Analysis of the Hox epigenetic code

Zoheir Ezziane

Zoheir Ezziane, Welcome Trust Centre For Human Genetics, University of Oxford, Roosevelt Drive, Oxford, OX3 7BN, United Kingdom

Author contributions: Ezziane Z soley contributed to the manuscript.

Correspondence to: Zoheir Ezziane, Scientific Leadership Fellow, Welcome Trust Centre For Human Genetics, University of Oxford, Roosevelt Drive, Oxford, OX 3 7BN, United Kingdom. ezziane@well.ox.ac.uk

Telephone: +44-1865287652 Fax: +44-1865287501

Received: August 30, 2011 Revised: November 21, 2011 Accepted: April 1, 2012 Published online: April 10, 2012

Abstract

Archetypes of histone modifications associated with diverse chromosomal states that regulate access to DNA are leading the hypothesis of the histone code (or epigenetic code). However, it is still not evident how these post-translational modifications of histone tails lead to changes in chromatin structure. Histone modifications are able to activate and/or inactivate several genes and can be transmitted to next generation cells due to an epigenetic memory. The challenging issue is to identify or “decrypt” the code used to transmit these modifications to descent cells. Here, an attempt is made to describe how histone modifications operate as part of the histone code that stipulates patterns of gene expression. This work serves as an example to illustrate the power of the epigenetic machinery and its use in drug design and discovery.

© 2012 Baishideng. All rights reserved.

Key words: Epigenetic code; Histone code; Histone modifications; Hox gene expression

Peer reviewer: Partha P Banerjee, Associate Professor, Department of Biochemistry and Molecular and Cellular Biology, Medical-Dental Building, Room C406B 3900 Reservoir Road, NW, Washington, DC 20057, United States

Ezziane Z. Analysis of the Hox epigenetic code. World J Clin Oncol 2012; 3(4): 48-56 Available from: URL: http://www.wjgnet.com/2218-4333/full/v3/i4/48.htm DOI: http://dx.doi.org/10.5306/wjco.v3.i4.48

INTRODUCTION

The basic unit of chromatin corresponds to DNA that is packaged into periodic nucleoprotein structures known as nucleosomes[1]. The nucleosome comprises an octamer of eight core histone proteins (two H2A, H2B, H3 and H4) around which 146 base pairs of dsDNA are wrapped in 1.65 left-handed superhelical turns[2]. Histone H1 serves as a linker protein and directs the formation of a higher-order structure in the nucleosomal array. The histone N-terminal tails comprise between 25 and 40 residues and are exposed on the surface of the nucleosome. The amino acid sequences of these N-terminal tails are highly conserved, possibly due to the roles played by a number of important post-translational modifications at these sequences[3].

A number of selected amino acid residues are subject to a variety of enzyme-catalyzed posttranslational modifications. These modifications include acetylation and methylation of lysines (K) and arginines (R), phosphorylation of serines (S) and threonines (T)[4,5], which are carried out by a variety of chromatin modifying complexes, such as the COMPASS (for histone methylation), NuA4/Tip60 (for Histone H4 acetylation), and NuA3 (for Histone H3 acetylation) complexes. All of these chromatin modifying complexes contain one of the histone modification enzymes, such as histone acetyltransferase (HAT), histone deacetylase (HDAC), histone methyltransferase (HMT), histone demethylase (HDMT), and histone kinase. These chromatin modification complexes work in concert with ATP-dependent chromatin-remodeling complexes, including the SWI/SNF, ISWI and NURD/
Mi-2/CHD complexes, which recognize specific histone modifications to restructure and mobilize nucleosomes.

Histone tails represent a complex set of epigenetic information. There are 50 distinct acetylated isoforms of the eight histone proteins. In addition, several modifications can be applied to these isoforms including methylation of selected lysines and arginines (H3 and H4) and phosphorylation of serine (H3, H4, H2B). The methylation process includes the attachment of one, two, or three methyl groups. Other histone tail modifications also include ubiquitination and ADP-ribosylation. The nucleosome surface is then decorated with thousands of these modifications, which could comprise a histone code or an epigenetic code.

A challenging development occurs when a cell proliferates and generates two identical cells containing genes having the same status (expressed or repressed) as the ones in the mother cell. Every cell of an organism follows the same genetic code except germ cells and some cells of the immune system. Hence, the regulation of gene expression is not exclusively controlled by DNA but it is conducted in harmony with histones.

Cells control processes that permit them to remember the status of each gene before mitosis, and therefore preserve its phenotype. This transmission of gene expression patterns from mother cells to its descendants occur through a mechanism of gene bookmarking. Hence, the cell state (identity) is kept safe within the structure of the chromatin and the epigenetic code.

Components of chromatin including DNA and histones undergo dynamic post-synthetic covalent modifications. The dynamic and not permanent post-translational modifications on histones represent epigenetic signatures and are created and removed whenever needed to alter the expression states of loci. These marks involve activities of modifying enzymes (writers), enzymes removing modifications (erasers), and readers of the epigenetic code. The erasers are crucial targets for manipulation to further understand the histone code and its role in biology and human disease.

The inheritance of epigenetic information is orchestrated by histone code readers (proteins that identify particular histone modifications) and histone code writers (proteins that duplicate the histone modifications).

Histone code readers and writers include structural domains such as the bromodomain, the chromodomain, and the plant homedomain (PHD). These domains are required to recognize specific patterns of histone modifications including acetylation and methylation at given locations. The bromodomain is located mainly in HATs and chromatin remodeling proteins, whereas the chromodomain is found for example in HATs, HMTs, and HP1 (Figure 1). It has been shown that proteins involved in writing epigenetic information collaborate to maintain an epigenetic stability in the midst of great dynamic events at the molecular level.

Despite their phenotypic differences, Caenorhabditis elegans (C. elegans), a roundworm with a genome about 30 times smaller than human genome, however it encodes 22,000 proteins. In addition, approximately 35% of C. elegans genes are closely related to human genes, and both organisms have at least 80% amino acid sequence identity between their core histones. For example, MES-2, the ortholog of human EZH2 has been reported to be a HMT for H3K27[18], and MES-4, a SET domain containing protein, has recently been shown to be required for H3K36 di-methylation (H3K36 me2) in mitotic and early meiotic germline nuclei and in early embryonic cells. Whetstine et al. discovered the histone demethylase JMJD2A in mammalian cells and that has led to the identification of the C. elegans homolog, JMJD-2. This protein family was reported to be required in chemical methylation for H3K9/k36 me3.

There is accurate machinery that allows cells to recognize themselves and undertake specific tasks. This machinery represents the blueprint of various patterns of gene activation/inactivation throughout the cell cycle. Lack of expression or repression leads to an irregular outcome for the cell including altered genetic programs and increased rate of cell transformation. This “knowledge” is located mainly in the amino-terminal tails of the core histones. The first association between a histone tail modification and a particular functional state of chromatin was reported by Pogo et al. and Hebbes et al.. It was shown that transcriptionally active chromatin fractions are enriched in acetylated histones, whereas regions of facultative heterochromatin and transcriptionally silent constitutive were located in underacylated regions.

As depicted in Figure 1, the set of histone tail modifications includes at least two subsets. The first subset represents the modifications that lead to on-going transcription and usually are classified as cell signaling, and the second subset represents the modifications that are heritable. This heritability of transcriptional states is the component that unambiguously identifies the histone code. In addition, these histone modifications are also suggested to be used combinatorially to instruct genes for activation right after cellular differentiation. This latter proposition could be used to model the pro-
Ezziane Z. Epigenetic code

grammed activation of tissue-specific transcription factors throughout differentiation of ES cells[24].

Histone modifications associate closely with various biological functions. For example, as is depicted in Table 1, in C. elegans, methylation of H3K4/K36 correlates with transcriptionally competent euchromatin. Alternatively, methylation of H3K9/K27 correlates to a component of constitutive heterochromatin. Finding these patterns and the corresponding correlations with the transcriptional status of selected genes will lead the way to illustrate the process of an epigenetic code.

FROM HOX GENES TO HISTONE CODE

This study provides a detailed analysis of the Hox epigenetic code mainly in C. elegans. Methods used to propose such a code are based on a manual data mining approach and a thorough analysis of data gathered from various references and websites. A few discrepancies and contradictions were encountered during the design of Figures 2-4. For example, it is mentioned in a number of repositories were encountered during the design of Figures

Table 1 Methylation of H3K4, H3K9, H3K27 and H3K36

| i  | H3K4me(i) | H3K9me(i) | H3K27me(i) | H3K36me(i) |
|----|-----------|-----------|------------|------------|
| 0  | Off       | On        | On         | Off        |
| 1  | On        | Off       | Off        | On         |
| 2  | On        | Off       | Off        | On         |
| 3  | On        | Off       | Off        | On         |

i=0 the me(i) part will be equal to zero which means that the histone is not methylated. Here the “On” state represents the transcriptionally euchromatin; and the “off” state represents the constitutive heterochromatin.

tories for C. elegans that Sem-4 inhibits Lin-39. However, after investigating this issue further using the available literature and corresponding with many scientists, Sem-4 has been found to have an opposite role. Thus, patterns generated from data mining software should be manually checked to avoid similar discrepancies.

Although the histone code defined here targets a small organism, chromatin modifications in mammals including humans were used in this work to imply significant components of the Hox epigenetic code in C. elegans. In addition, there are many complexes that exist in both C. elegans and humans such as micro RNAs lin-4 and let-7 which have been connected to many cancers[27], and 153 kinase subfamilies which direct most cellular processes, particularly in signal transduction and coordination of complex pathways[28]. Similarities and homologs between both organisms are shown in Tables 2-5. Table 2 shows examples from the Ras-superfamily GTPases[29], Table 3 focuses on autophagy-related genes[30], Table 4 illustrates examples from the Ubiquitin-conjugating enzymes[31], and Table 5 shows specific similarities in Hox genes[32].

The development and maintenance of cellular identity is crucial in both embryonic and adult tissues for normal organ function. Hence the need to establish a stable transcriptional states within the cell, a process in which transcription factors have a vital role. One of those groups of transcription factors are known as Hox genes, representing a family of homeodomain-containing transcription factors that establish cellular identity during development, in addition to regulating numerous processes including apoptosis, receptor signalling, differentiation, motility and angiogenesis.
gene expression have been identified in abnormal development and malignancy, and re-expression in many cancers such as pancreatic cancer\cite{34}, leukemia\cite{35}, and neuroblastoma\cite{36}. In some tumors, altered expression of Hox genes directly drives tumorigenesis through escape from apoptosis\cite{37}, alterations to receptor signalling\cite{38} epithelial-mesenchymal transition (EMT)\cite{39} and tumour cell invasion\cite{40}. Therefore, Hox gene expression is a prospective diagnostic marker and therapeutic target.

Hox genes encode a family of transcription factors, are usually conserved within metazoans, and are involved in generating pattern along the anterior-posterior body axis. Their involvement occurs during early embryogenesis collinearly with their arrangement on the chromosome\cite{41,42}. In C. elegans, the Hox cluster includes six Hox genes arranged in three pairs spread out over 5 Mb of chromosome III. Ceb-13, lin-39, mab-5, and egl-5, are organized in a loose cluster\cite{43,44}, while the other two genes nob-1 and php-3 are located more than 1 Mb away on the same chromosome\cite{45,46}.

Kenyon et al\cite{47} reported that lin-39, mab-5 and egl-5 are required for postembryonic development. Emmons\cite{48} showed that mab-5 and egl-5 are involved in cell fate specifications in males, and Sternberg\cite{49} reported that lin-39 is mainly involved in vulval cell fates and selects the outcome of Ras signaling (Figure 2). Gener-
EXPLORING THE HISTONE CODE

Homeotic transformations that lead to body structure loss or duplication occur due to inappropriate expression of Hox genes. Thus, it is fundamental to identify a histone code that establishes a correlation between the histone modifications and a heritable histone code. In this work, only four Hox genes in C. elegans are investigated: lin-39, mab-5, egl-5, and cel-13. It is known that each C. elegans Hox gene is expressed in restricted regions of multiple diverse tissues and lineally unrelated cells and defines the region specific differentiation characteristics. Generally, Hox genes are globally repressed by the polycomb group (PcG) in mammals as well as in C. elegans (Figure 2). In addition, any mutations in PcG genes lead to ectopic Hox gene expression which will also in turn lead to posterior homeotic transformations in both Drosophila and vertebrates. A further analysis of Drosophila trxG/PcG double mutants showed that activity of TrxG/MLL complexes is required to block PcG-mediated silencing of transcribed Hox genes. The TrxG/MLL complex that catalyzes the H3K4me3 is associated with active transcription. Consequently, promoters of active genes develop to be enhanced with H3K4me3 modified nucleosomes. Similarly, in C. elegans, the MLL2...
Table 5  Hox genes of the Caenorhabditis elegans: Homologs of humans

| Gene product | Mammalian relative(s) | Molecular function |
|--------------|-----------------------|--------------------|
| EGL-5        | PcG                    | Hox transcription factor. Upregulated by Ras signaling. |
| LIN-39       | Abnormal cell          | Hox transcription factor. |
|              | LINLineage             | Upregulated by Ras signaling. |

complex plays the same role as in Drosophila (Figure 2).

Chromatin within mouse embryonic stem (mES) cells includes M'1H3K4 and M'1H3K27 marks at Hox gene promoters, in both repressive and activating chromatin modifications were referred to as “bivalent domains”[63]. These bivalent domains may lead Hox genes to an activation state. A challenging task is to determine how Hox genes become transcriptionally activated during ES cells differentiation or embryonic development.

Components of the MLL2 complex in humans were shown to be initially recruited at the promoters of the most anterior HOXA and HOXB genes, with H3K4 becoming tri-methylated[60]. The presence of UTB (Ubiquitously transcribed tetratricopeptide repeat, X chromosome, linked with histone demethylation) with a simultaneous loss of PRC2 and H3K27me3 marks from the promoters resulted in a rapid activation of these genes. These findings suggest that UTB could be essential for activating Hox genes, since its loss of expression did lead to a strong decrease in HOXB1 transcription. These findings are used later to support a particular hypothesis in conceiving the Histone code in C. elegans.

It has been reported in C. elegans that mab-5 is expressed in the V5 and V6 cell lineages, which directs these cells to develop into rays. Further, mab-5 is expressed only in the V6 lineage, which is required for the development and differentiation of V6 rays[60]. The normal development of the C. elegans male tail requires S0P-2, M6S-2/3/-6 (PcG) genes and lin-49/lin-59 (trithorax-related genes). As it is depicted in Figure 2, the mis-regulation of mab-5 and egl-5 is associated with the defects of ray development in lin-49, lin-59, S0P-2, and M6S-mutants[61,62]. In C. elegans as well as in Drosophila, PcG proteins operate as transcription repressors, whereas tri-thorax proteins operate as transcription activators[63].

Mutations in Hox genes lead to irregular patterns of programmed cell death. For example, in C. elegans, mab-5 has been reported to be essential for the programmed cell deaths of two linearly related cells generated in the P11 and P12 lineages[64]. Further, Figure 2 shows that lin-39 was reported to control vulval cell development[65], and ceh-13 is required for development, and its ectopic expression during embryogenesis lead to embryonic lethality[66]. This latter is the orthologue of the Drosophila labial and the human HOCl genes.

Various parts of Figures 2-4 were constructed from exploring Wormbase (www.wormbase.org), which represents a major repository for C. elegans information.

Figure 2 illustrates the fact that when H3K4 is tri-methylated, it binds with the complex Lin-49/Lin-59 which then expresses mab-5 and egl-5. In normal cell development, mab-5 and lin-39 repress each other in turn. The loss of H3K4me3 leads to X inactivation, whereas its increase occurs when rbr-2 (Jarid1 family) is inhibited, which then lead to a defect in vulval cells. However, it is not clear why H3K4me3 binds with Jmjd2-A, and which proteins express or repress ceh-13, although its first expression is detected in the male tail from I.3 until mid I.4. In humans, components of the MLL2 complex were shown to be initially recruited at the promoters of the most anterior Hox A and Hox B genes, with H3K4 becoming tri-methylated[60,67]. This finding suggests that H3K4me3 could be involved in expressing ceh-13.

Figure 3 shows that all levels of methylated H3K36 represent an activation mark and prevents transcriptional initiation downstream of the promoter region. This figure also shows a few correlative events. For example, H3K36me3 expresses lin-39, whereas H3K39m3 expresses lin-39. The depletion of Jmjd2-A (H3K9/K36 demethylase) leads to an increase of H3K9/K36me3 and to a P53-related apoptosis and an altered program of meiotic DSB repair. Like H3K4me3, H3K39me3 has also been observed to bind with Jmjd2-A. However, no clue is available to comprehend the purpose of this binding.

Figure 4 illustrates the importance of H3K27me3 as it represents a unique epigenetic state of pluripotent ES cells, and it is mainly down-regulated during differentiation into somatic cells. Generally, all forms of methylated H3K27 correspond to inactivation marks. However, H3K27me3 is specifically involved in inactivating the X chromosome as well as mab-5, egl-5, and lin-39. The depletion of F18E9.5 (member of Jmjd3 family that demethylates H3K27me3) causes defects in gonadogenesis, whereas its up-regulation has been detected in prostate cancer[40].

Figure 3 shows that the HMT met-2 catalyze H3K9 mono-, di- and tri-methylation in constitutive heterochromatin. The methylation of H3K9 binds with the chromodomain of hpl-2 in order to establish and maintain the heterochromatin structure.

Polycomb and trithorax groups are involved in maintaining the epigenetic code and the cell identity[40]. Polycomb complexes are found in closed chromatin structures and are thus involved in gene silencing, whereas trithorax complexes are found in open chromatin structure and are involved in maintaining active genes. Polycomb and trithorax groups are considered as HMTs and play a role in epigenetic inheritance[70,71]. Figure 4 depicts the mono-, di-, and tri- methylation of H3K27 by the polycomb MES-2/-3/-6 proteins. In addition, it also shows that the di- and tri-methylation of H3K27 are involved in repressing mab-5, egl-5, and lin-39. Further, Figure 2 shows that the trithorax complex Lin-49/Lin-59 binds with H3K4me3 and then activates mab-5 and egl-5.

Figures 2-4 illustrate various paths that lead to expression and repression of Hox genes in C. elegans, and eventually help to describe the histone code: (1) H3K4me3 is involved in activating mab-5 and egl-5; (2)
H3K36me3 plays a role in activating lin-39; (3) H3K9me3 is known in repressing lin-39; (4) H3K27me2 and H3K27me3 both repress mab-5, egl-5, and lin-39; and (5) although it is known that a high level of pop-1 represses ceb-13 and a low level of pop-1 expresses it, nonetheless it is worthwhile investigating whether any histone modifications are involved in expressing or repressing it. Presently, evident data only indicates that H3K4me3 may perhaps express it. However experimental work is needed to support such a claim.

Histone acetylation is not yet demonstrated to be involved in epigenetic memory, since it is mainly a dynamic modification and is maintained by the ongoing activity of HATs and HDACs.[29] In addition, histone demethylase removes a methyl group from a particular histone tail. For example, rbr-2 (jardil family) demethylates H3 at lysine 4 (Figure 2); JMJD2A protein demethylates H3 at lysine 36 (Figure 2); and F18E9.5 (JmjD3 family) removes the tri-methyl group from H3K27 (Figure 4). Correspondingly, other post-translationally modifications including phosphorylation, ubiquitylation, sumoylation, and ADP-ribosylation have not been shown to have an important role in epigenetic memory. Nevertheless, HATs and HDACs have been used in therapeutic targets in several diseases including cancer[22,75].

CONCLUSION
Histone modifications are clearly conserved within metazoans and correspond to a very ancient form of basal genetic regulation. Generally, each individual histone modification has the same biological effect in various organisms. For example, methylation of H3K4 represents an activation mark in both humans and C. elegans. Evidently, the epigenetic code identified as the heritable transcriptionally states will contribute in biomedical research and particularly in epigenetic therapy. In addition, epigenetic regulation is shown to have a role in mental disorders, autoimmune diseases and many other complex diseases.[99]

A number of silenced tumor suppressor genes are shown to be lost due to epigenetic deactivation rather than sequence damages, although epigenetic changes co-operate with genetic changes to initiate the development of a cancer since they are mitotically heritable[77,78]. Further, epigenetic irregularities are pharmacologically reversible as opposed to genomic damage[90]. This fact provides an incentive for the research community to devote more efforts to epigenetic therapy.

There is an on-going quest to discover drugs for diseases with genetic defects like cancer[80-83]. The purpose of investigating the histone code is to uncover the power of the epigenetic code and its use in drug design and discovery. Understanding the epigenetic machinery of the Hox genes and their cofactors could enable new targets for future therapies. As the investigation on Hox genes unravels, more translation to clinical application is expected. Hox genes have been used as biomarkers such as HoxA9[84], MLL translocation[85] and NUP98 fusions[86] in leukemias. In breast cancer, other groups have investigated the developed of a two-gene test using qRT-PCR to determine the ration of HoxB13 expression to IL17RB expression that leads to predict the tumor recurrence in patients with eR-positive tumors taking tamoxifen[87,88].

REFERENCES
1. Kornberg RD. Lorch Y. Twenty-five years of the nucleosome, fundamental particle of the eukaryote chromosome. Cell 1999; 98: 285-294
2. Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ. Crystal structure of the nucleosome core particle at 2.8 A resolution. Nature 1997; 389: 251-260
3. Kouzarides T. Chromatin modifications and their function. Cell 2007; 129: 693-705
4. Marqueron R, Trojer P, Reinberg D. The key to development: interpreting the histone code? Curr Opin Genet Dev 2005; 15: 165-176
5. Schaner CE, Kelly WG. Germline chromatin. WormBook, 2006: 1-14
6. Spotswood HT, Turner BM. An increasingly complex code. J Clin Invest 2002; 110: 577-582
7. Hansen JC, Tse C, Wolfe AP. Structure and function of the core histone N-termini: more than meets the eye. Biochemistry 1998; 37: 17637-17641
8. Strahl BD. Allis CD. The language of covalent histone modifications. Nature 2000; 403: 41-45
9. Jennewein T, Allis CD. Translating the histone code. Science 2001; 293: 1074-1080
10. Turner BM. Histone acetylation and an epigenetic code. Bioessays 2000; 22: 836-845
11. Varmuza S. Epigenetics and the renaissance of heresy. Genome 2003; 46: 963-97; discussion 963-97
12. Bronner C, Chatagnieau T, Schini-Kerth VB, Landry Y. The “Epigenetic Code Replication Machinery”, ECREM: a promising drugable target of the epigenetic cell memory. Curr Med Chem 2007; 14: 2629-2641
13. Marmorstein R, Trievel RC. Histone modifying enzymes: structures, mechanisms, and specificities. Biochim Biophys Acta 2009; 1789: 58-68
14. Seet BT, Dikic I, Zhou MM, Pawson T. Reading protein modifications with interaction domains. Nat Rev Mol Cell Biol 2006; 7: 473-483
15. Mellor J. It takes a PHD to read the histone code. Cell 2006; 126: 22-24
16. Dodg IB, Michaelen MA, Sneppen K, Thon G. Theoretical analysis of epigenetic cell memory by nucleosome modifications. Cell 2007; 129: 813-822
17. Vanfleteren JR, Van Bun SM, Van Beemen JJ. The histones of Caenorhabditis elegans: no evidence of stage-specific isoforms. An overview. FEBS Lett 1989; 257: 233-237
18. Bender LB, Cao R, Zhang Y, Strome S. The MES-2/MES-3/MES-6 complex and regulation of histone H3 methylation in C. elegans. Curr Biol 2004; 14: 1639-1643
19. Bender LB, Suh J, Carroll CR, Fong Y, Fingerman IM, Briggs SD, Cao R, Zhang Y, Reinke V, Strome S. MES-4: an autonomous-associated histone methyltransferase that participates in silencing the X chromosomes in the C. elegans germ line. Development 2006; 133: 3907-3917
20. Whetstone JR, Nottke A, Lan F, Huarte M, Smolikov S, Chen Z, Spooner E, Li E, Zhang G, Colaiacovo M, Shi Y. Reversal of histone lysine trimethylation by the JmjD2 family of histone demethylases. Cell 2006; 125: 467-481
21. Turner BM. Cellular memory and the histone code. Cell 2002; 111: 285-291
22. Pogo BG, Allfrey VG, Mirsky AE. RNA synthesis and his-
tone acetylation during the course of gene activation in lymphocytes. Proc Natl Acad Sci U S A 1966; 55: 805-812

23 Hebbes TR, Thorne AW, Crane-Robinson C. A direct link between core histone acetylation and transcriptionally active chromatin. EMBO J 1988; 7: 1395-1402.

24 Jeppesen P, Turner BM. The inactive X chromosome in female mammals is distinguished by a lack of histone H4 acetylation, a cytogenetic marker for gene expression. Cell 1993; 74: 281-289.

25 Turner BM. Defining an epigenetic code. Nat Cell Biol 2007; 9: 2-6

26 Bernstein FE, Kamal M, Lindblad-Toh K, Bekiranov S, Bailey DK, Hubeert DJ, McMahon S, Karlsson EK, Kulbokas EJ, Gingeras TR, Schreiber SL, Lander ES. Genomic maps and comparative analysis of histone modifications in human and mouse. Cell 2005; 120: 169-181.

27 Vella MC, Slack FJ. C. elegans microRNAs. WormBook, 2005: 1-9.

28 Darby C. Interactions with microbial pathogens. WormBook, 2005: 1-15.

29 Lundquist EA. Small GTPases. WormBook, 2006: 1-18.

30 Meléndez A, Levine B. The C. elegans Research Community. WormBook, 2009.

31 Kirepo ET. Ubiquitin-mediated pathways in C. elegans. WormBook, 2005: 1-24.

32 Sundaram MV. RTK/Ras/MAPK signaling. WormBook, 2006: 1-19.

33 Shah N, Sukumar S. The Hox genes and their roles in oncogenesis. Nat Rev Cancer 2010; 10: 361-371.

34 Gray S, Pandha HS, Michael A, Middleton G, Morgan R. Hox genes in pancreatic development and cancer. JOP 2011; 12: 216-219.

35 Calvo KR, Sykes DB, Pasillas MP, Kamps MP. Nup98-HoxA9 immortalizes myeloid progenitors, enforces expression of Hoxa9, Hoxa7 and Meis1, and alters cytokerin-specific responses in a manner similar to that induced by retroviral co-expression of Hoxa9 and Meis1. Oncogene 2002; 21: 4247-4256.

36 Zhang X, Hamada J, Nishimoto A, Takahashi Y, Murai T, Tada M, Moriiuch T. HOXC6 and HOXC11 increase transcription of S100beta gene in BrdU-induced in vitro differentiation of GOTO neuroblastoma cells into Schwannian cells. J Cell Mol Med 2007; 11: 299-306.

37 Chen H, Zhang H, Lee J, Liang X, Wu X, Zhu T, Lo PK, Zhang X, Sukumar S. HOXAS acts directly downstream of retinoid acid receptor beta and contributes to retinoic acid-induced apoptosis and growth inhibition. Cancer Res 2007; 67: 8007-8013.

38 Miao J, Wang Z, Provencher H, Muir B, Daiya S, Carney E, Leong CO, Sgroi DC, Orsulic S. HOX13B promotes ovarian cancer progression. Proc Natl Acad Sci U S A 2007; 104: 17093-17098.

39 Wu X, Chen H, Parker B, Rubin E, Zhu T, Lee JS, Argani P, Sukumar S. HOX87, a homeodomain protein, is overexpressed in breast cancer and confers epithelial-mesenchymal transition. Cancer Res 2006; 66: 9527-9534.

40 Zhai Y, Kuick R, Nan B, Ota I, Weiss SJ, Trimble CL, Fearon ER, Cho KR. Gene expression analysis of preinvasive and invasive cervical squamous cell carcinomas identifies HOXC10 as a key mediator of invasion. Cancer Res 2007; 67: 10163-10172.

41 Gehring WJ, Affolter M, Bürglin T. Homeodomain proteins. Annu Rev Biochem 1994; 63: 487-526.

42 Kenyon CJ, Austin J, Costa M, Cowing DW, Harris JM, Hogberg L, Hunter CP, Maloof JN, Muller-Immergück MM, Salser S, Waring DA, Wang BB, Wrischik LA. The dance of the Hox genes: patterning the anteroposterior body axis of Caenorhabditis elegans. Cold Spring Harb Symp Quant Biol 1997; 62: 293-305.

43 Bürglin TR, Finney M, Coulson A, Ruvkun G. Caenorhabditis elegans has scores of homeobox-containing genes. Nature 1989; 341: 239-243.

44 Bürglin TR, Ruvkun G, Coulson A, Hawkins NC, McGhee JD, Schaller D, Wittmann C, Müller F, Waterston RH. Nematode homeobox cluster. Nature 1991; 351: 703.

45 Bürglin TR, Ruvkun G. The Caenorhabditis elegans homebox gene cluster. Curr Opin Genet Dev 1993; 3: 615-620.

46 Ruvkun G, Hobert O. The taxonomy of developmental control in Caenorhabditis elegans. Science 1998; 282: 2033-2041.

47 Van Auker K, Weaver DC, Edgar LG, Wood WB. Caenorhabditis elegans embryonic axial patterning requires two recently discovered posterior-group Hox genes. Proc Natl Acad Sci USA 2000; 97: 4499-4503.

48 Aboobaker A, Blaxter M. Hox gene evolution in nematodes: novelty conserved. Curr Opin Genet Dev 2003; 13: 593-598.

49 Emmons SW. Male development. WormBook, 2005: 1-12.

50 Sternberg PW. Vulval development. WormBook, 2005: 1-28.

51 Cowding D, Kenyon C. Correct Hox gene expression established independently of position in Caenorhabditis elegans. Nature 1996; 382: 253-256.

52 Streit A, Kohler R, Marty T, Belfiore M, Takacs-Vellai K, Vigan MA, Schnabel R, Affolter M, Muller F. Conserved regulation of the Caenorhabditis elegans labial/Hox1 gene ceh-13. Dev Biol 2002; 242: 96-108.

53 Bock C, Lengauer T. Computational epigenetics. Bioinformatics 2008; 24: 1-10.

54 Tian E, Zhang H. (2007). Identification and characterization of novel PcG-like genes in C. elegans. International C. elegans Meeting, Los Angeles, CA.

55 Soshnikova N, Duboule D. Epigenetic regulation of Hox gene activation: the waltz of methyls. Bioessays 2008; 30: 199-202.

56 Müller J, Hart CM, Francis NJ, Vargala ML, Sengupta A, Wild B, Miller EL, O’Connor MB, Kingston RE, Simon JA. Histone methyltransferase activity of a Drosophila Polycomb group repressor complex. Cell 2002; 111: 197-208.

57 Bernstein BE, Mikkelsen TS, Xie X, Kamal M, Huebert DJ, Cuff J, Fry B, Meissner A, Wernig M, Plath K, Jaenisch R, Wagschal A, Feil R, Schreiber SL, Lander ES. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell 2006; 125: 315-326.

58 Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, Wei G, Chepelve I, Zhao K. High-resolution profiling of histone methylations in the human genome. Cell 2007; 129: 823-837.

59 Aeger K, Cloos PA, Christensen J, Pasini D, Rose S, Raapilder J, Issaeva I, Canaani E, Salcini AE, Helin K. UTX and JMJD3 are histone H3K27 demethylases involved in Hox gene regulation and development. Nature 2007; 449: 731-734.

60 Ferreira HB, Zhang Y, Zhao C, Emmans SW. Patterning of Caenorhabditis elegans posterior structures by the Abdominal-B homolog, egl-5. Dev Biol 1999; 207: 215-228.

61 Chamberlin HM, Thomas JH. The bromodomain protein LIN-49 and trithorax-related protein LIN-59 affect development and gene expression in Caenorhabditis elegans. Development 2000; 127: 713-723.

62 Ross JM, Zarkower D. Polycomb group regulation of Hox gene expression in C. elegans. Dev Cell 2003; 4: 891-901.

63 Grimaud C, Négre N, Cavalli G. From genetics to epigenetics: the tale of Polycomb group and trithorax group genes. Chromosome Res 2006; 14: 363-375.

64 Herman MA. Hermaphrodite cell-fate specification. WormBook, 2006: 1-16.

65 Ferguson R, Eisenmann DM. (2007). Identification of transcription factors that control the temporal and spatial expression of the C.elegans Hox gene lin-39 using a Yeast-1-Hybrid system. 16th International C. elegans Meeting, Los Angeles, CA.

66 Knier S, Streit A. (2007). Semi-automated genetic screen for temperature sensitive mutations that abolish the early
Ezziane Z. Epigenetic Code

embryonic expression of the hox gene ceh-13. 16th International C. elegans Meeting, Los Angeles, CA

Ferrier DE, Holland PW. Ancient origin of the Hox gene cluster. Nat Rev Genet 2001; 2: 33-38

Xiang Y, Zhu Z, Han G, Lin H, Xu L, Chen CD. JMJD3 is a histone H3K27 demethylase. Cell Res 2007; 17: 850-857

Orlando V. Polycomb, epigenomes, and control of cell identity. Cell 2003; 112: 599-606

Beisel C, Imhof A, Greene J, Kremmer E, Sauer F. Histone methylation by the Drosophila epigenetic transcriptional regulator Ash1. Nature 2002; 419: 857-862

Cao R, Wang L, Wang H, Xia L, Erdjument-Bromage H, Tempst P, Jones RS, Zhang Y. Role of histone H3 lysine 27 methylation in Polycomb-group silencing. Science 2002; 298: 1039-1043

Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Siddappa NB, Ranga U, Kundu TK. Curcumin, a novel p300/CREB-binding protein-specific inhibitor of histone acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. J Biol Chem 2004; 279: 51163-51171

Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov 2006; 5: 769-784

Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev Cancer 2006; 6: 38-51

Karam JA, Fan J, Stanfield J, Richer E, Benaim EA, Frenkel E, Antich P, Sagalowsky AI, Mason RP, Hsieh JT. The use of histone deacetylase inhibitor FK228 and DNA hypomethylating agent 5-azacytidine in human bladder cancer therapy. Int J Cancer 2007; 120: 1795-1802

Feinberg AP. Phenotypic plasticity and the epigenetics of human disease. Nature 2007; 447: 433-440

Esteller M. Cancer epigenomics: DNA methylomes and histone-modification maps. Nat Rev Genet 2007; 8: 286-298

Jones PA, Baylin SB. The epigenomics of cancer. Cell 2007; 128: 683-692

Yoo CB, Jones PA. Epigenetic therapy of cancer: past, present and future. Nat Rev Drug Discov 2006; 5: 37-50

Kleinman HK, Liu G. Gene therapy for antiangiogenesis. J Natl Cancer Inst 2001; 93: 965-967

Cassileth BR, Deng G. Complementary and alternative therapies for cancer. Oncologist 2004; 9: 80-89

Ezziane Z. Molecular docking and analysis of survivin delta-ex3 isoform protein. Open Med Chem J 2008; 2: 16-20

Ezziane Z. Challenging issues in molecular-targeted therapy. Ther Clin Risk Manag 2009; 5: 239-245

Golub TR, Slotim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, Coller H, Loh ML, Downing JR, Caligiuri MA, Bloomfield CD, Lander ES. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science 1999; 286: 531-537

Armstrong SA, Golub TR, Korsmeyer SJ. MLL-rearranged leukemias: insights from gene expression profiling. Semin Hematol 2003; 40: 268-273

Chou WC, Chen CY, Hou HA, Lin LI, Tang JL, Yao M, Tsay W, Ko BS, Wu SJ, Huang SY, Hsu SC, Chen YC, Huang YN, Tseng MH, Huang CF, Tien HF. Acute myeloid leukemia bearing t(7;11)(p15;p15) is a distinct cytogenetic entity with poor outcome and a distinct mutation profile: comparative analysis of 493 adult patients. Leukemia 2009; 23: 1303-1310

Goetz MP, Suman VJ, Ingle JN, Nibbe AM, Visscher DW, Reynolds CA, Lingle WL, Erlander M, Ma XJ, Sgroi DC, Perez EA, Couch FJ. A two-gene expression ratio of homeobox 13 and interleukin-17B receptor for prediction of recurrence and survival in women receiving adjuvant tamoxifen. Clin Cancer Res 2006; 12: 2080-2087

Jansen MP, Sieuwerts AM, Look MP, Rittstier K, Meijer-van Gelder ME, van Staveren IL, Klijn JG, Foekens JA, Berns EM. HOXB13-to-IL17BR expression ratio is related with tumor aggressiveness and response to tamoxifen of recurrent breast cancer: a retrospective study. J Clin Oncol 2007; 25: 662-668

S- Editor Yang XC L- Editor A E- Editor Yang XC