Journal of Molecular Biomarkers & Diagnosis

Moradzadeh et al., J Mol Biomark Diagn 2015, 6:4
DOI: 10.4172/2155-9929.1000240

Review Article Open Access

The Role of Histone Deacetylase (HDAC) as a Biomarker in Cancer

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Abstract

Histone acetylases [HAT] and histone deacetylases [HDACs] are responsible for the addition and removal of acetyl-groups to or from specific lysine residues located within histone tails and a number of non-histone proteins. HDACs, as one of the epigenetic mechanisms, play a central role in the regulation of cellular properties that related to development and progression of cancer. Recently, researches began to focus on the expression patterns of HDAC isoforms as a biomarker in cancer. It could be used to find new agents that are very effective in inducing apoptosis, differentiation, and/or cell growth arrest in neoplasia. Approximately, all of studies showed HDAC expression level differ in human tumors. For example, in most tumor entities class I HDAC expression was higher in late stage, high-grade tumors with strong proliferative activity and Class II HDACs down regulated in human tumors and high expression in some tumors was linked to a better prognosis. Thus, this factor allowed to opens new possibilities for a molecularly targeted approach to treatment.

Keywords: Histone deactylase [HDAC]; Biomarker, Cancer

Introduction

Nowadays, Histone acetylation, as one of the epigenetic mechanisms, is considered in the development of human cancer [1,2]. Histone acetylases [HAT] and histone deacetylases [HDACs] are responsible for the addition and removal of acetyl-groups to or from specific lysine residues located within histone tails and a number of non-histone proteins (Table 1) [3,4]. A disequilibrium of the HDACs leads to transcriptional repression in genes responsible for regulation of proliferation, migration, angiogenesis, differentiation, invasion, and metastasis [5-7]. Overall, HDACs is might be as a good biomarker in cancer diagnosis.

Recently, researchers focused on the expression of HDAC isoforms in human tumors and, the most important findings on this topic are presented here.

HDAC biology

HDACs remove the acetyl moieties from the ε-amino groups of lysine residues present within the N-terminal extension of the nucleosomal histones, and in turn lead to a more condensed form of chromatin, the so-called heterochromatin, and gene silencing. On the other hand, histone acetyl transferases [HATs] with cofactor acetyl-CoA, lead to a more open form of chromatin, the so-called euchromatin (Figure 1) [8-11].

HDAC family

At present, there are 18 HDAC isoforms into four classes that summarized in Figure 1 [12,13]. The Class I HDACs [HDAC 1, 2, 3 and 8], which are generally nuclear, ubiquitously expressed in various human tissues, and may be more significant in regulating proliferation [14]. HDAC2 has been shown to suppress apoptosis in tumor cells [15-18].

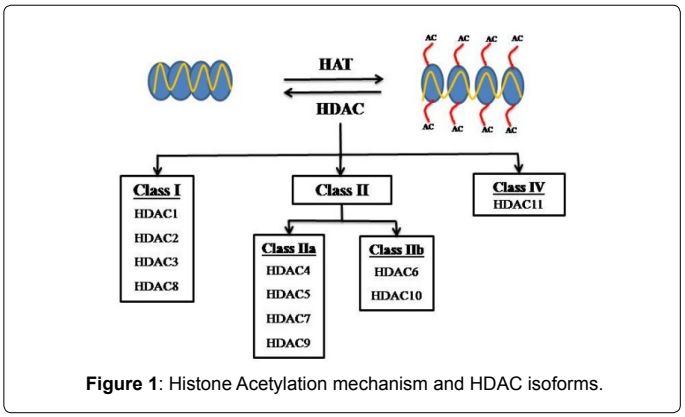

Figure 1: Histone Acetylation mechanism and HDAC isoforms.

Class II HDACs [HDAC 4, 5, 6, 7, 9, and 10], which are selectively distributed among tissues, share domains with yeast HDAC-1 [19,20]. HDAC4 acts as a repressor of chondrocyte hypertrophy through interacting with the myocyte-specific enhancer factor 2C transcription factor [21-23] and HDAC7 functions in the negative regulation and apoptosis of T-cells reflecting its interaction with the orphan nuclear receptor Nur77 . HDAC6, located in the cytoplasm where it acts as a tubulin deacetylase, may participate in regulating cell viability in response to mis-folded proteins [17]. HDAC6 also has the capacity to

Tumor suppressor	p53, pRb
Transcription factor	UBF, E2F, HIF1a, MEF2, YY1, GATA1
Chaperone	HSP90, HSP70
Oncogene	Bcl6, c-Myc
Non-histone chromosomal proteins	HMG1 and HMG2
Hormone & growth factor signalling	ER, b-Catenin, Importin
Cytoskeletal	α-Tubulin, Cortactin
DNA binding	TCF

Table 1: Examples of Non Histone Proteins.

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Received May 24, 2015; **Accepted** July 27, 2015; **Published** July 29, 2015

Citation: Moradzadeh M, Tabarraei A, Sadeghnia HR (2015) The Role of Histone Deacetylase (HDAC) as a Biomarker in Cancer. J Mol Biomark Diagn 5: 240. doi:10.4172/2155-9929.1000240

bind directly to ubiquitinated proteins through an ubiquitin-binding domain, and target cargo proteins for subsequent processing [18].

The Class III HDACs [Sir 1-7], which are homologues of the yeast protein Sir 2, require the cofactor NAD^+ for their deacetylase function, and are not targeted by the currently available HDAC inhibitors [24].

Class IV HDACs [only comprising HDAC-11], which localize in the nucleus, exhibit properties of both Class I and Class II HDACs [21] All the above HDACs are zinc dependent proteases.

Alteration of HDACs

Alteration of HDACs has been found in both hematological malignancies and solid tumors for a long time [25]. Genes coding for HDACs have been always found normal in such cancer cells [26], but altered expression and aberrant recruitment of HDACs in tumors have been found. In colon, breast, prostate, thyroid, cervical, and gastric cancers, some HDACs such as HDAC1, HDAC2, HDAC3, HDAC6, and SIR 7 have been found over expressed. Aberrant recruitment of HDACs results from chromosomal translocations has been found to have a causal role in tumorigenesis [27,28].

Histone acetylation

The most extensively used biomarker in HDAC inhibitor trials to date has been histone acetylation, in particular H3 and H4. Preclinical

Cancer	HDAC	Results
Gastric Carcinoma	HDAC1 HDAC2 HDAC3	78% of cases a moderate or strong acetylation of Histone H4. Over expression HDAC1, HDAC2 and HDAC 6 in 60%, 32% and 15% case respectively. Over expression HDAC6 show improved survival times that is independent of tumor aggressiveness [30]
Colorectal Carcinoma	HDAC1 HDAC2 HDAC3	Moderately expression of Class I HDACs 1, 2 and 3 in glandular and foveolar antral and corpus gastric epithelium. Over Expression of HDAC2 in tumors with nodal metastases and advanced tumor stage. HDAC2 protein expression had independent prognostic impact on overall survival [OS] [31,32]. Low acetylation of histone H4 in Class I HDACs [33]. Over expression of HDAC1 showed a negative association with patient survival and acetylation on H3K9 and H4K16 did not correlate with patient prognosis. Hyperacetylation of H3 was associated with poor tumor grade and diffuse type cancers [34].
Hepatocellular Carcinoma	HDAC1 HDACII	Over expression HDAC1, 2 and 3 in the level of mRNA and protein with overall protein expression 37% , 58% and 73% respectively. High expression of HDAC1 and HDAC2 was associated with enhanced tumor cell proliferation and negative prognostic impact on OS, only HDAC2 had an independent prognostic impact [35]. Negative prognostic impact of high HDAC1 mRNA levels on OS [36] Loss of expression of HDACI isoforms [37].
Pancreatic Carcinoma	HDAC1	Over HDAC1 protein expression in hepatocellular carcinomas that correlated with higher tumor stage and poor tumor differentiation [38]. Class II HDACs 4,5,6,7 and 10 , higher expression levels of both mRNA and protein have been reported in HCC [39].
Brain Tumors	HDAC9 HDAC11	High HDAC1 expression in 56% of pancreatic carcinomas that had significant prognostic impact on OS [40,41].
Prostate Carcinoma	HDAC1 HDAC2 HDAC3 HDAC4	Expression class I HDAC mRNA were lower than class II and IV isoforms. Low expression of HDAC9 (class II) and HDAC11 (class IV) mRNAs in high-grade tumors compared to low-grade tumors. High histone H3 acetylation levels in high-grade glioblastoma compared to low-grade gliomas [42].
Ovarian Carcinoma	HDAC1 HDAC2 HDAC3	High expression HDAC1, 2 and 3 protein in prostate adenocarcinomas and expression patterns these isoforms in high-grade Prostatic Intraepithelial Neoplasia (PIN) paralleled with invasive cancers. Disease-free survival (DFS) in patients with high-level HDAC2 protein expression reduced. Strong HDAC1 and HDAC2 protein expression associated with high Gleason grade and with high proliferative capacity [43]. High expression HDAC1 in hormone refractory cancers [44]. High expression HDAC4 in benign prostate hyperplasia, prostate cancers and hormone refractory cancers [45].
Endometrial Carcinoma	HDAC1 HDAC2 HDAC3	Over expression class I HDACs in ovarian carcinoma that positivity rates differ in tumor subtypes such as mucinous carcinomas (71%), high-grade serous (64%), clear cell (54%) and endometrioid subtypes (36%) and expression was usually higher in strongly proliferating tumors. Disease Specific patient Survival (DSS) in serous, mucinous, and clear cell carcinomas had no statistical significant but in endometrioid ovarian cancer had negative impact on patient survival [46,47].
Non-Small Cell Lung Carcinoma (NSCL)	HDACI HDACII	Over expression class I HDAC isoforms in endometrial carcinomas and like in ovarian carcinomas, clear cell (83%) and serous subtypes (69%) showed significantly higher expression rates of class I HDACs than endometrioid carcinomas. Strong HDAC1 protein expression but no HDAC2 and HDAC3 were associated with poor prognosis. None of the class I HDACs had independent prognostic impact on DSS [47].

Breast Carcinoma	HDAC1 HDAC3 HDAC6	Downregulation of HDAC4 mRNA in lung tumors [48,49]. Overexpression HDAC1 in stage III/IV tumors compared to stage I/II tumors [50]. Overexpression HDAC class I in NSCLC. mRNA HDAC7expression levels in node-negative low stage tumors higher than advanced tumors with nodal metastasis. RNA level class I HDAC expression had no impact on overall patient prognosis [51]. High mRNA expression of class II HDACs 4,5,6,7 and 10 was predictive of a better prognosis. Deacetylation of H3K9 in stage I NSCLC conferred a better prognosis, the same was true for patients with NSCLCs stage II and deacetylation on H2AK5 [52].
		HDAC1 and HDAC3 protein expression was high in estrogen and progesterone receptor positive tumors. High HDAC1 mRNA expression predicted better OS and DFS. HDAC1 expression predicted significantly DFS better than OS in patients with invasive breast cancers. HDAC3 protein expression had no impact on either DFS or OS. RNA expression of HDAC1 was not an independent predictor of either OS or DFS [53,54]. Reported no differences in OS and DFS in HDAC6 expression, however, and in the subgroup of ER positive patients with strong HDAC6 expression was an independent prognosticator of better DFS [55] Class II HDAC6 expression was positive in breast cancer and prominent in small, low-grade, estrogen and progesterone receptor positive tumors compared to larger high-grade hormone receptor negative cancers [55]. High HDAC6 protein had a negative prognostic influence [56].

Table 2: Histone deacetylase (HDAC) expression in human tumors.

and clinical studies have shown that there are several advantages of measuring histone acetylation. First, histone acetylation is a direct downstream modification regulated by HDAC, which can be detected within the tumor tissue. Second, histone acetylation can be measured in peripheral blood mononuclear cells [PBMCs], which are often taken as a surrogate tissue for tumors where biopsies are unobtainable without invasive procedures.

The use of the biomarker for hyperacetylation of histones [both in blood lymphocytes and tumor cells] has been useful as a guide to target specificity in early studies of HDAC inhibitors, and this biomarker has been the most extensively developed so far. Changes of this biomarker can be determined via Western blot, flowcytometry analysis or immunohistochemical methods.

There are various studies in cancer and tumor tissue that revealed changes in the acetylation levels and the expression of the HDAC enzymes, which summarized in (Table 2). In hematologic malignancies, the aberrant recruitment of HDACs to promoters plays a causal role in tumorgenesis [29].

Concluding Remarks

1. Histone deacetylases play a central role in the regulation of several cellular mechanisms.
2. The majority of studies showed an enhanced expression of class I HDAC isoforms in solid human tumors and was high in locally advanced dedifferentiated, strongly proliferating tumors.
3. In some but not all entities elevated class I HDAC expression was associated with patient prognosis.
4. Expression of class II HDACs has been found reduced in tumors and high expression of these isoforms in some entities predicted better patient outcome.
5. Since all of these data point to a potential biological role of differences in HDAC expression in human tumors, future translational studies will focus on the question, whether HDAC expression patterns are predictive for response to treatment with histone deacetylase inhibitors.

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