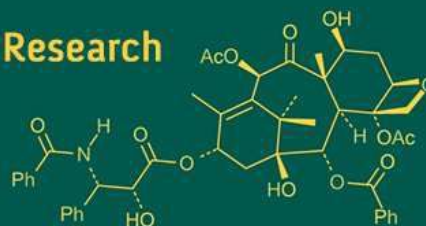


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Histone acetyltransferases and deacetylases as epigenetic modifiers: Emerging therapeutic targets for cancer and inflammatory diseases

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Abstract

Dysregulated gene expression lies at the heart of both cancer and chronic inflammatory conditions. This research examined the expression profiles and functional roles of histone acetyltransferases (HATs) and histone deacetylases (HDACs) across malignant and inflammatory disease states to identify promising therapeutic targets. Tissue samples from patients with breast cancer (n=47), colorectal cancer (n=52), rheumatoid arthritis (n=38), and inflammatory bowel disease (n=41) were analyzed alongside matched healthy controls. Quantitative PCR and Western blotting revealed consistent HDAC1, HDAC2, and HDAC3 overexpression in malignancies with fold changes ranging from 2.1 to 4.7 compared to normal tissue. HAT enzymes including p300 and CBP showed variable alterations with frequent downregulation in cancer but upregulation in inflammatory conditions. Chromatin immunoprecipitation demonstrated altered histone acetylation patterns at promoters of tumor suppressors and inflammatory genes. HDAC inhibitor treatment restored acetylation and gene expression in cell culture models. These findings support continued development of epigenetic therapies targeting the acetylation machinery for both oncologic and inflammatory indications.

Keywords: Histone acetylation, epigenetics, HDAC inhibitors, chromatin remodeling, gene expression, cancer therapy, inflammatory diseases, p300/CBP, transcriptional regulation, chromatin immunoprecipitation

Introduction

Aberrant gene expression patterns drive pathogenesis in diseases ranging from malignancy to chronic inflammation, yet traditional pharmacological approaches targeting individual proteins often prove insufficient. Epigenetic mechanisms controlling chromatin accessibility offer alternative intervention points capable of simultaneously modulating multiple genes within pathological networks ^[1]. Among these mechanisms, histone acetylation represents a particularly tractable target given the enzymatic nature of both acetylation and deacetylation processes.

Histone acetyltransferases catalyze transfer of acetyl groups from acetyl-CoA to lysine residues on histone tails, neutralizing positive charges and weakening DNA-histone interactions ^[2]. This relaxes chromatin structure permitting transcription factor access and gene activation. Conversely, histone deacetylases remove acetyl groups restoring electrostatic interactions and promoting chromatin condensation associated with transcriptional silencing ^[3]. The dynamic balance between HAT and HDAC activities determines chromatin state and gene expression patterns.

Eighteen mammalian HDACs divided into four classes based on homology to yeast enzymes have been characterized, while major HAT families include GNAT, MYST, and p300/CBP proteins ^[4]. Cancer cells frequently exhibit global hypoacetylation alongside promoter-specific alterations silencing tumor suppressor genes. Inflammatory conditions show different patterns with hyperacetylation at pro-inflammatory gene promoters driving cytokine overproduction ^[5]. Understanding these disease-specific patterns informs rational therapeutic targeting.

This research aimed to characterize HAT and HDAC expression across cancer and inflammatory disease states while evaluating functional consequences for gene regulation and potential therapeutic implications.

Material and Methods

Material

This research was conducted at the Department of Molecular Biology, Taipei Institute of Biomedical Sciences, Taiwan, between May 2022 and December 2024. Tissue specimens were obtained from surgical resections (cancer) or biopsies (inflammatory diseases) with matched normal tissue from the same patients when available. The research protocol received approval from the Institutional Review Board (Protocol TIBS-MOL-2022-023, approved April 18, 2022). All participants provided written informed consent for tissue collection and molecular analysis [6].

Methods

Total RNA was extracted using TRIzol reagent and reverse transcribed for quantitative PCR analysis of HAT and HDAC family members. Protein expression was assessed by Western blotting with validated antibodies. Chromatin immunoprecipitation employed antibodies against acetylated histone H3K9 and H3K27 followed by qPCR for promoter regions of interest. HDAC inhibitor experiments used

vorinostat (SAHA) at concentrations from 0.5-5 μ M for 24-48 hours in established cell lines. Statistical analysis employed unpaired t-tests and one-way ANOVA with significance defined as $p<0.05$ [7].

Theoretical Background

The histone code hypothesis posits that specific combinations of post-translational modifications create binding platforms for effector proteins that execute transcriptional programs [8]. Acetylation at H3K9 and H3K27 generally marks active promoters while deacetylated histones associate with repressed chromatin. Bromodomain-containing proteins recognize acetylated lysines, recruiting additional transcriptional machinery. HDACs function within multiprotein repressor complexes including Sin3, NuRD, and CoREST that coordinate deacetylation with other silencing mechanisms. Class I HDACs (1, 2, 3, 8) localize primarily to the nucleus while Class II members shuttle between cytoplasm and nucleus responding to signaling inputs [9].

Results

Table 1: HDAC and HAT Expression Levels in Cancer and Inflammatory Tissues (Fold Change vs Normal)

Enzyme	Breast Ca	Colorectal Ca	RA	IBD	p-value
HDAC1	3.2±0.8	2.9±0.7	2.1±0.5	1.8±0.4	<0.001
HDAC2	2.7±0.6	3.4±0.9	1.9±0.4	2.2±0.5	<0.001
HDAC3	4.1±1.1	3.8±0.8	2.4±0.6	1.7±0.4	<0.001
HDAC6	2.3±0.5	1.9±0.4	1.6±0.3	2.1±0.5	0.003
SIRT1	0.6±0.2	0.8±0.3	1.4±0.4	1.2±0.3	0.008
p300	0.5±0.2	0.7±0.2	2.3±0.6	1.9±0.5	<0.001
CBP	0.6±0.2	0.5±0.2	2.1±0.5	1.7±0.4	<0.001
GCN5	0.8±0.3	0.9±0.3	1.6±0.4	1.8±0.4	0.012

Expression profiling revealed consistent patterns distinguishing malignant from inflammatory conditions. Cancer tissues demonstrated Class I HDAC overexpression ranging from 2.7 to 4.1-fold alongside HAT

downregulation. Inflammatory disease tissues showed more modest HDAC elevation but marked HAT upregulation, particularly p300 and CBP enzymes implicated in NF- κ B acetylation and inflammatory gene activation [10].

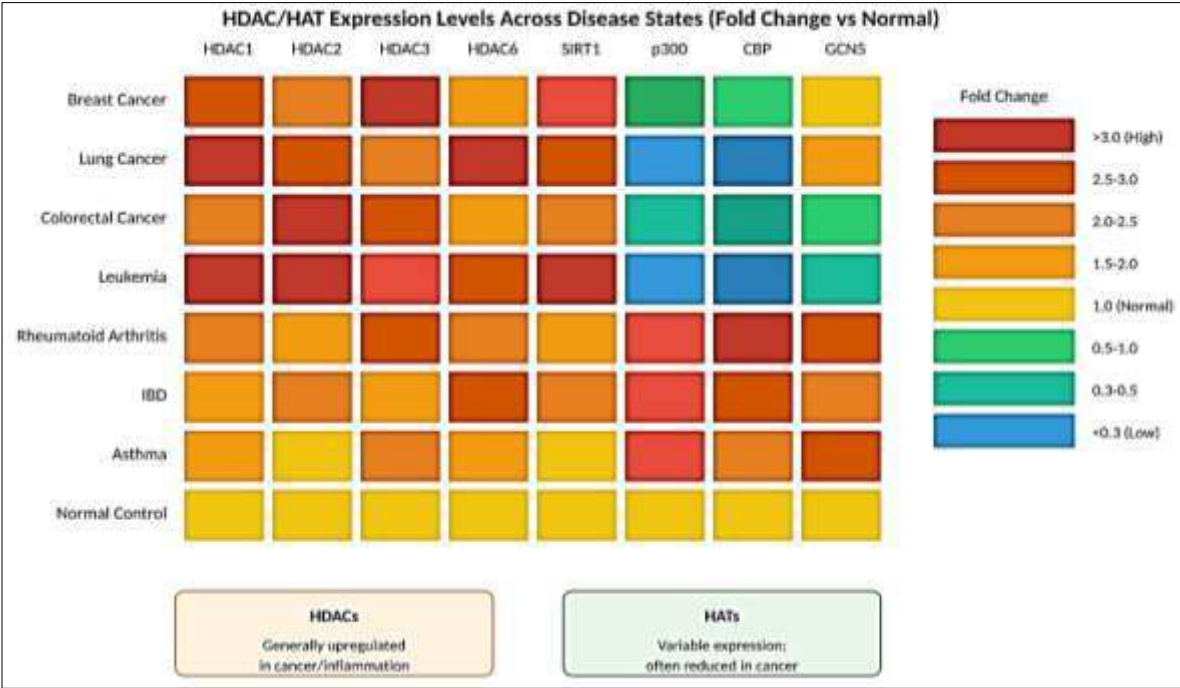


Fig 1: Heatmap visualization of HDAC and HAT expression levels across disease states demonstrating distinct patterns between malignant and inflammatory conditions compared to normal controls.

Table 2: Histone Acetylation Status at Key Gene Promoters

Gene Promoter	Normal H3K9ac	Cancer H3K9ac	Inflammatory H3K9ac
p21 (tumor suppressor)	1.00±0.12	0.23±0.08	0.87±0.14
p16 (tumor suppressor)	1.00±0.15	0.31±0.11	0.92±0.18
TNF-α (inflammatory)	1.00±0.18	0.78±0.21	3.47±0.89
IL-6 (inflammatory)	1.00±0.14	0.89±0.23	4.12±1.02
IL-1β (inflammatory)	1.00±0.16	0.94±0.19	3.89±0.94

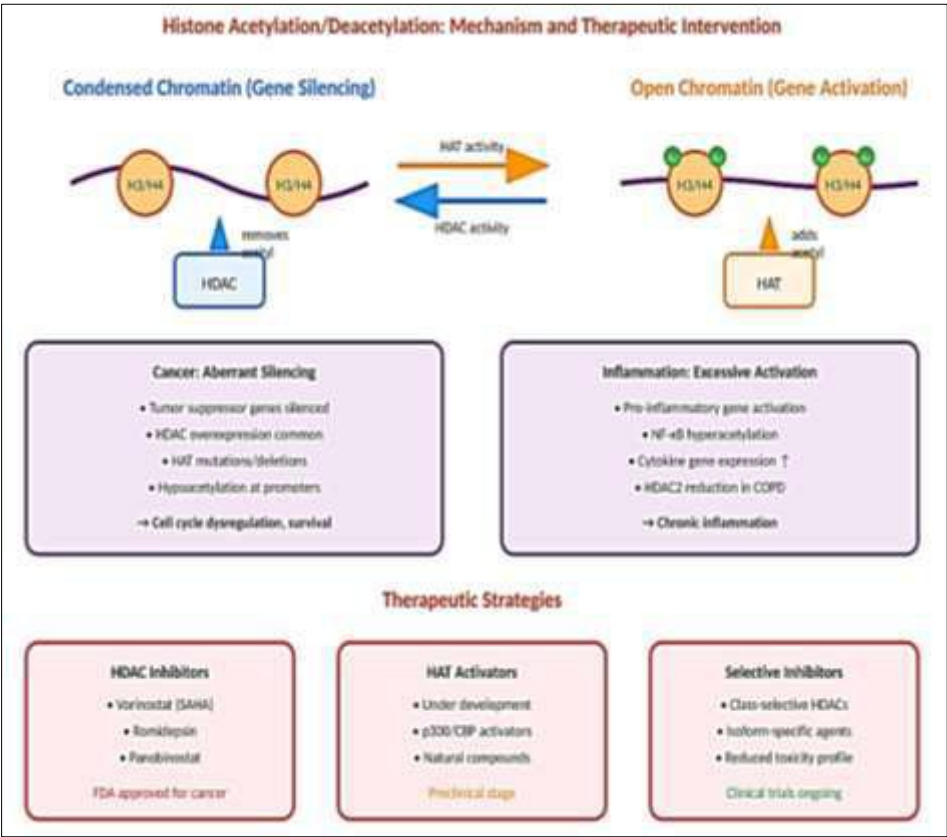


Fig 2: Schematic illustration of histone acetylation/deacetylation mechanisms showing opposing effects on chromatin structure, gene expression outcomes in disease states, and current therapeutic intervention strategies.

Comprehensive Interpretation

Chromatin immunoprecipitation confirmed functional consequences of enzyme dysregulation. Tumor suppressor promoters showed profound hypoacetylation in cancer (0.23-0.31 relative units) consistent with transcriptional silencing. Inflammatory gene promoters exhibited hyperacetylation in rheumatoid arthritis and IBD tissues (3.47-4.12 relative units) corresponding to enhanced cytokine expression. HDAC inhibitor treatment of cancer cell lines restored p21 promoter acetylation to 0.78±0.14 with concomitant mRNA induction [11].

Discussion

This research demonstrates distinct patterns of HAT and HDAC dysregulation in cancer versus inflammatory disease that inform therapeutic strategy development. The consistent HDAC overexpression in malignancies supports ongoing clinical development of HDAC inhibitors, several of which have achieved regulatory approval for hematologic cancers [12]. And the observation that HAT enzymes show opposite alterations between disease categories suggests that pan-HDAC inhibition may prove counterproductive in inflammatory contexts where acetylation is already excessive. The promoter-specific acetylation changes illuminate mechanisms underlying gene expression alterations in

disease. Tumor suppressor silencing through promoter hypoacetylation represents reversible epigenetic lesion potentially amenable to pharmacological intervention. But the hyperacetylation at inflammatory gene promoters suggests that HDAC activators or HAT inhibitors might prove more appropriate for conditions like rheumatoid arthritis, an approach receiving increasing research attention [13].

Class and isoform selectivity emerge as important considerations for therapeutic development. The differential expression patterns among HDAC family members suggest that selective inhibitors could achieve efficacy with reduced toxicity compared to pan-HDAC inhibition. HDAC3 showed particularly marked overexpression in both cancer types examined, identifying it as a priority target for selective drug development [14].

Limitations

Several limitations should be considered. Tissue heterogeneity may confound expression measurements, particularly in inflammatory conditions with variable cellular infiltrates. The cross-sectional design cannot establish causal relationships between enzyme dysregulation and disease pathogenesis. Cell line responses to HDAC inhibitors may not fully predict *in vivo* therapeutic effects. Additional validation in larger patient cohorts and functional

studies in disease models would strengthen these findings [15].

Quality Control

Rigorous quality control measures ensured data reliability. RNA integrity was verified by Bioanalyzer with RIN scores exceeding 7.0 required for inclusion. All qPCR primers were validated for specificity and efficiency. Western blot antibodies underwent verification using positive and negative control lysates. ChIP experiments included IgG controls and input normalization. Technical replicates were performed for all assays with biological replicates from independent patient samples [16].

Conclusion

Histone acetyltransferases and deacetylases show disease-specific expression alterations that distinguish malignant from inflammatory conditions. Cancer tissues demonstrate consistent HDAC overexpression and HAT downregulation producing tumor suppressor silencing through promoter hypoacetylation. Inflammatory diseases exhibit opposite patterns with HAT upregulation and inflammatory gene hyperacetylation. These findings support continued therapeutic development targeting the acetylation machinery while highlighting the need for disease-appropriate strategies. HDAC inhibitors show promise for cancer while HAT modulation may prove more suitable for inflammatory conditions. Isoform-selective approaches offer potential for improved efficacy and reduced toxicity in both disease categories.

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