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Gene Section

Review

HDAC1 (histone deacetylase 1)

Emanuely Silva Chrun, Filipe Modolo, Filipe Ivan Daniel

Federal University of Santa Catarina, Florianopolis, Santa Catarina, emanuely.silva@gmail.com (ESC), Pathology Department, Federal University of Santa Catarina, Florianopolis, SC, Brazil. filipe.modolo@ufsc.br; filipe.daniel@ufsc.br (FM, FID)

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Abstract

HDAC1 is a Class I histone deacetylase (HDACs) encoded by this gene. HDACs remove acetyl group from amino-terminal tail of histone lysine recovering the positive charge of histone tail, permitting interactions between negatively charged DNA and histone protein, resulting in chromatin structure condensation which is associated with gene repression. Overexpression of this protein has been related to several malignancies, controlling tumour suppressor genes expression, feasible prognostics factor, and medications target. This paper propound data about HDAC1 gene, its protein encoded and function.

Keywords
Histone deacetylase 1, gene expression regulation, epigenetic repression.

Identity

Other names
RPD3, RPD3L1, GON-10, HD1

HGNC (Hugo)
HDAC1

Location
1p35.2-p35.1

DNA/RNA

Description

Located in chromosome 1. The entire HDAC1 gene is approximately 41,550 bases (start: 32,292,086 and end: 32,333,635 bp; orientation: Plus strand) and contains 14 exons.

Protein

Description

HDAC1 protein consists of 482 amino acids with a molecular theoretical weight of 55.18 kDa. Human HDAC1 protein (GenBank Accession No. NM_004964), full length with C-terminal His-tag and C-terminal FLAG-tag, MW = 56 kDa, expressed in baculovirus expression system. Recombinant HDAC1 forms a complex with endogenous HSP70 and is co-purified with tubulin. The identity of Hsp70 and tubulin was confirmed by MALDITOF mass spectrometry.

Expression

Ubiquitously.

Localisation

HDAC1 is found mainly in the nucleus.

Function

HDAC1 is an enzyme responsible for epigenetic alterations leading to modulation of chromatin structure and transcriptional regulation across lysine residues deacetylation on the N-terminal part of the

core histones (H2A, H2B, H3 and H4) (Fig. 1). It shows a role in cell cycle regulation and haematopoiesis (Dovey, et al. 2010). Deacetylation of TP53 by HDAC1 is a mechanism that participate of physiological activity of TP53 (Juan, et al. 2000 2000). It was also observed an important participation in cellular proliferation through direct regulation of CDKN1A (p21) gene (Zupkovitz, et al. 2010) 2010. HDAC2 is a HDAC1 homologue that, in part, compensates its loss and has redundant functions (Zupkovitz, et al. 2006 2006). These enzymes act through multiprotein co-repressor complexes such as: SIN3, NuRD, RCOR1 (CoREST) (Kelly and Cowley 2013).

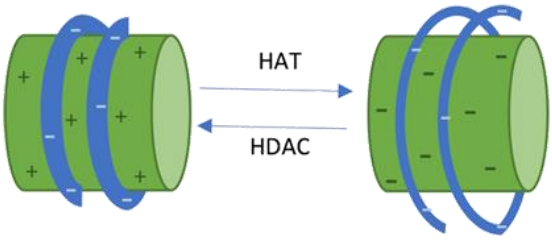

Fig. 1. Chromatin remodeling by histone acetylation changes. HATs catalyse the addition of acetyl groups turning histone tail charge to negative, leading to chromatin opening, while HDACs remove acetyl group from amino-terminal tail of histone lysine recovering its positive charge, closing the chromatin structure.

Homology

HDAC1 shares high homology between diverse species (Table 1).

Table 1. Comparative identity of human HDAC1 and its homologs in other species).

Gene		Identity	
H. sapiens **vs.**	Symbol	Protein	DNA
P. troglogytes	HDAC1	99.8	99.4
P. troglogytes	HDAC1	99.6	99.4
M. mulata	LOC708441	99.8	97.8
C. lupus	HDAC1	99.2	94.1
B. taurus	HDAC1	99.2	93.9
M. musculus	Hdac1	99.4	90.5
R. norvegicus	Hdac1	99.2	90.9
G. gallus	Hdac1	93.3	79.2
D. melanogaster	Rpd3	82.1	72.2
A. gambiae	AgaP_AGAP006511	83.1	72.8
C. elegans	hda-3	69.5	63.5
S. cerevisiae	RPD3	64.8	60.3
K. lactis	KLLA0E01981g	65.4	61.2
E. gossypii	AGOS_AGR395W	65.0	62.2
S. pombe	clr6	64.5	63.2
M. oryzae	MGG_05857	66.7	63.9
N. crassa	NCU00824	66.1	62.8
A. thaliana	HD1	67.6	63.4
O. sativa	Os02g02124900	68.3	64.0
O. sativa	Os06g0583400	69.2	65.4

Mutations

Note

A total of 60 substitution missense, 5 substitution nonsense, 29 substitution synonymous, no insertion frameshift, no deletions inframe, 2 deletion frameshift, none complex and none other mutations are reported in COSMIC (Catalogue of somatic mutations in cancer); it was found 110 mutated samples from a total of 29924 tested samples.

Implicated in

Oral squamous cell carcinoma

HDAC1 overexpression was found in 55.10% of 49 mobile tongue squamous cell carcinoma evaluated whereas most of the cells from non-neoplastic epithelium presents negative immunoexpression for HDAC1 (Theocharis, et al. 2011). HDAC1 was overexpressed in 70% of lip squamous cell carcinoma (Fig.2) and in 77% of actinic cheilitis, with immunoexpression increasing in preneoplastic cases with severe epithelial dysplasia, and in neoplastic cases with poor differentiation (Chrun, et al. 2017).

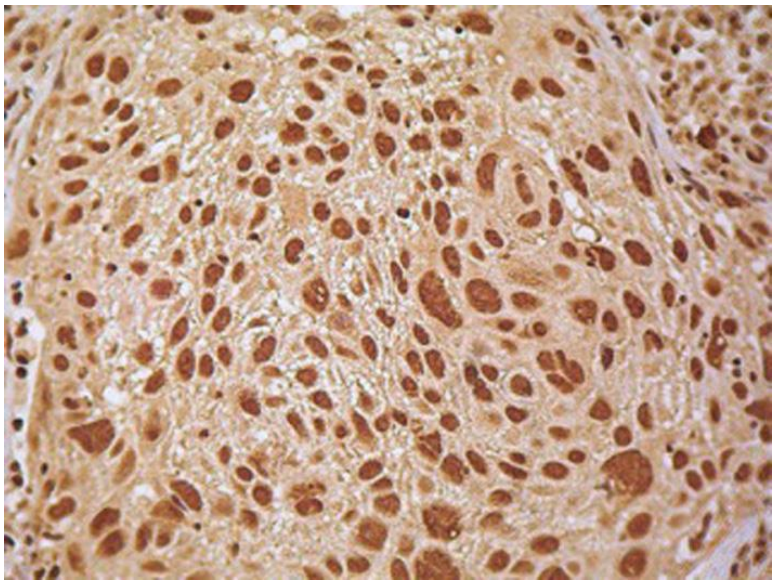

Fig. 2. Immunoexpression of HDAC1 in lip squamous cell carcinoma.

Esophageal cancer

Comparing H4 acetylation and HDAC1 expression, it was observed hyperacetylation of H4 and decreased HDAC1 expression from esophageal normal tissue through esophageal carcinoma, suggesting that the equilibrium between HDAC and HAT is interrupted in this carcinoma (Toh, et al. 2003). Few cases of esophageal cancer were reported with HDAC1 overexpression when compared to normal esophageal mucosa (15%) (Nakagawa, et al. 2007). Esophageal adenocarcinoma also presented subexpression in majority of cases and was not associated to prognostic factor (Langer, et al. 2010).

Thyroid cancer

HDAC1 immunoexpression was found in 99% of 47 thyroid malignances (papillary, follicular, medullary, and anaplastic thyroid carcinomas) and 23 benign thyroid tumors, with significant relation to tumor size, without difference in expression between malignant and benign thyroid tumors (Giaginis, et al. 2014). Nakagawa and collaborators reported immunoreactivity in all evaluated cases of papillary thyroid tumors (Nakagawa, et al. 2007).

Gastric cancer

HDAC1 overexpression was detected by semi-quantitative RT-PCR, immunoblot analysis, and immunohistochemistry in gastric cancer tissues compared to its corresponding normal tissue (Choi, et al. 2001; Nakagawa, et al. 2007). Sudo and colleagues found association between HDAC expression and aggressive behavior of primary gastric cancer. In this study, HDAC1 overexpression was found by quantitative reverse transcription-PCR in gastric cancer tissue in 77% of the cases, with higher expression correlated to lymph vessel and vascular vessel permeations, advanced stage of the disease, and lymph node metastasis (Sudo, et al. 2011).

Colorectal cancer

When comparing colorectal carcinoma cells and normal colonic mucosa by reverse transcription (RT)-PCR (Ishihama, et al. 2007) and immunohistochemistry (Nakagawa, et al. 2007) there was a greater HDAC1 expression in cancer than in normal colonic epithelium. Bernard and collaborators evaluated tissue microarray (TMA) with 254 colorectal adenocarcinomas samples and 50 normal colorectal tissues, showing no significant difference between normal and cancerous tissues, but suggested combination of higher HDAC expression and clinical outcomes for these patients (Benard, et al. 2015).

Pancreatic cancer

HDAC1 with HDAC2 and SIN3A were recognized as complex silencing regulators of CDH1 (E-cadherin), thus involved in pancreatic adenocarcinoma metastasis (von Burstin, et al. 2009; Aghdassi, et al. 2012). Several HDACs were evaluated in (pNET): higher expression of HDAC1 was observed in high grade pNET and its expression showed positive correlation with mitotic (pHH3) and proliferation (Ki-67) index (Klieser, et al. 2017).

Lymphomas

Hodgkin`s lymphoma exhibited higher immunoexpression of HDAC1 when analysing 283 TMA (Adams, et al. 2010). In diffuse large B-cell lymphomas (DLBCL) HDAC1 immunoexpression was higher in comparison to reactive lymphoid hyperplasia which was correlated to cell proliferation index (Ki67) in the development of DLBCL, and associated with aggressiveness/poor survival of DLBCL patients (Min, et al. 2012). On the other hand, Lee and colleagues found faintly nuclear staining in few cases of 91 DLBCL samples submitted to immunohistochemistry (Lee, et al. 2014).

Leukemias

Moreno and collaborators evaluated 94 cases of childhood acute lymphoblastic leukaemia (ALL) and found HDAC1 mRNA increased expression in T-cell ALL when compared to B-cell ALL. Yang et al. also found higher HDAC1 mRNA in ALL. (Moreno, et al. 2010). Quantitative real-time polymerase chain reaction also revealed higher HDAC1 expression in ALL (Yang, et al. 2015). Clinicopathological parameters indicated that overexpression of HDAC1 may be related to unfavourable prognosis of childhood ALL (Gruhn, et al. 2013).

Lung cancer

HDAC1 is highly expressed in lung cancer (Nakagawa, et al. 2007). A correlation between HDAC1 mRNA and protein levels showed that HDAC1 gene expression might be involved with lung cancer progression (Sasaki, et al. 2004).

Prostate cancer

Up-regulation of HDAC1 in prostate cancer compared to benign prostatic hyperplasia was demonstrated by immunohistochemistry (Patra, et al. 2001; Nakagawa, et al. 2007). Weichert and collaborators achieved immunohistochemistry for Class I HDAC isoforms in prostate carcinomas, showing HDAC1, HDAC2 and HDAC3 stronger expression accompanied by tumor cell proliferation raising (Weichert, et al. 2008). Overexpression of HDAC1 was also related to major increase of hormone refractory in prostate cancer and augmentation of proliferation (Halkidou, et al. 2004).

Breast cancer

HDAC1 was evaluated in TMA from 238 patients with primary breast cancer and presented wide variation in positive imunnoexpression (Muller, et al. 2013). While Nakagawa (Nakagawa, et al. 2007) and Ververis (Ververis and Karagiannis 2012) showed higher expression of HDAC1 by immunohistochemistry and immunofluorescence respectively. Suzuki and colleagues detected a decrease in its expression from normal tissue through invasive ductal carcinoma, and from high grade through intermediate/low grade carcinoma (Suzuki, et al. 2009). Higher expression of HDAC1 was related to molecular subtypes (Luminal A, Luminal B, HER overexpressed, and triple-negative) and with improved overall survival (Seo, et al. 2014).

Ovarian cancer

HDAC1 immunoexpression showed positive correlation with Ki-67 and inverse correlation with E-cadherin in 115 cases of ovarian tumors, suggesting an important participation of HDAC1 in cellular proliferation. Its overexpression was also associated with poor outcome (Hayashi, et al. 2010). Immunoreactivity for HDAC1 was sighted in 95% of cases evaluated, but without significant difference between histological subtypes of ovarian cancer (Nakagawa, et al. 2007). By immunohistochemistry and qRT-PCR, HDAC1 and DNMT3B revealed positive correlation in ovarian cancer; HDAC1 was highly expressed in comparison to normal ovarian tissue (Gu, et al. 2013). In a population-based cohort of 465 ovarian carcinomas, Weichert and collaborators observed higher level expression of HDAC1 and positive correlation with Ki67, indicating its participation in cell proliferation without significant interference in prognostic (Weichert 2009).

Endometrial cancer

Strong HDAC1 immunoexpression was observed in endometrial stromal sarcoma, and it was suggested that this expression is linked to lower than 10 years disease free survival (Baek, et al. 2016). Endometrial adenocarcinomas compared to normal endometrium exhibited reduction in HDAC1 expression (Krusche, et al. 2005). However, in other research, endometrial carcinomas presented higher HDAC1 expression in comparison to normal endometrial tissue (Fakhry, et al. 2010). Weichert and colleagues evaluated 149 endometrial carcinomas and showed a higher level of HDAC1 expression that was positively correlated with cell proliferation indicator (Ki-67) and associated to 10 years survival decrease (Weichert 2009).

To be noted

High expression of HDAC1 was found in majority of cancer types studied. Epigenetic alterations are heritable and reversible phenomenon; thus, these histone modifiers proteins represent targets to antineoplastic agents, with some medications (belinostat, vorinostat, and romidepsin) already approved by Food and Drugs Administration for treatment of hematological malignances. HDAC inhibitors have been studied with potential outcomes to improve conventional therapy in several tumors. These findings may expand cancer treatment strategies in a short time.

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