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Gene Section
Review

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

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Identity

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

HGNC (Hugo): SIRT1

Location: 10q21.3

DNA/RNA

Description

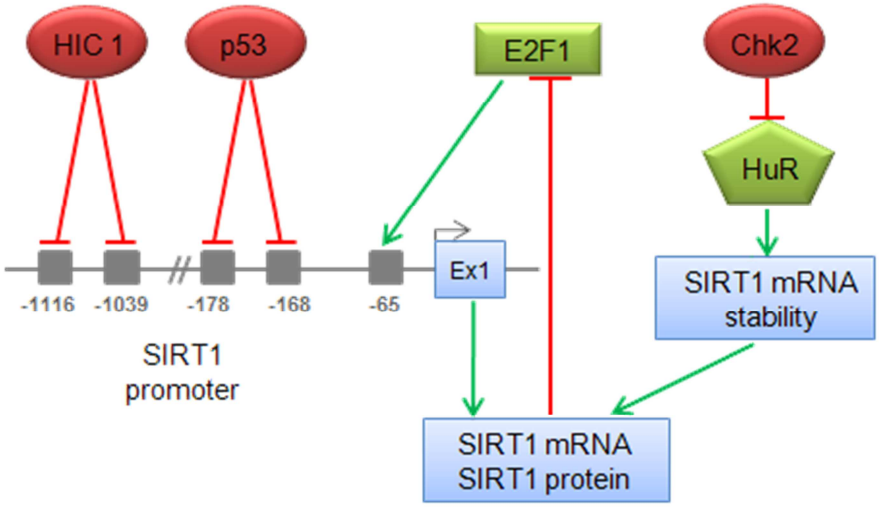
The SIRT1 gene spans about 34 kb including nine exons. The SIRT1 promoter contains a CCAAT box and a number of NFkappaB and GATA transcription factor binding sites in addition to a small 350-bp CpG island in the 5' flanking genomic region. The gene encodes a 747 amino acids protein with a predictive 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 activated 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.



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

By contrast, the tumor suppressor HIC1 and SIRT1 form a transcriptional repression complex that directly binds SIRT1 promoter via its N-terminal POZ domain 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. In addition, two functional p53 binding sites (-178 bp and -168 bp), which normally repress SIRT1 expression, have been identified.
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.

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.

Expression

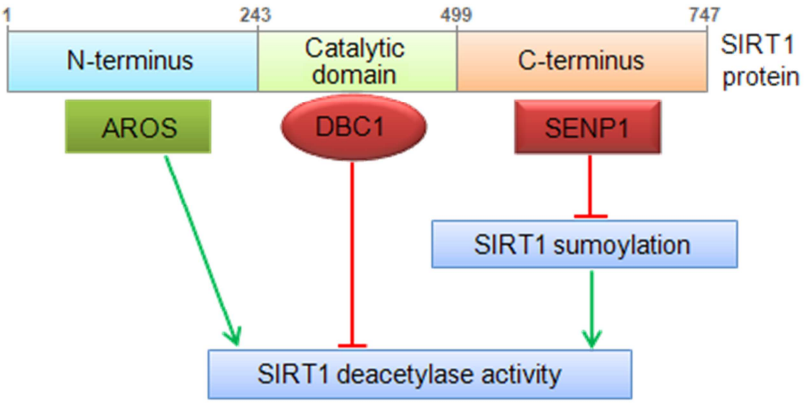
Expression appears to be ubiquitous in adult tissues (although at different levels). Two proteins have been identified to regulate the SIRT1 activity both positively and negatively through complex formation in the context of the cellular stress response. The first identified direct regulator of SIRT1 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.

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

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.

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.

Implicated in

Lung cancer

Note
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

Note
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.

Brain tumor

Note
SIRT2 resides in a genomic region frequently deleted in human gliomas and ectopic expression of SIRT2 in glioma-derived cell lines markedly reduces their capacity to form colonies in vitro. Exogenously expressed SIRT2 blocks chromosomal condensation and hyperploidy in glioma cell lines, accompanied by the presence of cyclin B/cdc2 activity in response to mitotic stress. Thus, SIRT2 may be a novel metaphase check-point protein that promotes genomic integrity and inhibits the uncontrolled proliferation of transformed cells.

Kidney diseases

Note
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.

Cardiac hypertrophy

Note
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.

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