

# Epigenetic information in chromatin and cancer

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## Abstract

It is now widely recognised that epigenetic changes are implicated in human cancer. Epigenetic information in chromatin (known as the ‘histone code’) has been proposed to extend and modulate the genetic (DNA) code in the regulation of key cellular processes. Histone modifications and histone modifying complexes have been traditionally associated with transcriptional regulation; however, recent studies indicated that the mechanisms involving the histone code play important roles in DNA replication, DNA damage detection and DNA repair. The histone code is believed to be ‘read’ by cellular machineries to regulate accessibility to, and functions of, chromatin DNA and the disruption of this code may lead to diseases, notably cancer.

## Epigenetic mechanisms

The term ‘epigenetic’ defines all heritable changes in gene expression and chromatin structure that are not coded in the DNA sequence itself. All differentiation processes (with minor exceptions of T- and B-cells of the immune system) are guided and maintained through epigenetic mechanisms. Epigenetic inheritance includes DNA methylation, histone modifications and RNA-mediated silencing, all of which are essential mechanisms that allow the stable propagation of gene activity states from one generation of cells to the next [1,2]. Recent mechanistic studies provide the evidence linking distinct epigenetic mechanisms; in other words, DNA methylation, histone modifications and RNA interference “talk” to each other and work together to establish and maintain a repressive or permissive chromatin state and regulate gene transcription [3].

Histone modifications of core histones include acetylation, methylation, phosphorylation and ubiquitination, all of which are believed to play an important role in diverse cellular processes. These covalent modifications occur at conserved lysine residues on the amino-terminal portions (“tails”) of histones. Recent

studies in this rapidly expanding field of modern biology have led to a concept known as the “histone code” [4]. This concept proposes that different histone modifications generate a code that is read by cellular machineries. This code may thus dictate functional outcomes by modulating different DNA-based processes. Histone modifications and the histone code play multifaceted roles in key cellular processes including gene transcription, DNA repair, recombination, DNA replication and self-renewal/differentiation of stem cells, and their deregulation is implicated in human malignancies [2,5].

## Histone modification and cellular processes

Covalent modifications of histone tails are important for all cellular processes which require access to the DNA template, including transcription, DNA repair, and replication [6,7].

### *Transcription*

Histone acetylation and methylation have been traditionally associated with gene transcription. Acetylation of lysines within histone tails was initially associated with the activation of transcription. The addition of acetyl groups to histone tails was proposed to neutralise the histone charge, which weakens histone-DNA interaction, relaxing the chromatin structure and facilitating the access of transcription machinery. In addition, two other mechanisms by which histone acetylation facilitates transcription have been proposed. First, there is evidence that histone acetylation may serve as a specific docking site for the recruitment of transcription regulators. Second, histone acetylation may also act in combination with other histone modifications (methylation, phosphorylation and ubiquitination) to form the “histone code” which dictates biological outcomes including gene transcription. These three models are not mutually exclusive and different acetylation-based mechanisms may coexist depending on the physiological context.

### DNA repair

DNA breaks are continuously produced during the life of a cell and are believed to be the most dangerous for genomic integrity and cell viability. DNA breaks occur randomly within genomic DNA and those occurring in compacted chromatin are inaccessible to DNA repair factors. Recent studies demonstrate that histone modifications play important roles in DNA repair and in some instances the mechanism appears to be similar to that underlying transcriptional activation [7,8].

### Replication

Although the role of the histone code in replication is still poorly understood, recent studies provide evidence that histone modifications can control the efficiency and/or timing of replication origin activity [5].

Different chromatin-based processes including transcription, replication and DNA repair require an open chromatin structure and are mediated by the same chromatin modifying complexes. This suggests that these chromatin modifications and modifier complexes regulate different and often conflicting processes. Although the experimental evidence for the coordination of these different processes is still scarce, there are reasons to believe in its existence. For example, DNA breaks in actively transcribed loci or regions undergoing replication may represent a danger for genomic integrity and therefore a chromatin state that favours DNA repair and suppresses replication/transcription is required.

### Histone modifications and cancer

Disruption of any of the three main epigenetic mechanisms may lead to inappropriate gene expression, inefficient DNA repair, aberrant DNA replication and cell division, resulting in cancer development and other 'epigenetic diseases' [9–11].

While aberrant DNA methylation is the most extensively studied epigenetic change in cancer, recent discoveries have revealed that deregulation of histone modifications and chromatin remodelling are also implicated in cancer [2]. Alterations in histone modifications and chromatin-based processes could lead to mutations in oncogenes, tumour suppressor genes or DNA repair genes resulting in genomic instability, oncogenic transformation and the development of cancer.

Aberrant activity of histone modifying factors may promote cancer development by misregulating chromatin structure and activity, an example of which

is frequently found in human leukaemia. Aberrant epigenetic regulation of key cellular processes, most notably gene transcription and DNA repair, is likely to be involved in oncogenesis. However, despite the fact that progress in determining different forms of epigenetic information in chromatin has been remarkably rapid, the way histone modifications are disrupted in cancer remains largely unknown.

In summary, remarkable progress has been made in the field to extend the knowledge on TRRAP (TRansformation/tRanscription domain-Associated Protein) and histone acetylation. Future studies are likely to provide important insights into the function of histone modifications and the mechanisms by which these complexes mediate normal cellular processes and abnormal events leading to tumour development. Aberrant activity of histone modifiers and histone modifications proved to be attractive molecular targets for therapeutic intervention in cancer. This is highlighted by the fact that a number of drugs that target histone acetylation (i.e. HDAC inhibitors) are in clinical trials, and that the first HDAC inhibitors have recently been approved by the U.S. Food and Drug Administration for treatment of specific human malignancies. Therefore, the information obtained from future studies will contribute to the understanding of chromatin modifications underlying the transition from normal to malignant cells and may help in designing novel therapeutic and preventive strategies.

### Conflict of interest statement

None declared.

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### References

- 1 Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet* 2003;**33**(Suppl):245–54.

- 2 Feinberg AP, Ohlsson R, Henikoff S. The epigenetic progenitor origin of human cancer. *Nat Rev Genet* 2006;**7**(1):21–33.
- 3 Vaissiere T, Sawan C, Herceg Z. Epigenetic interplay between histone modifications and DNA methylation in gene silencing. *Mutat Res* 2008;**659**(1–2):40–8.
- 4 Strahl BD, Allis CD. The language of covalent histone modifications. *Nature* 2000;**403**(6765):41–5.
- 5 Shukla V, Vaissiere T, Herceg Z. Histone acetylation and chromatin signature in stem cell identity and cancer. *Mutat Res* 2008;**637**(1–2):1–15.
- 6 Carrozza MJ, Utley RT, Workman JL, Cote J. The diverse functions of histone acetyltransferase complexes. *Trends Genet* 2003;**19**(6):321–9.
- 7 Loizou JI, Murr R, Finkbeiner MG, Sawan C, Wang ZQ, Herceg Z. Epigenetic information in chromatin: the code of entry for DNA repair. *Cell Cycle* 2006;**5**(7):696–701.
- 8 Peterson CL, Cote J. Cellular machineries for chromosomal DNA repair. *Genes Dev* 2004;**18**(6):602–16.
- 9 Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. *Nat Rev Genet* 2002;**3**(6):415–28.
- 10 Feinberg AP, Tycko B. The history of cancer epigenetics. *Nat Rev Cancer* 2004;**4**(2):143–53.
- 11 Herceg Z. Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. *Mutagenesis* 2007;**22**(2):91–103.