

The Role of Histone Deacetylase (HDAC) in Cancer



Educational Slide Kit
Including Animations

The Role of Histone Deacetylase (HDAC) in Cancer

This PowerPoint slide program, *The Role of Histone Deacetylase (HDAC) in Cancer*, is intended as an educational resource.

A bibliography is included at the end of the slide program. Additional copies of *The Role of Histone Deacetylase (HDAC) in Cancer* will be available online at TargetHDAC.com.

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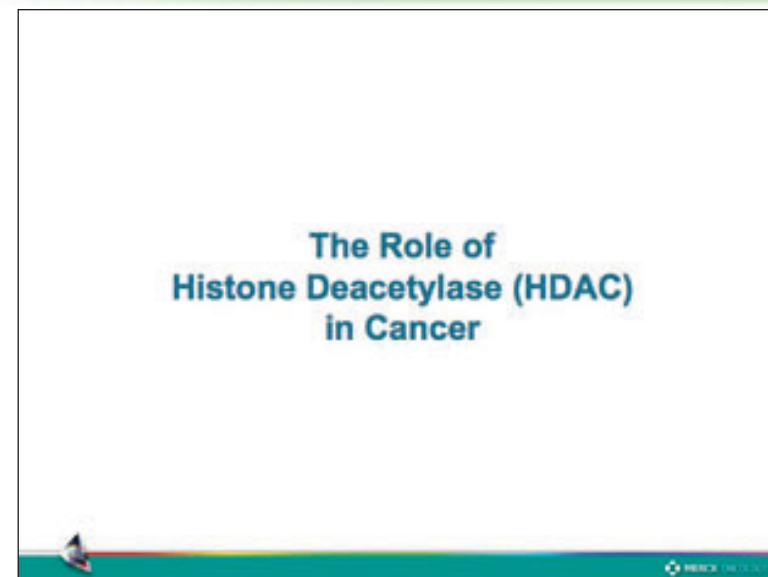
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The Role of Histone Deacetylase (HDAC) in Cancer

The following slides provide an introduction to HDAC and its role in the development of cancer. This presentation is intended to be used as an educational resource.

Topics for Discussion

- Epigenetics and its role in the development of cancer
- Chromatin structure, chromatin remodeling, and gene expression
- Histone protein modification via acetylation and deacetylation
- Role of histone acetyltransferase (HAT) and histone deacetylase (HDAC) in gene expression
- Role of HDAC in cancer
- Effect of HAT and HDAC on nonhistone proteins

Topics for Discussion

This slide program will present information on the following topics:

- Epigenetics and its role in the development of cancer
- Chromatin structure
- Chromatin remodeling leading to gene expression and suppression within the chromosome
- Histone protein modification via acetylation and deacetylation
- Role of histone acetyltransferase (HAT) and histone deacetylase (HDAC) in gene expression
- Role of HDAC in cancer
- Effect of HAT and HDAC on nonhistone proteins

Overview of Epigenetics

- Epigenetics refers to heritable modifications in gene activity that do not involve changes in the DNA sequence.¹
- Epigenetic processes affect gene regulation and expression by changing the structure and conformation of DNA within chromatin.²
- DNA conformation changes resulting from epigenetic processes can alter the ability of a gene to interact with transcription factors.^{2,3}

Overview of Epigenetics

Epigenetics is defined as heritable modifications in gene activity that occur without a change in the DNA sequence.¹ Epigenetic processes affect gene regulation by changing the structure and conformation of the DNA within chromatin.²

DNA methylation and histone acetylation are 2 examples of epigenetic processes.³


Changes in DNA conformation resulting from epigenetic processes alter the ability of a gene to interact with transcription factors and therefore affect gene expression.^{2,4}

Epigenetic processes modulate when genes are expressed or repressed. These processes also modulate the level at which genes are expressed or repressed.

References:

1. Spraycar M, ed. *Stedman's Medical Dictionary*. 26th ed. Baltimore, Md: Williams & Wilkins; 1995:583.
2. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. *Nature*. 2004;429:457-463.
3. Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. *Nat Rev Drug Discov*. 2002;1:287-299.
4. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.

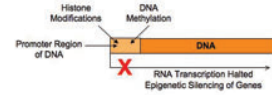
Epigenetics and Cancer



- Alterations in epigenetic processes involved in regulation of gene expression are associated with cancer.¹
- DNA methylation and histone modifications may result in epigenetic silencing of genes, such as tumor suppressor genes.^{2,3}
- Repressing the transcription of tumor suppressor genes may allow cancer cell proliferation.^{3,4}

1. Johnstone RW. *Nat Rev Drug Discov*. 2002;1:287-299.
2. Egger G et al. *Science*. 2004;303:918-922.
3. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.
4. Marks PA et al. *Curr Mol Chem*. 2002;1:2343-2350.

Epigenetics and Cancer (cont)



- Alterations in epigenetic processes involved in regulation of gene expression are associated with cancer.¹
- DNA methylation and histone modifications may result in epigenetic silencing of genes, such as tumor suppressor genes.^{2,3}
- Repressing the transcription of tumor suppressor genes may allow cancer cell proliferation.^{3,4}

1. Johnstone RW. *Nat Rev Drug Discov*. 2002;1:287-299.
2. Egger G et al. *Science*. 2004;303:918-922.
3. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.
4. Marks PA et al. *Curr Mol Chem*. 2002;1:2343-2350.

Epigenetics and Cancer

Alterations in epigenetic processes involved in the regulation of gene expression are associated with various types of cancer.¹⁻³

Histone deacetylation and other modifications can cause tightening of chromatin and can block transcriptional activation. Histone modification can also attract DNA methyltransferases to initiate cytosine methylation, which in turn can reinforce histone modification patterns conducive to silencing.³


Transcriptional repression of tumor suppressor genes may allow cancer cell proliferation.^{2,4}

To explain how the aberrations in this process can lead to cancer, we will describe chromatin structure and how it plays a role in DNA transcription and gene expression, the role of HDAC in chromatin remodeling, and the role of abnormal or sustained HDAC in cancer development.

References:

1. Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. *Nat Rev Drug Discov*. 2002;1:287-299.
2. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
3. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. *Nature*. 2004;429:457-463.
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Chromatin Structure^{1,2}



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1. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.
2. Zhang Y et al. *Genes Dev*. 2001;15:2343-2360.

Chromatin Structure

Within the chromosome, DNA is packaged into chromatin. Chromatin consists of DNA, structural histone proteins, and nonhistone proteins. Nucleosomes are the repeating units in chromatin. Nucleosomes are made up of approximately 146 base pairs of 2 superhelical turns of DNA wrapped around a core of 8 histones. The 8 histones are actually 2 copies of 4 different histones, H2A, H2B, H3, and H4.^{1,2}


Histones are responsible for maintaining the chromatin's shape and structure.¹⁻³

References:

1. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.
2. Zhang Y, Reinberg D. Transcription regulation by histone methylation: interplay between different covalent modifications of the core histone tails. *Genes Dev*. 2001;15:2343-2360.
3. Avers CJ. *Basic Cell Biology*. 2nd ed. Boston, Mass: Willard Grant Press; 1982:353-395.

Chromatin Remodeling: Histone Modifications

Histone modifications



Methylation Phosphorylation Acetylation

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- Chromatin structure is controlled by a variety of histone modifications, including methylation, phosphorylation, and acetylation.^{1,2}
- Histone modifications occur at the aminoterminal tails of the histones that protrude from the nucleosomes.²
- Chromatin remodeling directly affects gene expression.³

1. Marks PA et al. In: Cancer Principles & Practice of Oncology, 7th ed. Lippincott Williams & Wilkins, 2005:426-445.
2. Meunier D et al. In: Verdin E, ed. Histone Deacetylases: Transcriptional Regulation and Other Cellular Functions. Humana Press, 2006:3-22.
3. Johnstone RW. Nat Rev Drug Discov. 2002;1:287-299.

Chromatin Remodeling: Histone Modifications

The chromatin structure is controlled by a variety of histone modifications, including methylation, phosphorylation, and acetylation, that occur at the aminoterminal tails of the histones that protrude from the nucleosomes.^{1,2}

Extending out of the nucleosome are the charged aminoterminal tails of lysine. Lysine is one of the amino acids within the histone proteins that undergo biochemical modification. Specifically, the positively charged aminoterminal tails of lysine extend out of the nucleosome and may undergo modification such as acetylation.³

Other covalent modifications of histones include methylation of lysines and arginines and phosphorylation of serines and threonines.⁴

Acetylation of lysine changes the electrostatic environment of the histones and alters the way DNA can be wrapped around the histones.

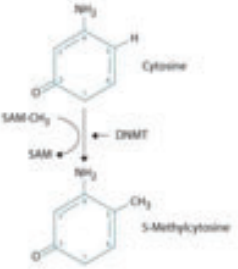
The modified amino acids in the histones may subsequently undergo a modification that results in the removal of methyl, acetyl, or phosphate groups.

References:

- Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*, 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.
- Meunier D, Seiser C. Histone deacetylase 1. In: Verdin E, ed. *Histone Deacetylases: Transcriptional Regulation and Other Cellular Functions*. Totowa, NJ: Humana Press; 2006:3-22.
- Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. *Nat Rev Drug Discov*. 2002;1:287-299.
- Lund AH, van Lohuizen M. Epigenetics and cancer. *Genes Dev*. 2004;18:2315-2335.

Chromatin Remodeling: DNA Methylation

- DNA methylation can also be involved in chromatin remodeling.^{1,2}
 - Methylation of DNA occurs at cytosine residues in CpG islands in the promoter region of a gene.
 - Methylation of DNA prevents gene transcription.
 - Methylation of DNA can also recruit HDAC, inducing transcriptional repression.



1. Egger G et al. Nature. 2004;429:457-463.
2. Johnstone RW. Nat Rev Drug Discov. 2002;1:287-299.

Chromatin Remodeling: DNA Methylation

Aberrant methylation of the CpG islands in genes is the most common structural alteration that occurs in cancer cells.¹

DNA methylation occurs most commonly at the nucleic acid cytosine, in the promoter region of a gene called the CpG island. The CpG island is so named because it contains a large proportion of CG sequences (eg, cytosine and guanine) on the promoter region of the gene.¹

These nucleic acids in the DNA are normally free of methylation.¹

Methylation is mediated by a family of enzymes called DNA methyltransferases (DNMTs). The DNMT enzymes, and other CpG binding proteins, recruit HDAC to the area where the gene is located. HDAC subsequently deacetylates the histones, which causes tighter coiling of the DNA around the histone and a closed chromatin structure.^{1,2}


This deacetylation represses gene transcription.²

References:


- Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. *Nature*. 2004;429:457-463.
- Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. *Nat Rev Drug Discov*. 2002;1:287-299.

Chromatin Remodeling and Regulation of Gene Expression¹⁻³

- Coiling and uncoiling of DNA around histones regulates gene expression and suppression.
- Open chromatin structure is associated with transcriptional activation.
- Closed chromatin structure is associated with transcriptional repression.



Open chromatin
transcriptional activation



Closed chromatin
transcriptional repression

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1. Arts J et al. *Curr Med Chem*. 2003;10:2343-2350.
2. Calvo KR et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:61-72.
3. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.

Chromatin Remodeling and Regulation of Gene Expression

Chromatin remodeling refers to the coiling and uncoiling of DNA around histones. Chromatin remodeling regulates the expression and suppression of genes by determining which sections of the DNA are available for transcription.¹⁻³

For a gene to be transcribed, it must become physically accessible to transcriptional machinery.²

Uncoiling of the DNA through regulated chromatin remodeling, such as occurs in histone acetylation, results in an open chromatin structure. This allows binding sites on the DNA to become accessible to transcription factor complexes, resulting in gene transcription.¹⁻³

Tight coiling of the DNA around the histones, such as occurs in histone deacetylation, results in a closed chromatin structure. These genes are no longer accessible to transcriptional machinery.¹⁻³


Thus, histone deacetylation results in repression of gene transcription.¹⁻³

References:

1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
2. Calvo KR, Petricoin EF III, Liotta LA. Genomics and proteomics. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:51-72.
3. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.

Histone Modification via Acetylation and Deacetylation

- Acetylation and deacetylation of histone tails regulate chromatin remodeling and play a key role in gene expression and suppression.¹
- HAT acetylates histone tails, opening chromatin structure.²⁻⁴
- HDAC deacetylates histone tails, closing chromatin structure.²⁻⁴



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1. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.
2. Arts J et al. *Curr Med Chem*. 2003;10:2343-2350.
3. Di Gennaro E et al. *Amino Acids*. 2004;26:435-441.
4. Johnstone RW. *Nat Rev Drug Discov*. 2002;1:287-299.

Histone Modification via Acetylation and Deacetylation

Acetylation of histone tails is now generally acknowledged to play a key role in the regulation of gene expression.¹

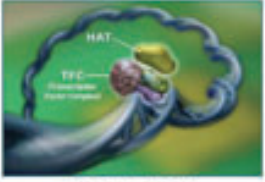
Two nucleosomal enzymes, HAT and HDAC, determine the acetylation status of the histones.²⁻⁴

References:

1. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.
2. Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. *Nat Rev Drug Discov*. 2002;1:287-299.
3. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
4. Di Gennaro E, Bruzese F, Caraglia M, Abruzzese A, Budillon A. Acetylation of proteins as novel target for antitumor therapy: review article. *Amino Acids*. 2004;26:435-441.

HAT and Gene Expression

- Recruitment of HAT by a transcription factor complex results in uncoiling of DNA.^{1,2}
- Binding sites on DNA become accessible to transcriptional machinery.³
- HAT recruitment plays a role in activating gene transcription.^{1,3}



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1. Arts J et al. *Curr Med Chem*. 2003;10:2343-2350.
2. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.
3. Calvo KR et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:51-72.

HAT and Gene Expression

It has been proposed that HAT is recruited by a transcription factor complex, resulting in acetylation of the histones. This makes genes accessible to transcriptional machinery.¹⁻³


Thus, HAT recruitment plays a role in promoting the transcription of genes.^{1,2}

References:

1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
2. Calvo KR, Petricoin EF III, Liotta LA. Genomics and proteomics. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:51-72.
3. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.

Gene Transcription and Translation

- Genes in DNA are transcribed into RNA.
- RNA is translated into proteins.
- Proteins are involved in regulation of¹:
 - Cell cycle
 - Cell proliferation
 - Cell differentiation



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1. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.

Gene Transcription and Translation

Genes contain the blueprint for a specific protein. The base sequences in DNA are transcribed into RNA. RNA is then translated into specific proteins.

These proteins are involved in a variety of biologic processes that regulate¹:


- Cell cycle
- Cell proliferation
- Cell differentiation

Reference:

1. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.

HDAC and Gene Expression¹⁻³

- Recruitment of HDAC by a transcription factor complex results in tightening of chromatin structure.
- Transcriptional machinery is prevented from accessing the DNA.
- Gene transcription is repressed.



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1. Arts J et al. *Curr Med Chem*. 2003;10:2343-2350.
 2. Calvo KR et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:61-72.
 3. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.

HDAC and Gene Expression

HDACs tighten the binding of the DNA to the histones, preventing certain genes access to transcriptional proteins.¹⁻³


It has been proposed that if HDAC is recruited to a transcription factor complex instead of HAT, the activation of gene transcription in that section of DNA is prevented.¹⁻³

References:

1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
2. Calvo KR, Petricoin EF III, Liotta LA. Genomics and proteomics. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:51-72.
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Excess HDAC and the Association With Cancer

- Overexpressed or sustained HDAC activity, occurring in some cancer cells, results in deacetylation of the histone tails.¹⁻³
- Histone deacetylation results in a more closed chromatin structure.^{1,2}
- Certain genes may become inaccessible to transcription factors and do not get transcribed.¹⁻³
- Histone deacetylation is thought to be a mechanism for silencing tumor suppressor genes and genes for cyclin-dependent kinase inhibitors.³
- Aberrant HDAC level and/or sustained activity has been found in various types of cancer.³



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1. de Ruijter AJM et al. *Biochem J*. 2003;370:737-749.
 2. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.
 3. Arts J et al. *Curr Med Chem*. 2003;10:2343-2350.

Excess HDAC and the Association With Cancer

Overexpressed or sustained HDAC activity, occurring in some cancer cells, results in deacetylation of the histone tails.¹⁻³

Histone deacetylation results in a more closed chromatin structure.^{1,2}

Certain genes may become inaccessible to transcription factors and do not get transcribed.¹

This is thought to be a mechanism for limiting or silencing tumor suppressor genes, such as p53, and genes for cyclin-dependent kinase inhibitors, such as p21.^{1,2}

Epigenetic silencing of these genes may play a role in the risk of cancer development resulting in uncontrolled cell growth.³

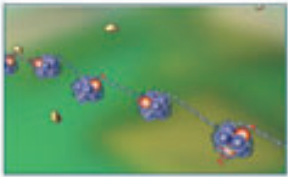
Aberrant HDAC levels that limit or silence gene expression have been described in leukemias and lymphomas, as well as other malignancies.³

References:

1. de Ruijter AJM, van Gennip AH, Caron HN, Kemp S, van Kuilenburg ABP. Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem J*. 2003;370:737-749.
2. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.
3. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.

Restoring Gene Expression

- Reestablishing the balance between HAT and HDAC allows for acetylation of histone tails.^{1,2}
- Histone acetylation opens the chromatin, restoring access to transcription factor binding sites.³
- Expression of cell cycle-regulating genes is reactivated.²⁻⁴



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1. Arts J et al. *Curr Med Chem*. 2003;10:2343-2350.
 2. Di Gennaro E et al. *Amino Acids*. 2004;26:435-441.
 3. de Ruijter AJM et al. *Biochem J*. 2003;370:737-749.
 4. Marks PA et al. In: *Cancer Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.

Restoring Gene Expression

Restoring the balance between HAT and HDAC allows acetylation of histone tails by HAT.^{1,2}

This leads to an open chromatin conformation, where binding sites on the DNA become accessible to transcription factors.³

As a result, the expression of genes, such as those involved in tumor suppression and cell-cycle regulation, is reactivated.²⁻⁴

References:

1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
2. Di Gennaro E, Bruzzese F, Caraglia M, Abruzzese A, Budillon A. Acetylation of proteins as novel target for antitumor therapy: review article. *Amino Acids*. 2004;26:435-441.
3. de Ruijter AJM, van Gennip AH, Caron HN, Kemp S, van Kuilenburg ABP. Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem J*. 2003;370:737-749.
4. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.

Effect of HAT and HDAC on Nonhistone Proteins

- Imbalances in HAT and HDAC activity may cause changes in the structure and activities of nonhistone proteins, including¹⁻³:
 - Tumor suppressor protein p53
 - Retinoblastoma protein (pRB)
 - Some transcription factor proteins involved in normal cell-cycle regulation
- Changes in these proteins can affect^{1,2}:
 - Cell-cycle progression
 - Cell proliferation
 - Apoptosis

1. Kelly WK et al. *Expert Opin Investig Drugs*. 2002;11:1695-1713.
 2. Marks PA et al. In: *Cancer Principles & Practice of Oncology*. 7th ed. Lippincott Williams & Wilkins; 2005:439-445.
 3. Weener D et al. In: Verdón E, ed. *Histone Deacetylase: Transcriptional Regulation and Other Cellular Functions*. Humana Press; 2006:3-22.

Effect of HAT and HDAC on Nonhistone Proteins

As we have discussed, imbalances in histone acetylation may lead to changes in chromatin structure and to dysregulation of gene transcription, such as those coding for tumor suppressor proteins, such as p53, and cyclin-dependent kinase inhibitors, such as p21.¹⁻³

HDAC has also been found to deacetylate nonhistone proteins, as well. Nonhistone proteins affected may include the tumor suppressor proteins and transcription factor proteins that are involved in normal cell-cycle regulation. Changes in the activities of these proteins can affect cell-cycle progression, proliferation, differentiation, and apoptosis.^{1,4}

References:

1. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.
2. de Ruijter AJM, van Gennip AH, Caron HN, Kemp S, van Kuilenburg ABP. Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem J*. 2003;370:737-749.
3. Marks PA, Rifkind RA, Richon VM, Breslow R, Miller T, Kelly WK. Histone deacetylases and cancer: causes and therapies. *Nat Rev Cancer*. 2001;1:194-202.
4. Kelly WK, O'Connor OA, Marks PA. Histone deacetylase inhibitors: from target to clinical trials. *Expert Opin Investig Drugs*. 2002;11:1695-1713.

Summary: HDAC and Regulation of Gene Expression

- Histone acetylation and deacetylation affect gene regulation by changing the conformation of DNA in chromatin.^{1,2}
- HAT and HDAC are enzymes that regulate histone acetylation and deacetylation.¹
- Aberrant HDAC levels or sustained HDAC activity results in histone deacetylation, tightly packaged chromatin, and dysregulation of gene transcription.¹

1. Arts J et al. *Curr Med Chem*. 2003;10:2343-2350.
2. Di Gennaro E et al. *Amino Acids*. 2004;26:435-441.

Summary: HDAC and Regulation of Gene Expression

Histone acetylation and deacetylation, as regulated by HAT and HDAC, are epigenetic processes that affect gene regulation by changing the conformation of DNA in chromatin.^{1,2}

Imbalances in histone acetylation can lead to changes in chromatin structure, interrupting normal gene expression.²

References:

1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
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Summary: HDAC and Cancer

- Histone deacetylation by HDAC may be a mechanism for silencing some tumor suppressor genes and other genes responsible for cell cycle progression, cell proliferation, differentiation, and apoptosis.^{1,2}
- Increasing evidence indicates that altered HAT and HDAC activity is associated with cancer.³

1. Marks PA et al. In: *Cancer: Principles & Practice of Oncology*, 7th ed. Lippincott Williams & Wilkins; 2005:439-445.
2. Kelly WK et al. *Expert Opin Investig Drugs*. 2002;11:1695-1713.
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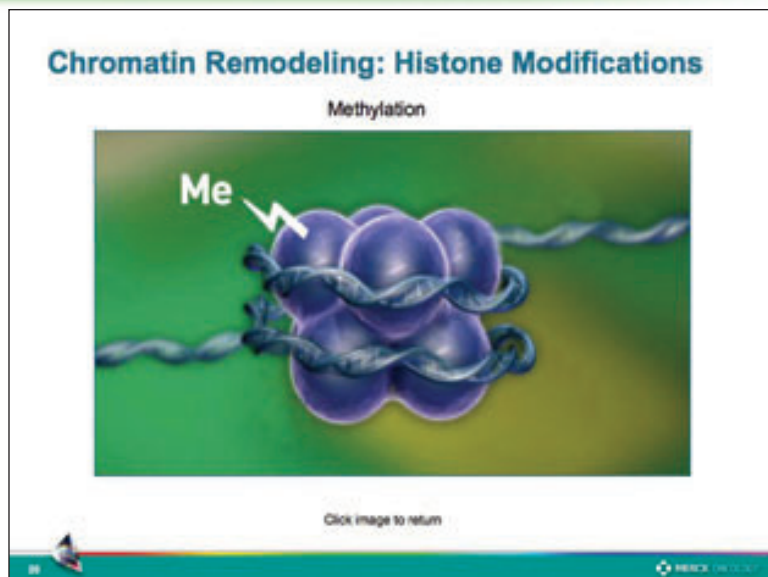
Summary: HDAC and Cancer

Deacetylation of histones, resulting from inappropriate HDAC levels, may be a mechanism for silencing the expression of some tumor suppressor genes and other genes responsible for cell-cycle progression, proliferation, differentiation, and apoptosis.^{1,2}

Loss of these gene products is believed to lead to cancer.³

References:

1. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*, 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.
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Chromatin Remodeling: Histone Modifications

The chromatin structure is controlled by a variety of histone modifications, including methylation, phosphorylation, and acetylation, that occur at the aminoterminal tails of the histones that protrude from the nucleosomes.^{1,2}

Extending out of the nucleosome are the charged aminoterminal tails of lysine. Lysine is one of the amino acids within the histone proteins that undergo biochemical modification. Specifically, the positively charged aminoterminal tails of lysine extend out of the nucleosome and may undergo modification such as acetylation.³

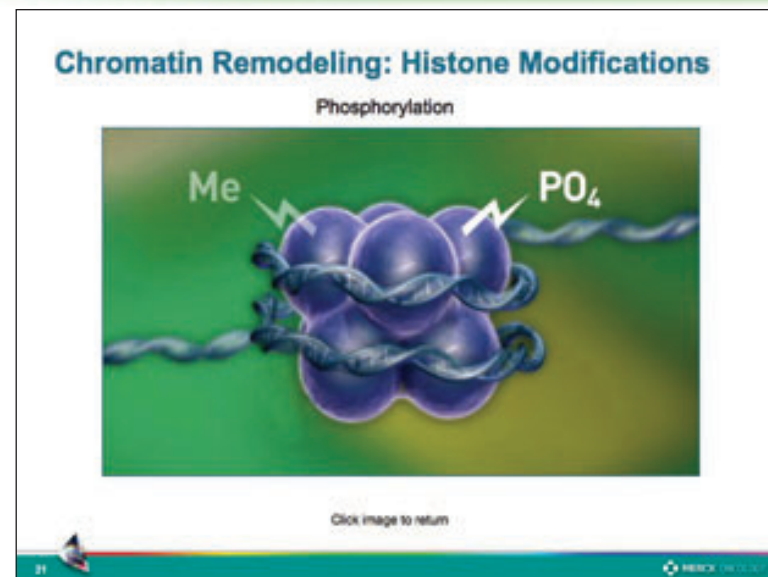
Other covalent modifications of histones include methylation of lysines and arginines and phosphorylation of serines and threonines.⁴

Acetylation of lysine changes the electrostatic environment of the histones and alters the way DNA can be wrapped around the histones.

The modified amino acids in the histones may subsequently undergo a modification that results in the removal of methyl, acetyl, or phosphate groups.

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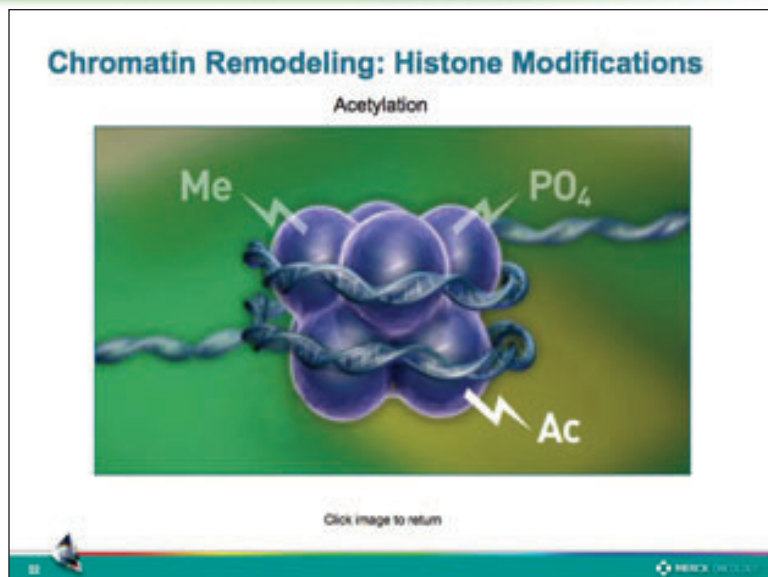
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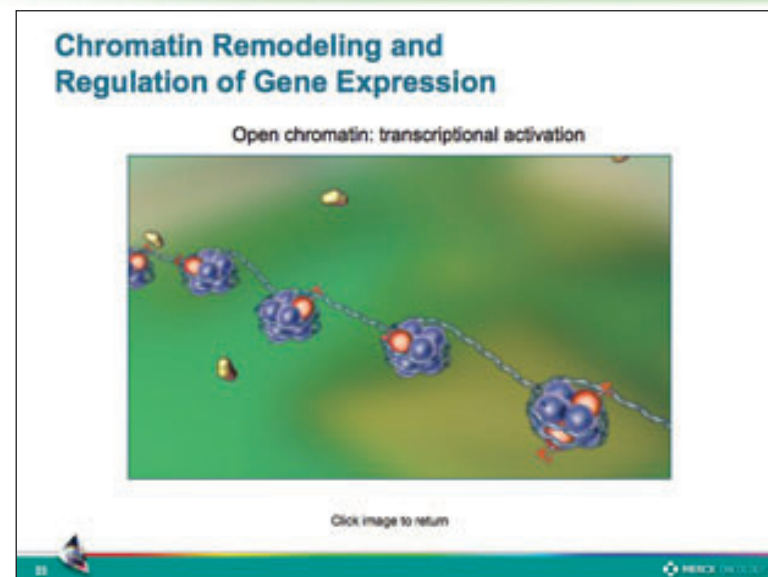
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Chromatin Remodeling and Regulation of Gene Expression

Chromatin remodeling refers to the coiling and uncoiling of DNA around histones. Chromatin remodeling regulates the expression and suppression of genes by determining which sections of the DNA are available for transcription.¹⁻³

For a gene to be transcribed, it must become physically accessible to transcriptional machinery.²

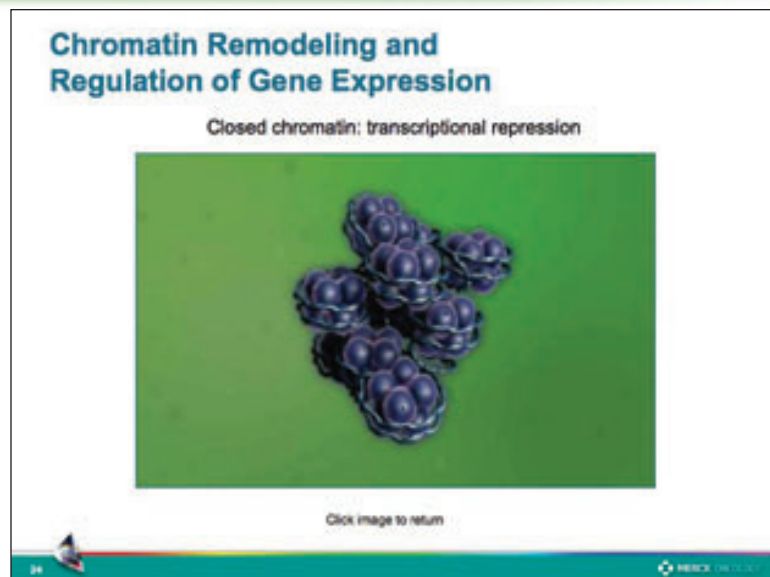
Uncoiling of the DNA through regulated chromatin remodeling, such as occurs in histone acetylation, results in an open chromatin structure. This allows binding sites on the DNA to become accessible to transcription factor complexes, resulting in gene transcription.¹⁻³

Tight coiling of the DNA around the histones, such as occurs in histone deacetylation, results in a closed chromatin structure. These genes are no longer accessible to transcriptional machinery.¹⁻³

Thus, histone deacetylation results in repression of gene transcription.¹⁻³

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1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
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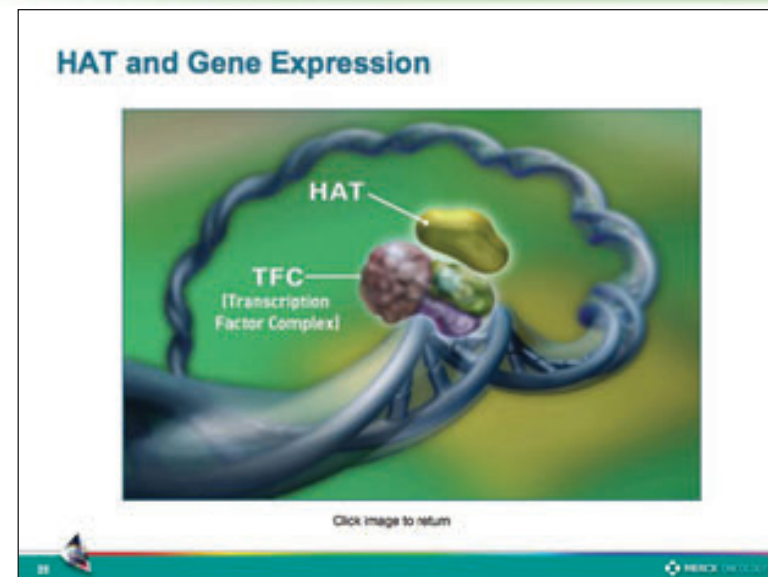
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HAT and Gene Expression

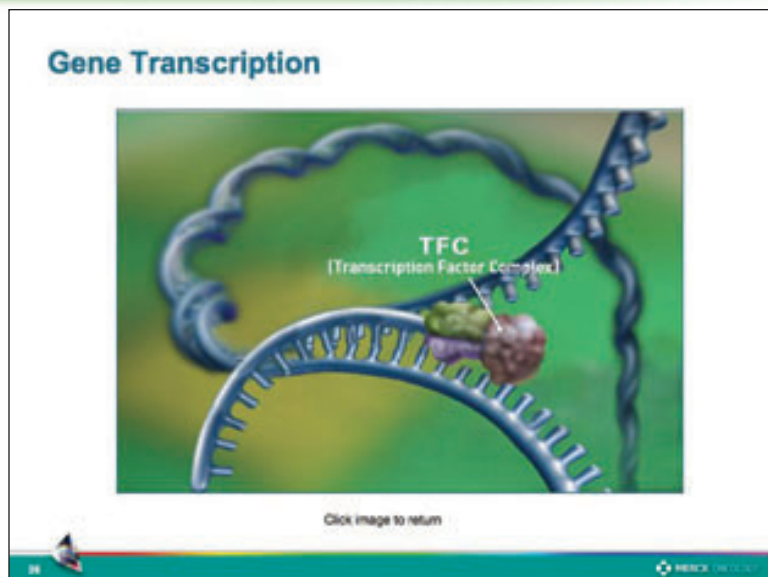
It has been proposed that HAT is recruited by a transcription factor complex, resulting in acetylation of the histones. This makes genes accessible to transcriptional machinery.¹⁻³

Thus, HAT recruitment plays a role in promoting the transcription of genes.^{1,2}

References:

1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem.* 2003;10:2343-2350.
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Enlargement of Slide 12 Image



Gene Transcription and Translation

Genes contain the blueprint for a specific protein. The base sequences in DNA are transcribed into RNA. RNA is then translated into specific proteins.

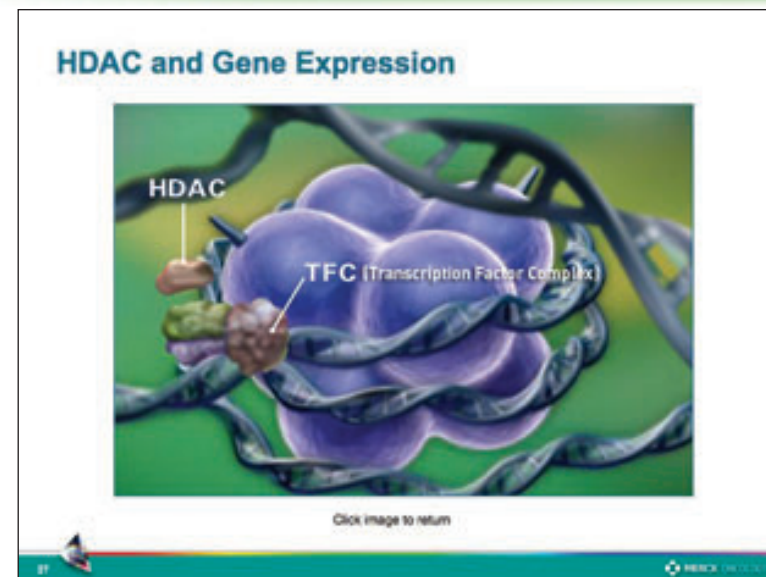
These proteins are involved in a variety of biologic processes that regulate¹:

- Cell cycle
- Cell proliferation
- Cell differentiation

Reference:

1. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.

Enlargement of Slide 13 Image



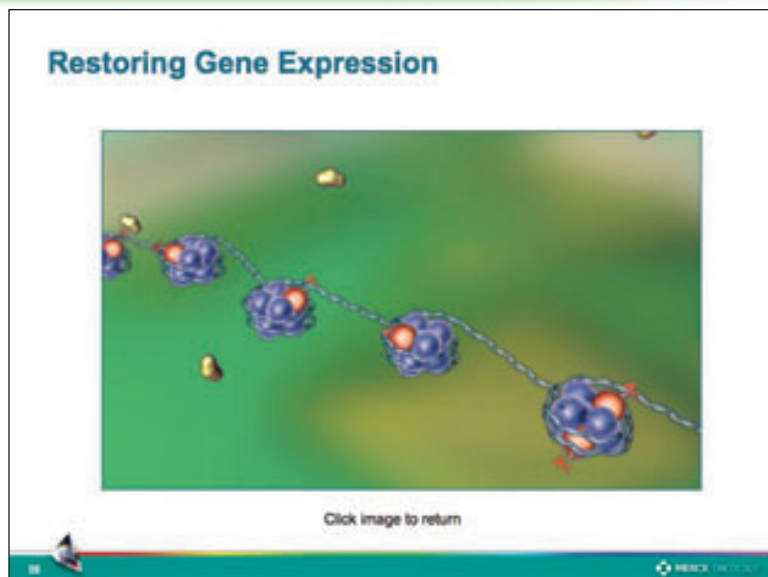
HDAC and Gene Expression

HDACs tighten the binding of the DNA to the histones, preventing certain genes access to transcriptional proteins.¹⁻³

It has been proposed that if HDAC is recruited to a transcription factor complex instead of HAT, the activation of gene transcription in that section of DNA is prevented.¹⁻³

References:

1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.
2. Calvo KR, Petricoin EF III, Liotta LA. Genomics and proteomics. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:51-72.
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Restoring Gene Expression

Restoring the balance between HAT and HDAC allows acetylation of histone tails by HAT.^{1,2}

This leads to an open chromatin conformation, where binding sites on the DNA become accessible to transcription factors.³

As a result, the expression of genes, such as those involved in tumor suppression and cell-cycle regulation, is reactivated.²⁻⁴

References:

1. Arts J, de Schepper S, Van Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem.* 2003;10:2343-2350.
2. Di Gennaro E, Bruzzese F, Caraglia M, Abruzzese A, Budillon A. Acetylation of proteins as novel target for antitumor therapy: review article. *Amino Acids.* 2004;26:435-441.
3. de Ruijter AJM, van Gennip AH, Caron HN, Kemp S, van Kuilenburg ABP. Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem J.* 2003;370:737-749.
4. Marks PA, Richon VM, Miller TA, Kelly WK. Histone deacetylase inhibitors: new targeted anticancer drugs. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*, 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:439-445.

Class I ^{1,2}	Class II ^{1,2}	Class III ^{1,3}
<ul style="list-style-type: none"> • HDAC 1, 2, 3, 8, 11 • Found almost exclusively in nucleus • Expressed in most cell types 	<ul style="list-style-type: none"> • HDAC 4, 5, 6, 7, 9a, 9b, 9c/HDRP, 10 • Shuttle between nucleus and cytoplasm • Expression tissue restricted 	<ul style="list-style-type: none"> • SIRT 1, 2, 3, 4, 5, 6, 7 • Homologous to yeast Sir2 • Found in nucleus, cytoplasm, mitochondria • Require cofactor NAD⁺

Classification of HDACs

There are 2 protein families with HDAC activity: the classical HDAC family, consisting of class I and class II HDACs, and the class III HDACs.¹

Class I comprises HDACs 1, 2, 3, and 8, and class II comprises HDACs 4, 5, 6, 7, 9a, 9b, 9c/HDRP, and 10.^{1,2}

Class I HDACs reside almost exclusively in the nucleus, whereas class II HDACs shuttle between the nucleus and cytoplasm in response to cellular signals.^{1,2}

While class I HDACs are widely expressed, the expression of class II HDACs shows varying degrees of tissue specificity.^{1,2}

The class III HDAC, Sir2, deacetylates p53, inhibiting p53-mediated transcriptional activation and apoptosis.³

References:

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