CPQ Cancer (2018) 1:3
Mini-Review

Histone Post-Translational Modifications and Cancer

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Received: 17 September 2018

Published: 23 October 2018

Keywords: *Cancer; Epigenetics; Heterochromatin; Enhancer of Zeste Homolog 2; Histone-Modifying Ezymes; Suppressor of Variegation 3/9; Epidrugs*

Abstract

Epigenetic involves mechanisms which control gene transcription but convey no changes in the DNA sequences. A series of epigenetic modifications have been described in several tumors and this knowledge is important for the adequate diagnosis and treatment of the disease. The epigenetic mechanisms involve, among others processes, histone modifications, such as the trimethylation of histone 3 lysine 9 (H3K9me3) and lysine 27 (H3K27me3), characteristics of constitutive and facultative heterochromatin, respectively, which are associated with gene silencing. Suppressor of Variegation 3-9 homolog 1 and 2 (SUV39H1, SUV39H2) are critical enzymes for trimethylation of H3K9, while Polycomb Repressor Complex 2 (PRC2) is responsible for the methylation of histone 3 lysine 27. These histone-modifying enzymes are evolutionarily conserved and their misexpression, as well as that of their corresponding histone marks, have been associated with different types of cancer, which leads us to believe that histone-modifying enzymes are promising targets for oncologic drugs.

Abbreviations

EDD - embryonic Ectoderm Development
EZH1/2 - enhancer of Zeste Homolog 1/2
H3K27ac - acetylation of histone 3 lysine 27
H3K4me3 - trimethylation of histone 3 lysine 4
H3K9ac - acetylation of histone 3 lysine 9
H4K20me3 - trimethylation of histone 3 lysine 20
HDACS - histone deacetylases
HMTs - histone methyltransferases
HP1 - heterochromatin Protein 1
KMTs - lysine methyltransferases
LBR - lamin B Receptor
PRC2 - polycomb repressor complex 2
SUV3-9 - suppressor of variegation 3-9
SUV39H1/SUV39H2 - SUV39 homolog 1 and 2
SUZ12 - suppressor of Zeste 12

Main Text

The field of epigenetics, first envisioned by Waddington, in 1942 [1], has enormously expanded in the last decades as we have gained increasing knowledge on the mechanisms that enable cells to stabilize different gene expression programmes using the same DNA template. In the early eighties, almost a decade after the role for DNA methylation in gene regulation was proposed by Holliday and Pugh [2], the notion that cancer cells gene expression alteration could be caused by epigenetics changes started to be sewed with the publication of the first works demonstrating that there were also changes in DNA methylation in cancer cells [3,4]. Today it is evident that epigenetic changes can drive some heritable phenotypes in cancer cells [5-7], such as inactivation of tumor suppressor genes [8,9], and since epigenetic changes are reversible, there is a growing area in developing drugs that can overturn these changes and can serve as new cancer therapies [10].

A series of epigenetic alterations have been described in several tumors [11-13], and this knowledge is important for the adequate diagnosis and treatment of the disease [14]. Epi-drugs, which are molecules that act in the epigenetic mechanisms of cells responsible for a certain disease, is now part of some protocols in oncology [15-17].

The epigenetic mechanisms involve, besides DNA methylation, histone modifications and the activity of non-coding RNAs [18]. All these players are closely interlinked and result in altered accessibility of the transcriptional machinery to the chromatin, leading to changes in gene expression without changes in the nucleotide sequence per se. In this mini-review, we will focus on epigenetic mechanisms involving histone post-translational modifications in cancer.

Basically, chromatin can be divided into two different enzymatic states: euchromatin, which represents chromatin regions with potential gene activity, and heterochromatin, which represents regions of gene silencing. Euchromatin is especially enriched in trimethylation of histone 3 lysine 4 (H3K4me3) and histone 3 acetylation marks such as H3K27ac and H3K9ac [19]. Some different histone modifications are combined in a given chromatin environment, eg. H3K4me3 associated with H3K9ac define euchromatin, and therefore the term "histone code" has been coined [20]. Histone deacetylases (HDACs) are usually involved in gene silencing [19], and inhibitors of HDACs are being part of cancer drugs clinical trials because of their potential of silencing genes involved in tumorigenesis [21,22].

On the other hand, heterochromatin, defined as regions of inactive gene transcription, can be divided into constitutive and facultative heterochromatin. In general constitutive heterochromatin is characterized by the trimethylation of histone 3 lysine 9, H3K9me3, and histone 4 lysine 20, H4K20me3 [19]. Constitutive heterochromatin is enriched in pericentromeric and telomeric genome regions, as well as in repetitive elements of the genome. The Suppressor of Variegation 3-9 (SUV39) are a subfamily of lysine methyltransferases (KMTs) and SUV39 homolog 1 and 2 (SUV39H1, SUV39H2) are critical enzymes for the di or trimethylation of H3K9 [23]. H3K9me3 deposition allows Heterochromatin Protein 1 (HP1) chromatin binding and, associated with the activity of specific constitutive heterochromatin HDACs and histone methyltransferases (HMTs), leads to a higher chromatin compaction [19,24]. HP1 also associates with the Lamin B Receptor (LBR) in the inner nucleus membrane, anchoring the constitutive heterochromatin regions to the nucleus periphery [25]. SUV39H1 and SUV39H2 are involved in genome stability [26], a cell characteristic critically lost during the tumorigenic process (Hanahan and Weinberg, 2011). SUV39H1 knockout mice show an increased risk of lymphomas [26] and loss or high expression of other SUV39 subfamily members has been involved in progression several types human cancers [23].

Facultative heterochromatin can potentially interconvert in euchromatin, so genes can be activated in certain circumstances, such as HOX genes in embryonic development [24]. The hallmark of facultative heterochromatin is the trimethylation of histone 3 lysine 27 (H3K27me3), which has been found enriched in homeotic genes, imprinted loci and inactive X chromosome [24]. The higher plasticity of facultative heterochromatin, when compared to constitutive heterochromatin, highlights its importance in the process of malignant transformation, since the tumorigenesis involves the cellular dedifferentiation with the activation of a series of silence genes and vice versa. Polycomb Repressor Complex 2 (PRC2) is responsible for the methylation of histone 3 lysine 27 and is evolutionary conserved in plants and in mammals, The PRC2 complex is basically formed by five subunits: Enhancer of Zeste Homolog 1/2 (EZH1/2), Suppressor of Zeste 12 (SUZ12), Embryonic Ectoderm Development (EED), and two Retinoblastoma-Associated proteins (RbAp46 and RbAp48) [27,28]. EZH1 or EZH2 are the catalytic subunits of PRC2 and share the same target genes, but while EZH1 is ubiquitously expressed in nondividing cells, EZH2 is expressed by proliferating cells and exhibits higher levels of histone lysine methyltransferase activity [29]. SUZ12 and EED participate in PCR2 nucleosome anchoring and are fundamental to EZH2 enzymatic activity [30,31]. RbAp46 and RbAp48 are histone chaperones binding to histone H3 and H4 [32,33]. PRC2/EZH2 seems to act by suppressing alternative cell fates as it silences some transcriptional programs [34,35].

Therefore, EZH2 overexpression and gain-of-function mutations, as well as low expression and loss-of-function mutations, have been associated with different types of cancer [17]. In thyroid cancer, EZH2 is overexpressed as tumorigenic cells lose their differentiation [36,37], and inhibition of EZH2 diminishes cell proliferation, migration, and invasion capacity [36]. Treating mice with malignant rhabdoid tumors with an inhibitor of EZH2 led to dose-dependent tumor regression [38]. Some EZH2 inhibitors are now in phase 1/2 clinical trial in patients with solid tumors with encouraging results [17].

Conclusions

Epigenetic involves mechanisms which control gene transcription but convey no changes in the DNA sequences. Epigenetic modifications have been associated with cancer and metastasis, which leads us to believe that histone-modifying enzymes are promising targets for oncologic drugs.

Conflicts of Interests

The authors declare no competing financial interests.

Bibliography

1. Waddington, C. H. (2012). The epigenotype. 1942. *Int J Epidemiol., 41*(1), 10-13.

2. Holliday, R. & Pugh, J. E. (1975). DNA modification mechanisms and gene activity during development. *Science, 187*(4173), 226-232.

3. Feinberg, A. P. & Vogelstein, B. (1983). Hypomethylation distinguishes genes of some human cancers from their normal counterparts. *Nature, 301,* 89-92.

4. Gama-Sosa, M. A., Slagel, V. A., Trewyn, R. W., Oxenhandler, R., Kuo, K. C., Gehrke, C. W. & Ehrlich, M. (1983). The 5-methylcytosine content of DNA from human tumors. *Nucleic Acids Res., 11*(19), 6883-6894.

5. Berdasco, M. & Esteller, M. (2010). Aberrant epigenetic landscape in cancer: how cellular identity goes awry. *Dev Cell., 19*(5), 698-711.

6. Esteller, M. (2007). Cancer epigenomics: DNA methylomes and histone-modification maps. *Nat Rev Genet., 8*(4), 286-298.

7. Jones, P. A. & Baylin, S. B. (2007). The epigenomics of cancer. *Cell, 128*(4), 683-692.

8. Han, F., Liu, W., Jiang, X., Shi, X., Yin, L., *et al.* (2015). SOX30, a novel epigenetic silenced tumor suppressor, promotes tumor cell apoptosis by transcriptional activating p53 in lung cancer. *Oncogene, 34*(33), 4391-4402.

9. Wang, C., Liu, Z., Woo, C. W., Li, Z., Wang, L., *et al.* (2012). EZH2 Mediates epigenetic silencing of neuroblastoma suppressor genes CASZ1, CLU, RUNX3, and NGFR. *Cancer Res., 72*(1), 315-324.

10. Esteller, M. (2007). Epigenetics provides a new generation of oncogenes and tumour-suppressor genes. *Br J Cancer, 94*(2), Suppl, R26-30.

11. Asa, S. L. & Ezzat, S. (2018). The epigenetic landscape of differentiated thyroid cancer. *Mol Cell Endocrinol., 469,* 3-10.

12. Castilho, R. M., Squarize, C. H. & Almeida, L. O. (2017). Epigenetic Modifications and Head and Neck Cancer: Implications for Tumor Progression and Resistance to Therapy. *Int J Mol Sci., 18*(7).

13. Ezzat, S., Cheng, S. & Asa, S. L. (2018). Epigenetics of pituitary tumors: Pathogenetic and therapeutic implications. *Mol Cell Endocrinol., 469,* 70-76.

14. Timp, W. & Feinberg, A. P. (2013). Cancer as a dysregulated epigenome allowing cellular growth advantage at the expense of the host. *Nat Rev Cancer., 13*(7), 497-510.

15. Arrowsmith, C. H., Bountra, C., Fish, P. V., Lee, K. & Schapira, M. (2012). Epigenetic protein families: a new frontier for drug discovery. *Nat Rev Drug Discov., 11*(5), 384-400.

16. Hajji, N., García-Domínguez, D. J., Hontecillas-Prieto, L., O'Neill, K., de Álava, E. & Syed, N. (2018). The bitter side of epigenetics: variability and resistance to chemotherapy. *Epigenomics.*

17. Kim, K. H. & Roberts, C. W. (2016). Targeting EZH2 in cancer. *Nat Med., 22*(2), 128-134.

18. Allis, C. D. & Jenuwein, T. (2016). The molecular hallmarks of epigenetic control. *Nat Rev Genet., 17*(8), 487-500.

19. Kouzarides, T. (2007). Chromatin modifications and their function. *Cell, 128*(4), 693-705.

20. Jenuwein, T. & Allis, C. D. (2001). Translating the histone code. *Science, 293*(5532), 1074-1080.

21. Glozak, M. A. & Seto, E. (2007). Histone deacetylases and cancer. *Oncogene, 26*(37), 5420-5432.

22. Minucci, S. & Pelicci, P. G. (2006). Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. *Nat Rev Cancer, 6*(1), 38-51.

23. Rao, V. K., Pal, A. & Taneja, R. (2017). A drive in SUVs: From development to disease. *Epigenetics., 12*(3), 177-186.

24. Trojer, P. & Reinberg, D. (2007). Facultative heterochromatin: is there a distinctive molecular signature? *Mol Cell., 28*(1), 1-13.

25. Worman, H. J. & Courvalin, J. C. (2000). The inner nuclear membrane. *J Membr Biol., 177*(1), 1-11.

26. Peters, A. H., O'Carroll, D., Scherthan, H., Mechtler, K., Sauer, S., *et al.* (2001). Loss of the Suv39h histone methyltransferases impairs mammalian heterochromatin and genome stability. *Cell, 107*(3), 323-337.

27. Kuzmichev, A., Nishioka, K., Erdjument-Bromage, H., Tempst, P. & Reinberg, D. (2002). Histone methyltransferase activity associated with a human multiprotein complex containing the Enhancer of Zeste protein. *Genes Dev., 16*(22), 2893-2905.

28. Schwartz, Y. B. & Pirrotta, V. (2007). Polycomb silencing mechanisms and the management of genomic programmes. *Nat Rev Genet., 8*(1), 9-22.

29. Margueron, R., Li, G., Sarma, K., Blais, A., Zavadil, J., Woodcock, C. L., Dynlacht, B. D. & Reinberg, D. (2008). Ezh1 and Ezh2 maintain repressive chromatin through different mechanisms. *Mol Cell, 32*(4), 503-518.

30. Cao, R. & Zhang, Y. (2004). SUZ12 is required for both the histone methyltransferase activity and the silencing function of the EED-EZH2 complex. *Mol Cell., 15*(1), 57-67.

31. Margueron, R., Justin, N., Ohno, K., Sharpe, M. L., Son, J., *et al.* (2009). Role of the polycomb protein EED in the propagation of repressive histone marks. *Nature, 461*(7265), 762-767.

32. Margueron, R. & Reinberg, D. (2011). The Polycomb complex PRC2 and its mark in life. *Nature, 469*(7330), 343-349.

33. Song, J. J., Garlick, J. D. & Kingston, R. E. (2008). Structural basis of histone H4 recognition by p55. *Genes Dev., 22*(10), 1313-1318.

34. Aldiri, I. & Vetter, M. L. (2012). PRC2 during vertebrate organogenesis: a complex in transition. *Dev Biol., 367*(2), 91-99.

35. Lin, B., Coleman, J. H., Peterson, J. N., Zunitch, M. J., Jang, W., Herrick, D. B. & Schwob, J. E. (2017). Injury Induces Endogenous Reprogramming and Dedifferentiation of Neuronal Progenitors to Multipotency. *Cell Stem Cell, 21*(6), 761-774.e765.

36. Borbone, E., Troncone, G., Ferraro, A., Jasencakova, Z., Stojic, L., Esposito, F., Hornig, N., Fusco, A. & Orlando, V. (2011). Enhancer of zeste homolog 2 overexpression has a role in the development of anaplastic thyroid carcinomas. *J Clin Endocrinol Metab., 96*(4), 1029-1038.

37. Masudo, K., Suganuma, N., Nakayama, H., Oshima, T., Rino, Y., *et al.* (2018). EZH2 Overexpression as a Useful Prognostic Marker for Aggressive Behaviour in Thyroid Cancer. *In Vivo, 32*(1), 25-31.

38. Knutson, S. K., Warholic, N. M., Wigle, T. J., Klaus, C. R., Allain, C. J., *et al.* (2013). Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. *Proc Natl Acad Sci U S A, 110*(19), 7922-7927.