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Gene Section
Review

HDAC3 (histone deacetylase 3)

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Identity

Hugo: HDAC3
Other names: HDAC3; HD3; RPD3-2; RPD3; SMAP45
Location: 5q31.3
Local order: 140,980,626 pb to 140,996,596 bp in minus strand orientation

DNA/RNA

Description

The HDAC3 gene consists of 15 exons and spans 15.97 kb of genomic sequence on chromosome 5 (from position 140,980,626 pb to 140,996,596 bp, in minus strand orientation).

Transcription

The mRNA transcribed from this gene is 1,934 nucleotides long. There are actually two described isoforms resulting from an alternative splicing in the 5' region.

Pseudogene

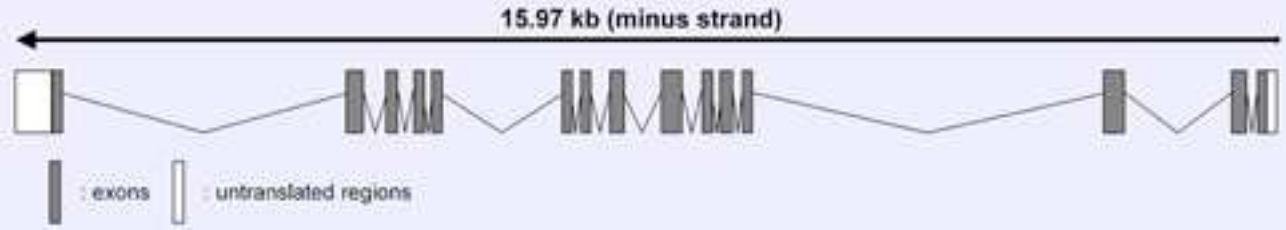
No pseudogene have been described.

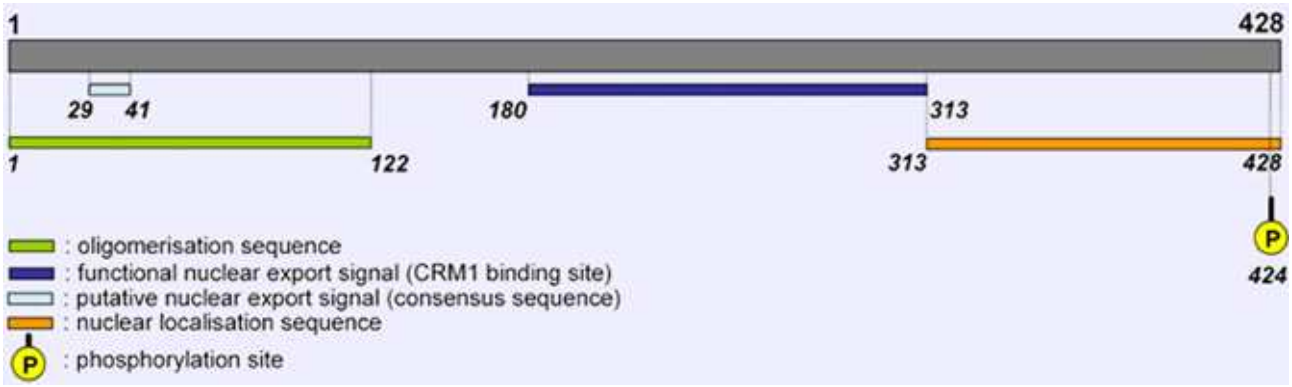
Protein

Note: HDAC3 interacts with other proteins, such as HDAC1, HDAC7, HDAC10, DACH1, YY1, DAXX, PML, RB1, RELA, JUN, SIN3A, BCOR, JMJD2A/JHDM3A, AKAP95, KLF6, DLK1, TR2, NRIP1 and SRY. Also described as a component of the N-CoR/SMRT repressor complexes by interacting with NCOR1/NCOR2.

Description

The HDAC3 protein is 428 amino acids long (isoelectric point: 4.98) and belongs to the class I histone deacetylase subfamily.
In spite of the presence of a sequence ressembling the canonical NES at the position 29-41, CRM1 binding is observed in the region 180-313 and these residues act as a NES (or as a binding site for a NES-containing protein) that uses CRM1 export pathway. A NLS has been characterised in the C-terminal region (313-428).
Another important sequence, required for oligomerisation of HDAC3 with itself and for the cell viability, is present in the N-terminal part (1-122) of the protein.





The HDAC3 protein can be phosphorylated on Ser424 by Caseine Kinase 2 and the same residue is dephosphorylated by protein serine/threonine phosphatase 4 (PP4). HDAC3 can also be symoylated in vitro.

Expression

Like the other members of class I HDACs, HDAC3 is widely expressed in organisms, whereas HDACs of other classes are tissue-specific.

Two different isoforms of HDAC3 are expressed depending on an alternative splicing of the mRNA. The resulting proteins differ in their first 15 N-terminal amino acids (MAKTVAYFYDPDVGN → MIVFKPYQASQHDMCR).

Localisation

As opposed to other class I HDACs that have been found predominantly nuclear, HDAC3 is located in both nuclear and cytoplasmic compartments as well as at the plasma membrane.

Function

In accordance to the limited homology of HDAC3 with the other HDACs (particularly in the C-terminal part of the protein) and its specific subcellular localisation, HDAC3 plays specific roles in the cell physiology and has substrates in the various cell compartments. Thus, unlike HDAC1/HDAC2, HDAC3 is required for cell growth and is involved in the apoptotic process of almost all cell types via the regulation of pro-apoptotic genes. Moreover, HDAC3 has been suggested to have a role in the cytoplasm, notably in signal transduction since it is a substrate of the membrane associated tyrosine kinase Src. So, in organisms, this protein plays a critical role in development, inflammation and metabolism.

As the other histone deacetylases, HDAC3 acts on the chromatin via the formation of large multiprotein complexes. But unlike HDAC1/2, that are implicated in the formation of Sin3, NuRD and CoREST complexes, HDAC3 is present in specific complexes containing members of the nuclear receptor co-repressor family N-CoR/SMRT (Silencing Mediator of Retinoid acid and Thyroid hormone receptor). HDAC3 is responsible for the deacetylation of lysine residues on the N-terminal part of the core histones (H2A, H2B, H3 and H4) that correlates with epigenetic repression. This deacetylation is involved in transcriptional regulation of genes important for cell cycle progression and development. Thus, HDAC3 has been implicated to play roles in governing cell proliferation via the inhibition of p15(INK4b) and p21(WAF1/cip1).

Many transcription factors can directly interact with HDAC3 and thus, may target the histone deacetylase to specific promoters. Thus, HDAC3 is able to regulate osteoblast differentiation and bone formation via its association with the osteoblast master protein, Runx2, and the inhibition of the trans-activity of Runx2. Likewise, in hematopoietic stem cells, HDAC3, but not other class I HDACs, directly associates with GATA-2 and suppresses its key transcriptional potential.

The deacetylase activity of HDAC-3 can also target non-histone proteins: for example, HDAC3 is responsible in the inhibition of the myogenesis via its association with the acetyltransferases p300 and p300/CBP-associated factor (PCAF) to reverse autoacetylation and thus, to repress the p300/PCAF/MEF2 -dependent transcription.

So, HDAC3 regulates many biological processes in a complex multi-levels manner.

The activity of HDAC3 is regulated by the phosphorylation of the Ser424 residue of the protein (see protein description above) and CK2 and PP4 are responsible for this regulation. Interaction with the other members within multiprotein complexes also regulates the deacetylase activity of HDAC3 (the nuclear receptor corepressor SMRT stimulated this activity towards MEF2 and PCAF). HDAC3 activity can also be indirectly regulated by post-translational modification of its associated proteins (for example, the phosphorylation of SMRT induces the disruption of the complex and the de-repression of the target promoter).

The cleavage of the HDAC3 protein is another type of regulation affecting this enzyme: thus, during apoptosis, removal of the C-terminal part of HDAC3 results in accumulation of the cleaved protein in the cytoplasm and so, in its inactivation towards nuclear histones (but a possible role of the cleaved protein in the cytoplasm cannot be excluded).

Homology

HDAC3 is very tightly conserved from plants to human. The histone deacetylase domain of HDAC3 (amino acids 3 to 316) is partly homologous to the other class I HDACs (HDAC1, HDAC2 and HDAC8) whereas C-terminal part of the protein is highly divergent. So, the HDAC3 protein is about 50% identical compared with other class I HDACs.

Mutations

Note: No mutation is actually known for HDAC3 but Single Nucleotide Polymorphisms have been described in mRNA UTR (TGGGGG/TTCACC), introns (GATCTA/GTATTA; AAGGAA/CACAAT; GAAGGA/GCCCAT; AAACTA/GTAAAA) or in exons where it induces synonymous (TCATGT/CTGGGA (Q/Q)) or non-synonymous (ACCCAA/GTGAGT (N/S); CCAATC/GGATCA (R/P)) coding (non-exhaustive list).

Implicated in

Cancers

Note: Phase I/II clinical trials are actually conducted in north America with isoselective inhibitors of class I HDACs for the treatment of the Hodgkin lymphoma (HDACs inhibitors alone), of the acute myeloid leukemia and myelodysplastic syndrome (in association with DNA methylation inhibitors) or of pancreatic cancers (in association with antimetabolites).

Disease

Histone Deacetylase 3 and other class I HDACs, that regulate cell maturation and p21 expression, are deregulated in numerous cancers such as colon, ovary, lung, stomach, muscle, bone or skin cancers. The overexpression of HDAC3 is observed in almost tumoral pathologies. The downregulation of HDAC3 in colon cancer cells, in which the enzyme is normally overexpressed, results in cell growth inhibition, differentiation and increased apoptosis.

Prognosis

HDAC3 in combination with other antigens may become a useful molecular biomarker with diagnostic or prognostic value for a subset of colon cancer patients.
There is no correlation between HDAC3 polymorphism and the risk of lung cancer.

Oncogenesis

HDAC3 was shown to be recruited by the tumor antigen MAGE-A to block the activation of the tumor suppressor p53. In leukaemia, the generation of oncogenic fusion proteins (TEL - AML1, ETO - AML1, MTG16a - AML1, PLZF - RARalpha) causes aberrant recruitment of N-CoR/SMRT-HDAC3 repressor complexes on promoters. Moreover, nuclear HDAC3 plays an anti-apoptotic role that is important for cancer cell growth.

Neurodegenerative and neuromuscular diseases

Note: Clinical trials are conducted with class I HDACs isoselective inhibitors for the treatment of Spinal Muscular Atrophy.
HDAC inhibitors are also tested to enhance neuronal survival in both in vitro and in vivo models of neurodegenerative diseases such as polyglutamine-related diseases and amyotrophic lateral sclerosis.

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