT1 function. SIRT1 activity is also regulated by cis-elements of its own peptides. The SIRT1 C-terminal region (aa 631-635) is a disordered domain, and it interacts with SIRT1 catalytic core domain by competing with DBC1 and activates SIRT1 activity (Kang et al., 2011). A small rigid region at the N-terminus (aa 190-244) of SIRT1 appears to mediates allosteric activators for the SIRT1 catalytic core function (Hubbard et al., 2013).
In addition, SIRT1 activity is subjected to regulation by other posttranslational modifications such as sumoylation, phosphorylation and methylation in response to stress signaling and cell cycle changes (reviewed in Wang and Chen, 2013).



SIRT1 deacetylase activity is modulated through protein-protein interaction and sumoylation at its three protein domains (Liu T et al., 2009).

As an NAD-dependent enzyme, SIRT1 activity is regulated by cellular NAD metabolism in which NAD salvage pathway enzyme nicotinamide phosphoribosyltransferase (NAMPT) is often co-activated with SIRT1 to maintain the deacetylase activity (Wang et al., 2011; Menssen et al., 2012).

Localisation

SIRT1 is predominately in the nucleus (although SIRT1 does have some important cytoplasmic functions as well). In addition to possessing two NLSs, SIRT1 contains two nuclear export signals. Thus, the exposure of nuclear localization signals versus nuclear export signals may dictate the cytosolic versus nuclear localization of SIRT1.

Function

SIRT1 has been reported to play a key role in a variety of physiological processes such as metabolism, neurogenesis and cell survival due to its ability to deacetylate both histone and numerous nonhistone substrates.

(1) Lysines 9 and 14 in the amino-terminal tail of histone H3 and lysine 16 of histone H4 are deacetylated by yeast Sir2 and mammalian SIRT1 (Sir2alpha).

(2) Metabolic homeostasis is controlled by SIRT1-mediated deacetylation and thus activation of the peroxisome proliferation activating receptor (PPAR)-gamma co-activator-1a (PGC-1a), which stimulates mitochondrial activity and subsequently increases glucose metabolism, which in turn improves insulin sensitivity. SIRT1 represses PPAR-gamma, a key regulator of adipogenesis, by docking with its cofactors NCoR (nuclear receptor co-repressor) and SMRT (silencing mediator of retinoid and thyroid hormone receptors). The upregulation of SIRT1 triggers lipolysis and loss of fat.

(3) The activation of SIRT1 appears to be neuroprotective in animal models for Alzheimer's disease and amyotrophic lateral sclerosis as well as optic neuritis mainly due to decreased deacetylation of the tumor suppressor p53 and PGC-1a.

(4) SIRT1 represses p53-dependent apoptosis in response to DNA damage and oxidative stress and promotes cell survival under cellular stress induced by etoposide treatment or irradiation.

(5) SIRT1 activates FOXO1 and FOXO4, which promote cell-cycle arrest by inducing p27kip1; SIRT1 also induces cellular resistance to oxidative stress by increasing the levels of manganese superoxide dismutase and GADD45 (growth arrest and DNA damage-inducible protein 45).

(6) SIRT1 inhibits the transcriptional activity of NF-kappaB by deacetylating NF-kappaB's subunit, RelA/p65, at lysine 310. Thus, although SIRT1 is capable of protecting cells from p53-induced apoptosis, it may augment apoptosis by repressing NF-kappaB. SIRT1 is reported to bind CTIP2 (BCL11B B-cell CLL/lymphoma 11B) and accelerate the transcriptional repression by this molecule. CTIP2 represses the transcription of its target genes and is implicated in hematopoietic cell development.

(7) SIRT1 deacetylates and activates functions of several DNA repair factors, including KU70, NBS1, APE1, XPA/C and WRN for multiple DNA damage repair pathways to cope with genotoxic stress. Stimulated repair may help cells avoid catastrophic genomic events and survive the damage.

(8) SIRT1 is involved in epigenetic regulation of genes and chromatin. SIRT1 deacetylates several histone tail lysines: histone H4 lysine 16 (H4K16), histone H3 K9 and K14, and histone H1 K26. These modifications of histone tails are closely related to gene silencing and heterochromatin formation that may underlie certain biological processes. SIRT1 can deacetylate DNA methyltransferase 1 (DNMT1) and can either enhance or hinder its methyltransferase activity, thus indirectly affecting global or local DNA methylation patterns.

SIRT1 is a component of the polycomb repressor complex (PRC) that is involved in silencing genes during normal development.
SIRT1 directly complexes with EZH2, a H3K27 methyltransferase within PRC II complex, and is an integral part of the PRC's silencing functions. A SIRT1-containing PRC complex, termed PRC4, is specifically found in transformed cells and embryonic stem cells.
In addition, SIRT1 interacts and deacetylates the SUV39H1 methyltransferase, promoting histone H3 methylation and fostering heterochromatin formation, and repressing rRNA transcription to protect cells from energy deprivation-dependent apoptosis (reviewed in Roth and Chen, 2014).

Homology

SIRT1 is the mammalian homologue closest to yeast NAD+-dependent deacetylase Sir2 (silent information regulation 2).
It was originally identified as a lifespan extending gene when over-expressed in budding yeast, Caenorhabditis elegans, and Drosophila melanogaster. The SIR2 gene is broadly conserved in organisms ranging from bacteria to humans. The accession numbers for the amino acid sequences used are as follows: yeast Sir2 (CAA25667), mouse Sir2alpha (AAF24983), human Sirt1 (AAD40849). All of the sirtuin proteins contain the ~275 residue sirtuin homology domain. In many instances a highly conserved protein domain represents a conserved functional binding site for a metabolite or biomolecule and such conserved binding site domains are often found within enzymatic catalytic domains.

Mutations

Germinal

A germ line mutation L107P of SIRT1 was found in a family with type I diabetes. Expression of this mutant SIRT1 in insulin-producing cells stimulated production of nitric oxide, cytokines and chemokines, and decreased anti-inflammatory activity of pancreatic beta cells (Biason-Lauber et al., 2013).

Somatic

A small number of SIRT1 somatic mutations were registered in human cancer databases but the mutation rate is typically very low (<0.5%) and their effect on SIRT1 function is unknown. Both gene amplification and deletion are found in human cancers depending on cancer types (reviewed in Roth and Chen, 2014).

Implicated in

Chronic myelogenous leukemia

SIRT1 plays an important role in drug resistance of chronic myelogenous leukemia (CML).

Disease
CML is a lethal malignant disease of hematopoietic stem cells. It is caused by reciprocal translocation of chromosomes 9 and 22, producing BCR-ABL fusion gene. BCR-ABL protein has aberrant tyrosine kinase activity and predominantly resides in the cytoplasm in contrast to predominantly nuclear localization of ABL protein. CML progresses from chronic phase to accelerated phase and blast crisis with increasing numbers of blast cells in bone marrow and blood. SIRT1 is activated by BCR-ABL oncogenic transformation in human CML stem/progenitor cells (Yuan et al., 2012; Li et al., 2012).

Prognosis
CML in chronic phase can be effectively treated tyrosine kinase inhibitors such as first-line drug imatinib, and second-line drugs nilotinb and dasatinib, which results in the five-year survival rate over 85%. However, the residual disease persists as these drugs do not eradicate CML leukemic stem cells, and the disease relapses if the drug is ceased. CML in advanced phases has much poorer prognosis and the disease typically relapses quickly on tyrosine kinase inhibitor treatment since the cells acquire BCR-ABL mutations that block the binding of the drugs to BCR-ABL.

Cytogenetics
Philadelphia chromosome, t(9;22) translocation.

Abnormal protein
BCR-ABL fusion protein with aberrant tyrosine kinase activity.

Oncogenesis
BCR-ABL transformation activates SIRT1 gene expression in both tyrosine kinase-dependent and independent manners, with the former mediating via STAT5 that binds on the SIRT1 promoter to stimulate the transcription. The mechanism for the kinase-independent SIRT1 activation is unknown. SIRT1 knockout significantly blocks BCR-ABL mediated leukemogenesis in a mouse model study (Yuan et al., 2012). Since blocking BCR-ABL kinase activity only partially reduces SIRT1 expression and the pathway remains active, SIRT1 inhibition sensitizes human CML leukemia stem cells to tyrosine kinase inhibitors and helps eradicate these cells by increasing p53 acetylation and activating p53 downstream target gene expression (Li et al., 2012). In addition, SIRT1 promotes acquisition of resistant BCR-ABL mutations for disease relapse in association with its ability to deacetylate and activate KU70 for increased error-prone DNA damage repair in blast crisis CML cells

(Wang et al., 2013). Targeting SIRT1 may have clinical implication to improve CML treatment.

Acute myeloid leukemia

SIRT1 plays an important role in drug resistance of acute myeloid leukemia (AML) with FLT-ITD mutation.

Disease

AML is a group of highly heterogenous myeloid leukemia with distinct oncogenic events including various chromosomal aberrations and mutations. AML is generally derived from myeloid progenitor cells. SIRT1 protein expression is more consistently increased in AML samples, particularly those harboring FLT-ITD alteration. The change of SIRT1 mRNA is less consistent in certain AML subcategories from one to another study (Sasca et al., 2014; Li et al., 2014).

Prognosis

AML with FLT-ITD mutation has poor prognosis.

Abnormal protein

FLT-ITD has constitutively activated tyrosine kinase activity.

Oncogenesis

Similar to BCR-ABL transformation of hematopoietic stem cells, SIRT1 expression change in AML cells is likely a result of cellular response to oncogenic stress. However, protein regulation of SIRT1 appears more important in the AML setting. SIRT1 protein is stabilized by USP22, a deubiquitinase that is induced by c-MYC in FLT-ITD AML cells (Li et al., 2014). In addition, SIRT1 activity is further regulated by ATM-DBC1 in a FLT-ITD dependent manner (Sasca et al., 2014). Inhibition of SIRT1 sensitizes FLT-ITD AML stem/progenitor cells to tyrosine kinase inhibitor treatment, and may help improve management of this category of AML.

Lymphoma

In large B-cell lymphoma patients, positive expression of SIRT1 protein was seen in 74% of patients, and significantly associated with shorter overall survival. Inhibition of SIRT1/2 by Cambinol induces apoptosis in Burkitt lymphoma cells (reviewed in Yuan et al., 2013).

Prognosis

Large B-cell lymphoma with SIRT1 upregulation showed poor prognosis.

Lung cancer

Distinct status of p53 acetylation/deacetylation and HIC1 alteration mechanism result from different SIRT1-DBC1 (deleted in breast cancer 1) control and epigenetic alteration in lung squamous cell carcinoma and lung adenocarcinoma. The lung squamous cell carcinoma patients with low p53 acetylation and SIRT1 expression mostly showed low HIC1 expression, confirming deregulation HIC1-SIRT1-p53 circular loop in clinical model. Expression of DBC1, which blocks the interaction between SIRT1 deacetylase and p53, led to acetylated p53 in lung adenocarcinoma patients.

Prognosis

Lung cancer patients with altered HIC1-SIRT1-p53 circular regulation showed poor prognosis.

Breast cancer

The breast cancer associated protein, BCA3, when neddylated (modified by NEDD8) interacts with SIRT1 and suppresses NF-kB-dependent transcription, also sensitizes human breast cancer cells (such as MCF7) to TNF-a-induced apoptosis. In addition, it has been shown recently that SIRT7 levels of expression increase significantly in breast cancer, and that SIRT7 and SIRT3 both are highly transcribed in lymph-node positive breast biopsies, a stage in which the tumour size is at least 2 mm and the cancer has already spread to the lymph nodes. SIRT1 up-regulation is also associated with decreased miR-200a in breast cancer samples, which targets the 3'UTR of SIRT1 mRNA and promotes epithelial-mesenchymal transition (EMT)-like transformation in mammary epithelial cells. SIRT1 is essential for oncogenic signaling of estrogen/estrogen receptor α (ERα) in breast cancer. SIRT1 inactivation suppresses estrogen/ERα-induced cell growth and tumor development, and induces apoptosis. SIRT1 is found to be significantly up-regulated in the invasive ductal carcinoma, and positively regulates the expression of aromatase, an enzyme responsible for a key step in the biosynthesis of estrogen in breast cancer. However, in HMLER breast cancer cells, SIRT1 was found to suppress EMT, and reduced SIRT1 expression increases metastasis of these cells in nude mice (reviewed in Yuan et al., 2013).

Prostate cancer

SIRT1 is significantly overexpressed in primary human prostate cancer tissues and cell lines. SIRT1 inhibition via nicotinamide, sirtinol, short hairpin RNAs or mutation of the 25 amino acid C-terminal SIRT1 activator sequence, results in a significant inhibition of prostate cancer cell growth, viability and chemoresistance. SIRT1 is highly expressed in advanced prostate cancer tissues and promotes prostate cancer cell invasion, migration and metastasis through MMP2, EMT inducing transcription factor ZEB1, and cortactin. Concomitant with SIRT1 activation, NAMPT is over-expressed in prostate cancer, likely enabling supply of NAD+ for SIRT1 functions. In the transgenic mouse model, SIRT1 expression promotes murine prostate carcinogenesis initiated by Pten-deficiency (reviewed in Yuan et al., 2013).

Liver cancer

SIRT1 expression is significantly elevated in hepatocellular carcinoma (HCC) tissues, and the expression levels correlate with tumor grades and predict poor prognosis. SIRT1 expression also positively correlates with c-MYC levels in HCC. SIRT1 and c-MYC regulate each other via a positive feedback loop and act synergistically to promote cell proliferation of both mouse and human liver tumor cells. SIRT1 promotes tumorigenesis and chemoresistance in HCC, and inhibition of SIRT1 suppresses the proliferation of HCC cells in vitro or in vivo via the induction of cellular senescence or apoptosis. Accordingly, expression of miRNA-34a is reduced in HCC, and the reduced expression of miRNA-34a is associated with worse outcome of HCC patients. Treatment of established HCC xenograft with miR-34a-expressing adenovirus in a mouse model results in complete tumor regression without recurrence (reviewed in Yuan et al., 2013).

Gastric cancer

SIRT1 protein expression in gastric cardiac carcinoma is significantly higher than that in normal gastric tissues and is associated with lymphatic metastasis, TNM [the extent of tumor (T), the extent of spread to lymph nodes (N), and the presence of distant metastasis (M)] stage, survival rate and mean survival time. In another study, positive expression of SIRT1 was seen in 73% of gastric cancer patients. SIRT1 expression is also significantly associated with shorter overall survival and relapse-free survival. SIRT1 is required for activating transcription factor 4 (ATF4)-induced multidrug resistance in gastric cancer cells. ATF4 facilitates multidrug resistance in gastric cancer cells through direct binding to SIRT1 promoter and activating SIRT1 expression. Significantly, inhibition of SIRT1 by RNAi or a specific inhibitor (EX-527) sensitizes gastric cancer cells to therapeutic treatment (reviewed in Yuan et al., 2013).

Pancreatic cancer

SIRT1 overexpression was observed in pancreatic cancer tissues at both mRNA and protein levels. Increased SIRT1 positivity is associated with patients' age (over 60 years old), larger tumor size (larger than 4 cm), and higher TNM stage. SIRT1 knockdown induces apoptosis and senescence, inhibits invasion and enhances chemosensitivity in pancreatic cancer cells. In pancreatic cancer, SIRT1 regulates ADM (acinar-to-ductal metaplasia) and supports cancer cell viability through deacetylating pancreatic transcription factor-1a and β-catenin. Inhibition of SIRT1 is effective in suppression of ADM and in reducing cell viability in established pancreatic ductal adenocarcinoma. In addition, SIRT1 promotes EMT ability as well as invasion of pancreatic cancer cell by forming a complex with Twist and MBD1 thus suppressing E-cadherin transcription activity. However, one study showed that SIRT1 inhibits proliferation of pancreatic cancer cells expressing oncogenic pancreatic adenocarcinoma up-regulated factor (PAUF), by suppression of β-catenin and cyclin-D1 (reviewed in Yuan et al., 2013).

Thyroid cancer

SIRT1 is overexpressed in human thyroid cancers and it is positively correlated with c-MYC protein levels. Transgenic SIRT1 expression promotes murine thyroid carcinogenesis initiated by Pten-deficiency. SIRT1 increases c-MYC transcription and stabilizes c-MYC protein in thyroid cancers from SIRT1 transgenic mice or cultured thyroid cancer cells (reviewed in Yuan et al., 2013).

Colon cancer

Highly-expressed c-MYC correlates with increased SIRT1 protein level in colorectal cancer.

In 121 colorectal serrated lesions, the higher expression of c-MYC and SIRT1 protein is strongly associated with higher grades of malignancy. In another study with a total of 485 colorectal cancer patients, SIRT1 overexpression was detected in 180 (37%) tumors.

SIRT1 expression is associated with microsatellite instability and CpG island methylator phenotype, although not patient prognosis. Reduced expression of miR-34a, a negative regulator of SIRT1 mRNA, is observed in drug-resistant DLD-1 colon cancer cells, and introduction of miR-34a induces apoptosis by downregulating SIRT1. However, one study showed that in colorectal adenocarcinoma, SIRT1 overexpression was observed in approximately 25% of stage I/II/III tumors but rarely in advanced stage IV tumors. Approximately 30% of carcinomas showed lower SIRT1 expression than normal tissues. In another clinical observation, SIRT1 protein expression is gradually decreased during the normal-adenoma-adenocarcinoma-metastasis stage in colorectal cancers, with the positivity 100%, 80.8%, 41.9%, and 35.7%, respectively (reviewed in Yuan et al., 2013).

Ovarian cancer

Expression of SIRT1 protein is significantly increased in malignant ovarian epithelial tumors compared to that in benign and borderline epithelial tumors. High proportion (86%) of serous ovarian cancer expressed SIRT1. Interestingly, increased SIRT1 protein in serous ovarian epithelial cancer was associated with increased overall survival (Jang et al., 2009).

Brain tumor

In glioblastoma, SIRT1 is highly expressed in tumor-derived CD133+ progenitor cells compared to CD133-cells and knockdown of SIRT1 expression

enhances the radio-sensitivity and radiation-induced apoptosis in the CD133+ cells. SIRT1 is also frequently expressed in human medulloblastomas relative to surrounding noncancerous cerebellar tissues and its expression is correlated with the formation and prognosis of medulloblastomas. SIRT1 and N-MYC form a positive feedback regulation loop during the tumorigenesis of neuroblastoma, and preventive treatment with the SIRT1 inhibitor Cambinol significantly reduces tumorigenesis in N-MYC transgenic mice (reviewed in Yuan et al., 2013).

Soft tissue sarcoma

SIRT1 is frequently over-expressed in soft tissue neoplasms with myoid differentiation including angiomyolipoma (4 out of 4 patients), glomus tumor (5 out of 5 patients), leiomyoma (9 out of 10 patients), leiomyosarcoma (76.5% of 51 patients), and rhabdomyosarcoma (87% of 24 patients), and thus could be a potential immunohistochemical marker and therapeutic target in these tumors (reviewed in Yuan et al., 2013).

Kidney diseases

SIRT1 attenuates TGF-beta (transforming growth factor-beta) apoptotic signaling that is mediated by the effector molecule Smad7. SIRT1-dependent deacetylation of Smad7 at Lys60 and Lys70 enhances its ubiquitin-dependent proteasomal degradation via Smurf1 (Smad ubiquitination regulatory factor 1), thus protecting glomerular mesangial cells from TGF-beta-dependent apoptosis. As a result, SIRT1 expression tends to have protective roles in diabetic kidney disease and excessive inflammatory response triggered by bacterial endotoxins. However, SIRT1 inhibition was found to delay kidney cyst formation in autosomal-dominant polycystic kidney disease through regulating Rb and p53 in cystic renal epithelial cells (Zhou et al., 2013).

Cardiac hypertrophy

Decreasing hypertrophy or apoptosis in cardiac myocytes can ameliorate the disease, and there is reason to suspect that SIRT1 activation may be useful in this regard. SIRT1 protects primary cultured myocytes from programmed cell death induced by serum starvation or by the activation of PARP-1 [poly(ADP-ribose) polymerase-1] in a p53-dependent manner. SIRT1 also deacetylates Lys115 and Lys121 of the histone variant H2A.Z, a factor known to promote cardiac hypertrophy. In doing so, SIRT1 promotes the ubiquitination and proteosome-dependent degradation of H2A.Z, which may help to protect against heart failure. However, in mouse models it was found that SIRT1 haploinsufficiency attenuates pressure overload-induced cardiac hypertrophy and heart failure (Oka et al., 2011). Contributing to this effect, SIRT1, coordinated by PPARα, suppresses genes involved in mitochondrial functions. In a separate study, cardiac hypertrophy is reduced in Sirt1 deficient mice in response to physical exercise and angiotensin II due to impaired Akt activation as a result of its acetylation (Sundaresan et al., 2011).

Breakpoints

No breakpoints are associated with SIRT1.

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