Epigenetic Modulation in Cancer: Molecular Mechanisms and Therapeutic Targets – A Review

Sher Zaman Safi

ABSTRACT

Cancer continues to be one of the leading causes of death and a major global health problem despite ongoing research efforts, advancement in medical technologies, and increased public health awareness. However, the understanding of human cancer as a heterogeneous disease has been significantly increased offering hope that the vital molecular and cellular mechanisms would pave the way for controlling cancer at its advanced stages. The transformation of normal cells into cancerous cells is a complex process achieved through a cascade of events and molecular modifications. A great deal of cancer research has been focusing on studying epigenetic alterations such as DNA methylation, histone modification, and non-coding RNA expression. These epigenetic changes modulate gene expression which is believed to play a potential role in cancer initiation, proliferation, and metastasis. This article aims to review how several aberrant epigenetic regulations impact gene expression and cellular reprogramming in cancer. It also discusses how hypomethylation can lead to increased expression of oncogenes and how hypermethylation silences key tumor suppressor genes. It also highlights how these aberrantly dysregulated genes can serve as potential therapeutic targets for cancer prevention and as biomarkers for early cancer detection.

Keywords: Cancer, Epigenetics, Gene expression, Methylation, Histone modification, nc-RNA

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Introduction

Despite the enormous research that has been undertaken over the last decades, cancer continues to be a major health concern and one of the deadliest diseases in the 21st century.[1] In 2022, approximately 9.7 million people died from cancer with nearly 20 million new cases worldwide.[1] The risk factors of cancer are complex and the current evidence suggests innumerable genetic, environmental, socioeconomic, and lifestyle-related factors that lead to carcinogenesis and tumorigenesis.[2,3]

Over 100 years ago, Theodore Boveri proposed the somatic mutation theory describing genetic mutations as the key drivers of cancer and uncontrolled division of cancer cells.[4] Though this theory is not a complete explanation of cancer, it has contributed significantly to explaining the origin of cancer and cancer biology. The theory-driven models have given a good foundation in the understanding of molecular aspects of cancer and in the implications of somatic mutations as stochastic events in cancer development are still relevant, however, the contemporary understanding of cancer goes beyond just somatic mutations.[5] Studies have unraveled the increasing role of other important factors such as genomic stability, metabolomics, and dysregulated epigenetic patterns in the progression and metastasis of cancer.[6–12]

Epigenetics which refers to alteration in DNA without changing the DNA sequence, is a comparatively new but fast growing field of biology. These changes including methylation, histone modification, and non-coding RNA significantly influence gene expression and other cellular and molecular mechanisms including proliferation and differentiation.[13–16] Epigenetics merges the genetic codes in the DNA and genome with various molecular and biochemical signals from intracellular, extracellular, and other environmental sources. In conjunction with the genome, the epigenome guides the specific gene expression of each cell type, shaping its functional identity throughout development and diseases.[17,18]

DNA methylation is the process of adding a methyl group to a DNA base, usually a cytosine in a CpG dinucleotide pair. This modification influences how DNA coils around histones and how it impacts the binding of transcription factors, partly by attracting methyl CpG binding proteins.[19,20] Studies have shown that hypomethylation activates oncogenes, leading to the oncogenic properties of cells.[21–23] Likewise, hypermethylation leads to the suppression of genes associated with tumor suppressor activities, and thus promotes tumorigenesis of tumors.[24,25] Histone modification is another hallmark of cancer in which post-translational changes occur to the tails of histone molecules such as H2A, H2B, H3, and H4.[26] Research has demonstrated a substantial association of these post-translational modifications with the pathogenesis of cancer.[27,28]

In cancer research, a wealth of literature is available that focuses on aberrant epigenetic regulations such as dysregulation of methylation, histone modification, and modulation of non-coding RNAs. The focus of this review is to summarize the epigenetics-related studies that play an important role in the metastasis of cancer. It will also highlight how aberrant epigenetic regulations can serve as potential therapeutic targets for cancer prevention.

Methodology

Literature Search Strategy

A total of 184 articles were retrieved from a range of relevant databases including Web of Science, ScienceDirect, Medline, PubMed, EMBASE, Google Scholar, and BioMed Central. The search strategy involved a comprehensive approach to identify the most relevant literature on epigenetic modulation in cancer. The overall approach was not limited to a single cancer type but examined all epigenetic regulations across various cancer types including but not limited to liver

cancer, colorectal cancer, breast cancer, gastric cancer, prostate cancer, and esophageal cancer.

Specific keywords such as epigenetics, methylation, cancer, histone modification, and non-coding RNA were used to search the databases. Different combinations of keywords such as "cancer and epigenetic regulation" "cancer and methylation", "cancer and histone modification", "cancer and non-coding RNA", "epigenetic modulation in different cancers" and "epigenetic-based therapeutic targets in cancer" were searched making sure to retrieve all relevant literature. Inclusion criteria comprised articles such as original articles, meta-analyses, and review articles that had a focus on the epigenetic regulation of cancer. All 184 articles were screened for quality and relevance, of which 111 were selected in this review article (Figure 1).

Overview of Cancer: Epidemiology, Incidence and Risk Factors

Cancers significantly contribute to the public health burden, and projections estimated that this trend will continue to rise over the next couple of decades.[29–32] According to the GLOBOCAN 2022 estimates,[1] the incidence of major cancer types varies significantly, with lung cancer leading at 2.480 million cases followed by breast and colorectal cancers with 2.296 million and 1.926 million respectively. The incidence of prostate and stomach cancers is 1.467 and 0.866 million respectively (Figure 2A). Similarly, the mortality rates also differ, with lung cancer having the highest mortality at 1.817 million deaths followed by colorectal cancer with 0.904 million deaths. Other cancers with high mortality rates reported by GLOBOCAN 2022 are liver and breast cancers with 0.758 and 0.666 million deaths respectively (Figure 2B).

It is often impossible to determine precisely why one person develops cancer while another does not. However, research has identified specific risk factors that can increase the likelihood of developing cancer. For instance, nearly 30% to 50% of all cancers could be reduced by minimizing tobacco smoking and other carcinogenetic factors prevalent in the environment, maintaining a healthy lifestyle, and adhering to the available cancer screenings methods.[33] Early detection and screening help in many cancers such as cervical and colorectal cancers could be prevented by spotting the lesions that can be removed before they progress into cancer.[34–36]

A systematic analysis in which the risk factors of cancer were evaluated from 2010–2019, reported obesity, smoking and alcohol consumption as the potential risk factors of cancer development.[37] Chronic infections are another risk factor that contributes to approximately 12% of the incidence of cancer globally.[38] Other factors that pose a potential risk of cancer include menopausal hormone therapy,[39,40] oral contraceptives,[42] air pollution,[43,44] exposure to radiation,[45–47] and family history (genetics).[48,49] These risk factors, whether individually or in combination, can affect the progression of cancers.

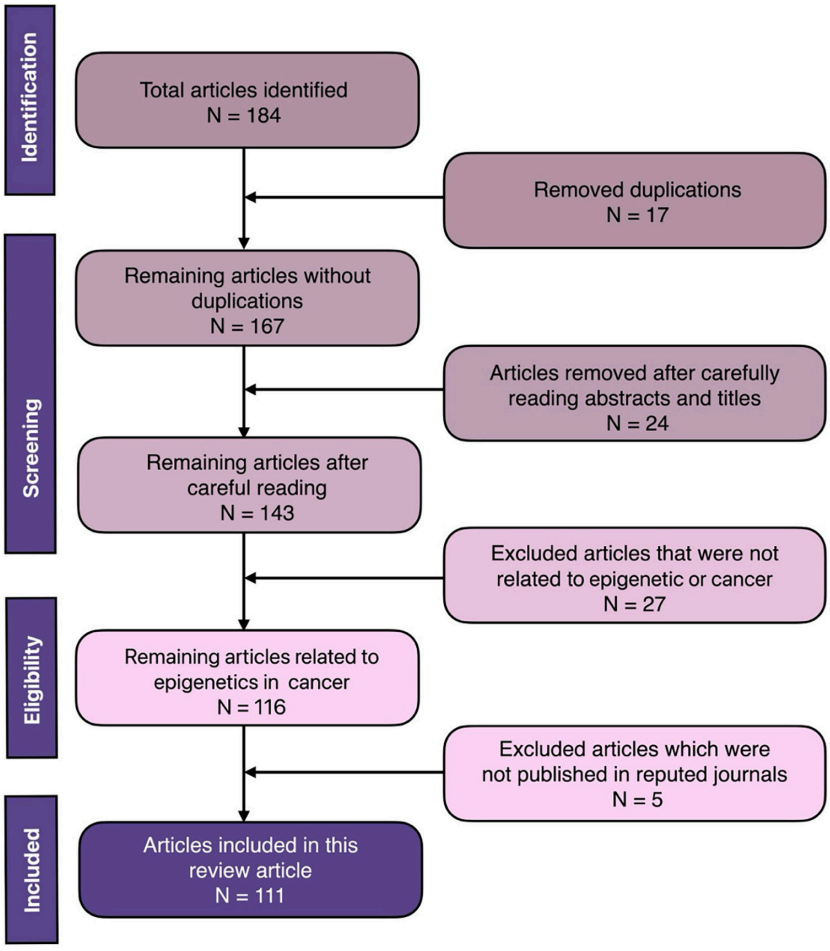

Fig 1 | A summary and flowchart of the included articles. A total of 184 articles were retrieved from multiple databases and after careful screening, 111 articles were included in this review

Role of Epigenetics in Cancer: Methylation, Histone Modification and nc-RNA

According to Hanahan and Weinberg, the classical hallmarks of cancer include cell proliferation, angiogenesis, evasion of cell death, invasion, and metastasis.[50] Studies have revealed significant epigenetic changes such as methylation, histone acetylation, and non- coding RNA expression in all these classical hallmarks of cancer. In the subsequent sections, we will explore how epigenetic modifications influence these molecular events in cancer.

DNA methylation is an alteration that has a potential role in controlling gene expression,[51] transposon silencing,[52] X chromosome inactivation,[53] genomic imprinting,[54] and genomic stability.[55] Briefly, DNA methylation refers to the process where a methyl group is added to the cytosine at the 5' end.[56] DNA methyltransferases (DNMTs) such as DNMT1, DNMT2, DNMT3a, and DNMT3b are a class of enzymes that have a significant role in DNA methylation. These enzymes transfer a methyl group to the fifth carbon of the cytosine pyrimidine ring.[57,58] Promoter methylation of a specific gene suppresses the expression of that gene by preventing the transcription factor from binding to the promoter. Similarly, loss of methylation leads to transcriptional activation, thereby contributing to the

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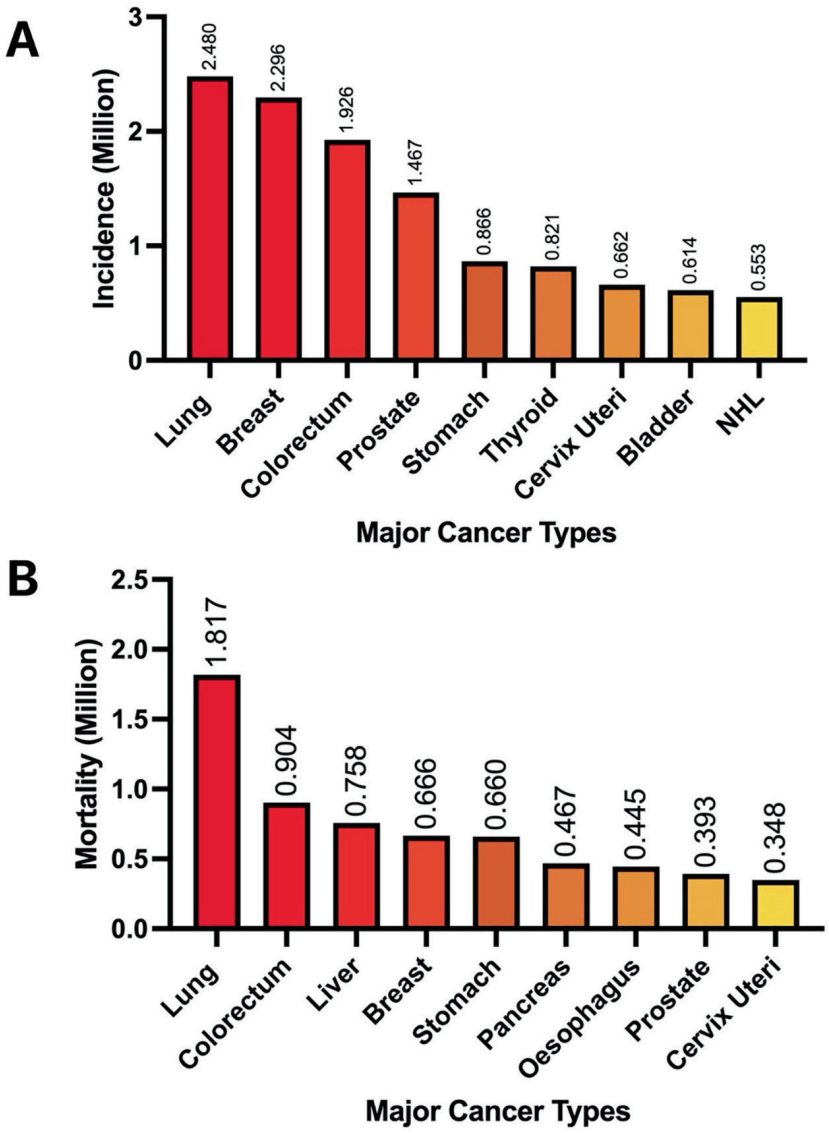

Fig 2 | A graphical representation illustrating the mortality and incidence rates of key cancer types including prostate cancer, pancreatic cancer, liver cancer, lung cancer, breast cancer, colorectal cancer, cervix uteri cancer, and stomach cancer (Source: GLOBOCAN 2022 Statistics)

tissue and cell-specific expression during cell differentiation and embryogenesis.[59]

Studies have revealed that the tight balance of methylation is lost in the process of cancer development.[60,61] Daskalos et al. reported that hypomethylation promoted genomic instability, leading to chromosomal aggregation and activation of transposable elements in non-small cell carcinomas.[62] The hypomethylation-induced genomic instability results in increased expression of oncogenes such as claudin4, mesothelin, and S100A4[63,64] (Figure 3). On the other hand, hypermethylation promotes the inactivation of important tumor suppressor genes including BRCA1, retinoblastoma (Rb), and adenomatous polyposis coli (APC) (Figure 3). An increase in methylation also inactivates key genes such as MGMT, DAPK, and GSTP1 involved in DNA repair, apoptosis, and antioxidation respectively.[64,65]

A range of studies have reported that hypomethylation is implicated in the progression of cancer at advanced stages[66–68] however studies have also reported it in the early stages of tumorigenesis.[69–71] Hypermethylation on the other hand is predominantly involved in the processes of DNA repair, cell cycle regulation, and tissue infiltration in cancer. Recent research efforts have identified nearly 100 genes which have high methylation in breast cancer.[72,73]

The reversible aspect of DNA methylation makes it an appealing target for cancer therapy. Experimental and clinical studies have successfully targeted DNA methylation as a potent therapeutic target using DNMT inhibitor, 5-aza-2′-deoxycytidine (5-AZA).[74] Inhibitor 5-AZA has been shown to reduce DNMT3b levels in breast cancer and restore the regulation of tumor suppressor genes such as RASSF1A in hepatocellular carcinoma,[75] CDKN2B in myelodysplastic syndrome[76] and P53 in melanoma.[77] Targeting DNMTs by 5-AZA and correcting methylation dysregulation through personalized epigenetic therapies can provide potential therapeutic avenues for treating different types of human cancers.

The expression of the EZH2 gene serves as an independent diagnostic marker, indicating malignancy in breast, endometrial and prostate cancers. The regulation of the DNA damage repair gene MGMT can reverse the effects of chemotherapy and radiotherapy;[79] thus, MGMT depletion through hypomethylation can produce a favorable treatment response. Additionally, epigenetic modifications can contribute to tumor formation, which can make them valuable diagnostic markers for assessing disease risk and severity.[80] In NSCLC, the presence of an unmethylated IGFBP3 promoter indicates a positive response to Cisplatin chemotherapy.[81]

The level of methylation could also be used to assess the treatment efficacy and overall disease risk assessment. For instance, methylation at the promoter of PITX2 can serve as a predictor of the primary outcome in people with breast cancer undergoing adjuvant Tamoxifen treatment.[82] Similarly, patients having bladder cancer, p16 hypermethylation may indicate a lower likelihood of relapse after giving IL2 treatment as compared to those without a hypermethylated p16.[83] Because epigenetic mechanisms influence genes and associated pathways, therefore they play a crucial role in finding out the most effective treatment and monitoring strategies for the patients.

Eukaryotic DNA is tightly wrapped around histone proteins to form organized chromatin. Nucleosomes, the basic units of chromatin, consist of 147 base pairs of DNA wrapped around a histone octamer, which includes two molecules each of histones H2A, H2B, H3, and H4.[84] Posttranslational modifications are critical biological processes by which genes and protein functions are regulated.[85] Histone modifications are post-translational modifications in which chemical changes take place at the histone proteins. These modifications could be the removal or addition of certain functional groups such as methyl and acetyl groups (Figure 4). Studies have shown diverse biological functions of

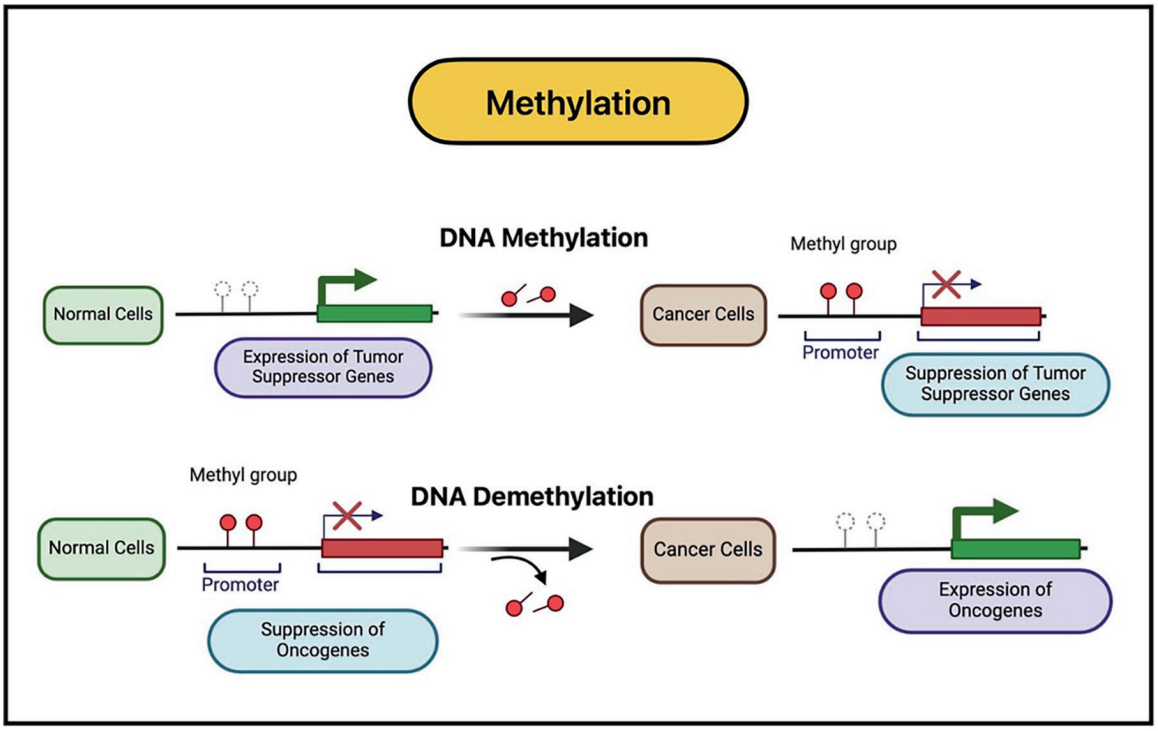

Fig 3 | Illustrates how DNA methylation regulates the expression of oncogenes and genes associated with tumor suppressor activities. DNA methylation adds methyl groups to the promoter region, leading to the suppression of these genes. Conversely, in normal cells, oncogenes are suppressed due to hypermethylation, while oncogenes are actively expressed due to the loss of methylation (hypomethylation) in cancer cells

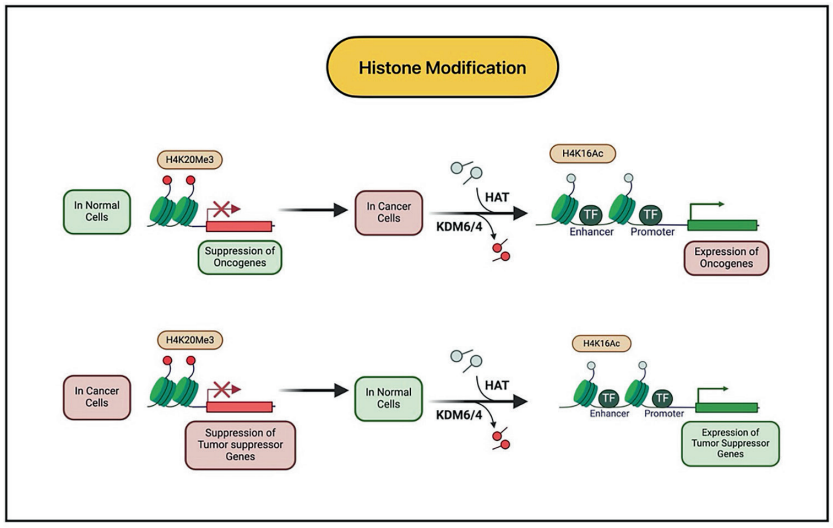

Fig 4 | A graphical representation on how histone modifications regulate gene expression in cancers. In normal cells, the presence of the H4K20Me3 on histones leads to the suppression of oncogenes. However, in cancer cells, the enzymes KDM6/4 and HAT modify histones, by the addition and removal of chemical groups, leading to the expression of oncogenes. On the other hand cancer cells, the H4K20Me3 mark suppresses tumor suppressor genes. Similarly, it causes the suppression of tumor suppressor genes in cancer cells while activating these genes in normal cells

these histone modifications including signal transduction, apoptosis, cell cycle, and chromatin structure.[86,87]

From a theoretical perspective, histone acetylation decreases the positive charge of histones, weakening their interaction with DNA and thereby enhancing gene expression. Typically, higher levels of histone acetylation are present in the promoters of active genes, influencing both the initiation and duration of transcription (Figure 4). Additionally, histone acetylation modifies chromatin structure, which impacts gene transcriptional activity.[88]

Considering the importance of these modifications, substantial research has been carried out to investigate their role in different types of malignancies. Studies have revealed reduced H4K16 acetylation in a range of cancers including liver, breast, brain, colon, and lung cancers.[89,90] Reduction in acetylation accompanied by reduced H4K20me3 methylation has also been observed in breast and lung cancer.[89,90] A recent meta-analysis has revealed that H3K4me2 hypomethylation and H3K4me3 hypermethylation are considered poor treatment outcomes in breast cancer patients.[91] Similarly, reduced levels of H3K4me2, H3K9me3, H3K9ac, and H3K18ac have been revealed to be strongly linked with poor prognosis and reoccurrence of lung cancer.[92] Furthermore, H3K9me3 has the potential to serve as a biomarker for prognosis of gastric cancer.[93]

The addition or removal of a methyl or acetyl group to the histone tails is achieved by specialized histone-modifying enzymes including histone methyltransferases (HMTs), histone acetyltransferases (HATs), histone deacetylases (HDACs), and histone demethylases (HDMs).[94] It is well documented that these HDACs are highly expressed in certain cancers such as gastric and prostate cancers.[95,96] In a study, Brehm et al. revealed that HDAC1 suppresses the transcription of cell-cycle-related protein cyclin E through Rb protein which results in the progression of tumorigenesis.[97]

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The aberrant regulation of histone methyltransferases and demethylases in cancer cells leads to abnormal histone modifications. In mice, the deletion of EZH2, a methyltransferase specific to H3K27, was linked to a high incidence of spontaneous T-cell leukemia. Additionally, elevated levels of EZH2 expression have been observed in prostate and breast cancers.[98–100]

The nature of histone modifications is reversible and that makes these HDACs one of the key therapeutic targets in cancer treatment.[101] For this obvious reason, PRMT1/SMARCA4 inhibitors have been under immense investigation.[102] Valproic acid, an HDAC inhibitor, can produce various effects in both metastatic and non-metastatic cancer cell lines. When used alone or in combination with 5-AZA-DC, a DNA demethylating agent, it may help identify the epigenetic profiles that contribute to the metastatic characteristics of colorectal cancer cells.[103] GSK126 is another methyltransferase inhibitor that targets both the wild-type and mutant forms of the EZH2 enzyme. Studies conducted in xenograft models have demonstrated that GSK126 tends to act as antitumor agent in diffuse large B-cell lymphoma with EZH2 mutations.[104] Although further research is needed to unravel the complex association of histone modification and their association with cancer, these findings suggest that there is a hope of finding novel epigenetic-based therapeutic targets for cancer.

Nearly 75% of the human genome is transcribed into RNA, but only about 3% is converted into protein-coding mRNAs. The remaining non-coding RNAs (ncRNAs) are categorized into various types such as long non-coding RNA (lncRNA), microRNA (miRNA), and circular RNA (circRNA).[105] ncRNAs are another avenue of cancer therapeutics, especially the lncRNAs, which play an important role in modulating oncogenic molecular networks in carcinogenesis and metastasis[106] (Figure 5).

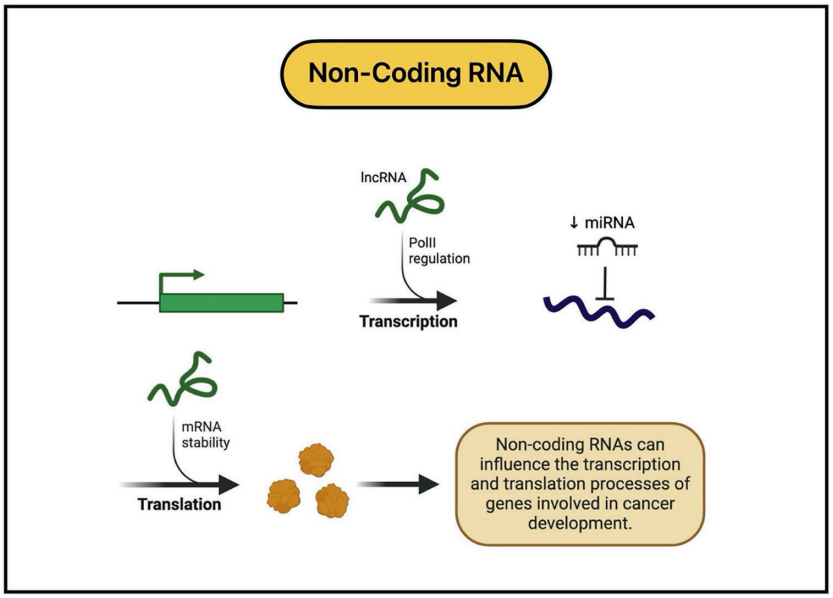

Fig 5 | Demonstrates the role of nc-RNAs in gene regulation. lncRNAs regulate transcription by influencing PolIII activity, while miRNAs affect mRNA stability and translation. These non-coding RNAs can significantly impact the transcription and translation processes of genes which are involved in cancer development

Studies have demonstrated an increasing role of ncRNAs in the development of certain cancers such as colorectal[107] and breast cancers.[108] In a study, Silva et al. found miR- 126 to be highly expressed in human B-cell acute lymphoblastic leukemia.[109] To validate, another study was conducted which revealed that a forced expression of miR-126 resulted in B-cell leukemia in a mouse model.[110] Likewise, lncRNAs also play a key role in the regulation of genes and their associated pathways in cancer. In a recent study, Luo et al. revealed that HOXA gene-derived HOTTIP was abnormally high in acute myeloid leukemia,[111] suggesting a role in the cancer development.

Future Prospects

The integration of epigenetic and genomic data holds promise for advancing personalized cancer medicine. By combining these two layers of information, researchers can develop more precise biomarkers and tailor treatments to individual patient's unique genetic and epigenetic profiles. This approach could lead to significant improvements in treatment efficacy and reduce side effects, as therapies can be customized to address the specific molecular abnormalities present in each patient's cancer.

Another exciting avenue for future research is the exploration of epigenetic mechanisms underlying drug resistance and cancer recurrence. Understanding how epigenetic modifications contribute to these challenges could lead to the development of novel therapeutic strategies to overcome resistance and prevent relapse. Furthermore, the role of epigenetics in cancer prevention and early detection is a growing field, with the potential for discovering new biomarkers and preventive interventions.

Conclusion

Cancer remains one of the diseases with the highest incidence and mortality worldwide. Over the last few decades, research has focused on finding the association between somatic mutations and cancers. However, the focus of research is shifting towards finding epigenetics-based solutions. The epigenetic imbalance that comes into play during tumorigenesis and metastasis stems from dysregulation in a range of cellular, biochemical, and molecular pathways. Emerging research in recent years has focused on the aberrant regulation of methylation, histone modifications, and other epigenetic hallmarks such as non-coding RNA expression and dysregulated phosphorylation. A number of tumor suppressor genes that are silenced during cancer are under immense research. Similarly, a range of oncogenes that are activated due to hypomethylation and acetylation are considered potential targets for the prevention and early detection of cancers.

References

1 Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2024;74(3):229–63.

2 Mbemi A, Khanna S, Njiki S, Yedjou CG, Tchounwou PB. Impact of gene – environment interactions on cancer development.

International journal of environmental research and public health. 2020;17(21):8089.
3 Parsa N. Environmental factors inducing human cancers. Iranian journal of public health. 2012;41(11):1.
4 Boveri T. Concerning the origin of malignant tumours by Theodor Boveri. Translated and annotated by Henry Harris. J Cell Sci 2008; 121(suppl 1): 1–84.
5 Wu S, Zhu W, Thompson P, Hannun YA. Evaluating intrinsic and non-intrinsic cancer risk factors. Nature communications. 2018;9(1):3490.
6 Patel SA, Rodrigues P, Wesolowski L, Vanharanta S. Genomic control of metastasis. British Journal of Cancer. 2021;124(1):3–12.
7 Gull H, Masood N. Genomic instability and cancer metastasis. Essentials of Cancer Genomic, Computational Approaches and Precision Medicine. 2020:143–53.
8 Ferguson LR, Chen H, Collins AR, Connell M, Damia G, Dasgupta S, Malhotra M, Meeker AK, Amedei A, Amin A, Ashraf SS. Genomic instability in human cancer: Molecular insights and opportunities for therapeutic attack and prevention through diet and nutrition. InSeminars in cancer biology 2015;(Vol. 35, pp. S5–S24). Academic Press.
9 Bassal MA. The Interplay between dysregulated metabolism and epigenetics in cancer. Biomolecules. 2023;13(6):944.
10 Ge T, Gu X, Jia R, Ge S, Chai P, Zhuang A, Fan X. Crosstalk between metabolic reprogramming and epigenetics in cancer: updates on mechanisms and therapeutic opportunities. Cancer Communications. 2022;42(11):1049–82.
11 Miranda-Gonçalves V, Lameirinhas A, Henrique R, Jerónimo C. Metabolism and epigenetic interplay in cancer: regulation and putative therapeutic targets. Frontiers in genetics. 2018;9:427.
12 Wong CC, Qian Y, Yu J. Interplay between epigenetics and metabolism in oncogenesis: mechanisms and therapeutic approaches. Oncogene. 2017;36(24):3359–74.
13 Gibney ER, Nolan CM. Epigenetics and gene expression. Heredity. 2010;105(1):4–13.
14 Duncan EJ, Gluckman PD, Dearden PK. Epigenetics, plasticity, and evolution: How do we link epigenetic change to phenotype?. Journal of Experimental Zoology Part B: Molecular and Developmental Evolution. 2014;322(4):208–20.
15 Feinberg AP. Epigenetics at the epicenter of modern medicine. Jama. 2008;299(11):1345–50.
16 Felsenfeld G. A brief history of epigenetics. Cold spring harbor perspectives in biology. 2014;6(1):a018200.
17 Murrell A, Rakyan VK, Beck S. From genome to epigenome. Human molecular genetics. 2005;14(suppl_1):R3–10.
18 Maunakea AK, Chepelev I, Zhao K. Epigenome mapping in normal and disease States. Circulation research. 2010;107(3):327–39.
19 Hamidi T, Singh AK, Chen T. Genetic alterations of DNA methylation machinery in human diseases. Epigenomics. 2015;7(2):247–65.
20 Liu R, Zhao E, Yu H, Yuan C, Abbas MN, Cui H. Methylation across the central dogma in health and diseases: new therapeutic strategies. Signal Transduction and Targeted Therapy. 2023;8(1):310.
21 Lu J, Tan T, Zhu L, Dong H, Xian R. Hypomethylation causes MIR21 overexpression in tumors. Molecular Therapy-Oncolytics. 2020;18:47–57.
22 Fain JS, Loriot A, Diacofotaki A, Van Tongelen A, De Smet C. Transcriptional overlap links DNA hypomethylation with DNA hypermethylation at adjacent promoters in cancer. Scientific Reports. 2021;11(1):17346.
23 Hur K, Cejas P, Feliu J, Moreno-Rubio J, Burgos E, Boland CR, Goel A. Hypomethylation of long interspersed nuclear element-1 (LINE-1) leads to activation of proto-oncogenes in human colorectal cancer metastasis. Gut. 2014;63(4):635–46.
24 Gregory GL, Copple IM. Modulating the expression of tumor suppressor genes using activating oligonucleotide technologies as a therapeutic approach in cancer. Molecular Therapy-Nucleic Acids. 2023;31:211–23.
25 Berndsen RH, Abdul UK, Weiss A, Zoetemelk M, Te Winkel MT, Dyson PJ, Griffioen AW, Nowak-Sliwinska P. Epigenetic approach for angiostatic therapy: promising combinations for cancer treatment. Angiogenesis. 2017;20:245–67.
26 Z Zhao, A. Shilatifard Epigenetic modifications of histones in cancer. Genome Biol. 20 (1) (2019), pp. 1–16
27 Seligson DB, Horvath S, Shi T, Yu H, Tze S, Grunstein M, Kurdistani SK. Global histone modification patterns predict risk of prostate cancer recurrence. Nature 2005;435: 1262–1266.
28 Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell Res 2011;21:381–395.
29 Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet. 2018;392(10159):2052–2090. doi:10.1016/S0140-6736(18)31694-5.
30 Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol. 2012;13(8):790–801. doi:10.1016/S1470-2045(12)70211-5
31 International Agency for Research on Cancer. World cancer report: cancer research for cancer prevention. Accessed March 1, 2021. https://publications.iarc.fr/Non-Series- Publications/World-Cancer-Reports/World-Cancer-Report-Cancer-Research-For- Cancer-Prevention-2020.
32 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 71(3):209–249.
33 Ma ZQ, Richardson LC. Peer reviewed: Cancer screening prevalence and associated factors among US adults. Preventing chronic disease. 2022;19.
34 Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2018;68(4):297–316. 10.3322/caac.21446.
35 National Cancer Institute. Cancer screening overview (PDQ)–patient version. Updated August 19, 2020. https://www.cancer.gov/about-cancer/screening/patient-screening-overview-pdq. Accessed March 3, 2022.
36 World Health Organization, International Agency for Cancer Research, Working Group on the Evaluation of Cancer Preventive Strategies. Cervix cancer screening. IARC handbooks of cancer prevention, volume 10. Lyon (FR): International Agency for Research on Cancer; 2005.
37 Tran KB, Lang JJ, Compton K, Xu R, Acheson AR, Henrikson HJ, Kocarnik JM, Penberthy L, Aali A, Abbas Q, Abbasi B. The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2022;400(10352):563–91.
38 White MK, Pagano JS, Khalili K. Viruses and human cancers: a long road of discovery of molecular paradigms. Clinical microbiology reviews. 2014;27(3):463–81.
39 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer, 2007. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy (Vol. 91). World Health Organization.
40 International Agency for Research on Cancer. Hormonal contraception and post-menopausal hormonal therapy. In Hormonal contraception and post-menopausal hormonal therapy 1999 (pp. 660–660).
41 Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, Chen W, Stampfer MJ, Willett WC. Oral contraceptive use and breast cancer: a prospective study of young women Cancer epidemiology, biomarkers & prevention 2010;19(10):2496–502.
42 La Vecchia C, Tavani A. Female hormones and benign liver tumours. Digestive and Liver Disease. 2006;38(8):535–6.
43 Turner MC, Andersen ZJ, Baccarelli A, Diver WR, Gapstur SM, Pope III CA, Prada D, Samet J, Thurston G, Cohen A. Outdoor air pollution and cancer: An overview of the current evidence and public health recommendations. CA: a cancer journal for clinicians. 2020;70(6):460–79.
44 Pritchett N, Spangler EC, Gray GM, Livinski AA, Sampson JN, Dawsey SM, Jones RR. Exposure to outdoor particulate matter air pollution and risk of gastrointestinal cancers in adults: a systematic review and meta-analysis of epidemiologic evidence. Environmental health perspectives. 2022;130(3):036001.
45 Ali YF, Cucinotta FA, Ning-Ang L, Zhou G. Cancer risk of low dose ionizing radiation. Frontiers in Physics. 2020;8:234.
46 Dahal S, Budoff MJ. Low-dose ionizing radiation and cancer risk: not so easy to tell. Quantitative imaging in medicine and surgery. 2019;9(12):2023.
47 Hong JY, Han K, Jung JH, Kim JS. Association of exposure to diagnostic low-dose ionizing radiation with risk of cancer among youths in South Korea. JAMA network open. 2019;2(9):e1910584.

48 Keivanlou MH, Amini-Salehi E, Joukar F, Letafatkar N, Habibi A, Norouzi N, Vakilpour A, Aleali MS, Rafat Z, Ashoobi MT, Mansour-Ghanaei F. Family history of cancer as a potential risk factor for colorectal cancer in EMRO countries: a systematic review and meta-analysis. Scientific Reports. 2023;13(1):17457.

49 Turati F, Edefonti V, Bosetti C, Ferraroni M, Malvezzi M, Franceschi S, Talamini R, Montella M, Levi F, Dal Maso L, Serraino D. Family history of cancer and the risk of cancer: a network of case–control studies. Annals of oncology. 2013;24(10):2651–6.

50 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. cell. 2011;144(5):646–74.

51 Siegfried Z, Eden S, Mendelsohn M, Feng X, Tsuberi BZ, Cedar H. DNA methylation represses transcription in vivo. Nature genetics. 1999;22(2):203–6.

52 Walsh CP, Chaillet JR, Bestor TH. Transcription of IAP endogenous retroviruses is constrained by cytosine methylation. Nature genetics. 1998;20(2):116–7.

53 Wolf SF, Jolly DJ, Lunnen KD, Friedmann T, Migeon BR. Methylation of the hypoxanthine phosphoribosyltransferase locus on the human X chromosome: implications for X-chromosome inactivation. Proceedings of the National Academy of Sciences, 1984;81(9), pp.2806–2810.

54 Li E, Beard C, Jaenisch R. Role for DNA methylation in genomic imprinting. Nature. 1993;366(6453):362–5.

55 Karpf AR, Matsui SI. Genetic disruption of cytosine DNA methyltransferase enzymes induces chromosomal instability in human cancer cells. Cancer research. 2005;65(19):8635–9.

56 Zemach A, McDaniel IE, Silva P, Zilberman D. Genome-wide evolutionary analysis of eukaryotic DNA methylation. Science 2010;328:916–919.

57 Gujar H, Weisenberger DJ, Liang G. The roles of human DNA methyltransferases and their isoforms in shaping the epigenome. Genes. 2019;10(2):172.

58 Jin B, Robertson KD. DNA methyltransferases, DNA damage repair, and cancer. Epigenetic alterations in oncogenesis. 2012;29:3–29.

59 Greenberg MVC, Bourc'his D. The diverse roles of DNA methylation in mammalian development and disease. Nat. Rev. Mol. Cell Biol. 2019;20:590–607.

60 Chen JJ, Wang AQ, Chen QQ. DNA methylation assay for colorectal carcinoma. Cancer biology & medicine. 2017;14(1):42.

61 Wang S, Fu J, Fang X. A novel DNA methylation-related gene signature for the prediction of overall survival and immune characteristics of ovarian cancer patients. Journal of Ovarian Research. 2023;16(1):62.

62 Daskalos A, Nikolaidis G, Xinarianos G, Savvari P, Cassidy A, Zakopoulou R, Kotsinas A, Gorgoulis V, Field JK, Liloglou T. Hypomethylation of retrotransposable elements correlates with genomic instability in non-small cell lung cancer. International journal of cancer. 2009;124(1):81–7.

63 Stone A, Zotenko E, Locke WJ, Korbie D, Millar EK, Pidsley R, Stirzaker C, Graham P, Trau M, Musgrove EA, Nicholson RI. DNA methylation of oestrogen-regulated enhancers defines endocrine sensitivity in breast cancer. Nature communications. 2015;6(1):7758.

64 Mahmoud AM, Ali MM. Methyl donor micronutrients that modify DNA methylation and cancer outcome. Nutrients. 2019;11(3):608.

65 Sproul D, Meehan RR. Genomic insights into cancer-associated aberrant CpG island hypermethylation. Briefings in functional genomics. 2013;12(3):174–90.

66 Yi J, Gao R, Chen Y, Yang Z, Han P, Zhang H, Dou Y, Liu W, Wang W, Du G, Xu Y. Overexpression of NSUN2 by DNA hypomethylation is associated with metastatic progression in human breast cancer. Oncotarget. 2017;8(13):20751.

67 Yegnasubramanian S, Haffner MC, Zhang Y, Gurel B, Cornish TC, Wu Z, Irizarry RA, Morgan J, Hicks J, DeWeese TL, Isaacs WB. DNA hypomethylation arises later in prostate cancer progression than CpG island hypermethylation and contributes to metastatic tumor heterogeneity. Cancer research. 2008;68(21):8954–67.

68 Barciszewska AM. Global DNA demethylation as an epigenetic marker of human brain metastases. Bioscience reports. 2018;38(5):BSR20180731.

69 Jackson K, Yu MC, Arakawa K, Fiala E, Youn B, Fiegl H, Müller-Holzner E, Widschwendter M, Ehrlich M. DNA hypomethylation is prevalent even in low-grade breast cancers. Cancer biology & therapy. 2004;3(12):1225–31.

70 Sunami E, de Maat M, Vu A, Turner RR, Hoon DS. LINE-1 hypomethylation during primary colon cancer progression. PloS one. 2011;6(4):e18884.

71 Costa FF, Paixão VA, Cavalher FP, Ribeiro KB, Cunha IW, Rinck Jr JA, O'Hare M, Mackay A, Soares FA, Brentani RR, Camargo AA. SATR-1 hypomethylation is a common and early event in breast cancer. Cancer genetics and cytogenetics. 2006;165(2):135–43.

72 Hinshelwood RA, Clark SJ. Breast cancer epigenetics: normal human mammary epithelial cells as a model system. Journal of molecular medicine. 2008;86:1315–28.

73 Widschwendter M, Jones PA. DNA methylation and breast carcinogenesis. Oncogene. 2002;21(35):5462–82.

74 Ghobadi A, Choi J, Fiala MA, Fletcher T, Liu J, Eissenberg LG, Abboud C, Cashen A, Vij R, Schroeder MA, Pusic I. Phase I study of azacitidine following donor lymphocyte infusion for relapsed acute myeloid leukemia post allogeneic stem cell transplantation. Leukemia research. 2016;49:1–6.

75 Wang XM, Wang X, Li J, Evers BM. Effects of 5-azacytidine and butyrate on differentiation and apoptosis of hepatic cancer cell lines. Annals of surgery. 1998;227(6):922–31.

76 Kuykendall JR. 5-azacytidine and decitabine monotherapies of myelodysplastic disorders. Annals of Pharmacotherapy. 2005;39(10):1700–9.

77 Shin TH, Paterson AJ, Grant III JH, Meluch AA, Kudlow JE. 5-azacytidine treatment of HA-A melanoma cells induces Sp1 activity and concomitant transforming growth factor α expression. Molecular and cellular biology. 1992;12(9):3998–4006.

78 Bachmann IM, Halvorsen OJ, Collett K, Stefansson IM, Straume O, Haukaas SA, Salvesen HB, Otte AP, Akslen LA. EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. Journal of clinical oncology. 2006;24(2):268–73.

79 Weller M, Stupp R, Reifenberger G, Brandes AA, Van Den Bent MJ, Wick W, Hegi ME. MGMT promoter methylation in malignant gliomas: ready for personalized medicine?. Nature Reviews Neurology. 2010;6(1):39–51.

80 Kanai Y. Genome-wide DNA methylation profiles in precancerous conditions and cancers. Cancer science. 2010;101(1):36–45.

81 Ibanez de Caceres I, Cortes-Sempere M, Moratilla C, Machado-Pinilla R, Rodriguez- Fanjul V, Manguan-Garcia C, Cejas P, López-Ríos F, Paz-Ares L, De Castrocarpeño J, Nistal M. IGFBP-3 hypermethylation-derived deficiency mediates cisplatin resistance in non-small-cell lung cancer. Oncogene. 2010;29(11):1681–90.

82 Martens JW, Margossian AL, Schmitt M, Foekens J, Harbeck N. DNA methylation as a biomarker in breast cancer. Future oncology. 2009;5(8):1245–56.

83 Jarmalaite S, Andrekute R, Scesnaite A, Suziedelis K, Husgafvel-Pursiainen K, Jankevicius F. Promoter hypermethylation in tumour suppressor genes and response to interleukin-2 treatment in bladder cancer: a pilot study. Journal of cancer research and clinical oncology, 2010;136, pp.847–854.

84 Cutter AR, Hayes JJ. A brief review of nucleosome structure. FEBS letters. 2015;589(20):2914–22.

85 Kouzarides T. Chromatin modifications and their function. Cell. 2007;128(4):693–705.

86 Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell research. 2011;21(3):381–95.

87 Zhao S, Allis CD, Wang GG. The language of chromatin modification in human cancers. Nature Reviews Cancer. 2021;21(7):413–30.

88 Zhang T, Cooper S, Brockdorff N. The interplay of histone modifications–writers that read. EMBO reports. 2015;16(11):1467–81.

89 Esteller M. Cancer epigenomics: DNA methylomes and histone-modification maps. Nature reviews genetics. 2007;8(4): 286–98.

90 Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, Schotta G, Bonaldi T, Haydon C, Ropero S, Petrie K, Iyer NG. Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. Nature genetics. 2005;37(4):391–400.

91 Li S, Shen L, Chen KN. Association between H3K4 methylation and cancer prognosis: A meta-analysis. Thoracic cancer. 2018;9(7):794–9.

92 Chervona Y, Costa M. Histone modifications and cancer: biomarkers of prognosis?. American journal of cancer research. 2012;2(5):589.

93 Lennartsson A, Ekwall K. Histone modification patterns and epigenetic codes. Biochimica et biophysica acta (BBA)-general subjects. 2009;1790(9):863–8.
94 Marmorstein R, Trievel RC. Histone modifying enzymes: structures, mechanisms, and specificities. Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms. 2009;1789(1):58–68.
95 Song J, Noh JH, Lee JH, Eun JW, Ahn YM, Kim SY, Lee SH, Park WS, Yoo NJ, Lee JY, Nam SW. Increased expression of histone deacetylase 2 is found in human gastric cancer. Apmis. 2005;113(4):264–8.
96 Halkidou K, Gaughan L, Cook S, Leung HY, Neal DE, Robson CN. Upregulation and nuclear recruitment of HDAC1 in hormone refractory prostate cancer. The Prostate. 2004;59(2):177–89.
97 Brehm A, Miska EA, McCance DJ, Reid JL, Bannister AJ, Kouzarides T. Retinoblastoma protein recruits histone deacetylase to repress transcription. nature. 1998;391(6667):597–601.
98 Simon C, Chagraoui J, Krosl J, Gendron P, Wilhelm B, Lemieux S, Boucher G, Chagnon P, Drouin S, Lambert R, Rondeau C, Bilodeau A, Lavallée S, Sauvageau M, Hébert J, Sauvageau G. A key role for EZH2 and associated genes in mouse and human adult T-cell acute leukemia. Genes Dev. 2012;26:651–656.
99 Kleer CG, Cao Q, Varambally S, Shen R, Ota I, Tomlins SA, Ghosh D, Sewalt RG, Otte AP, Hayes DF, Sabel MS, Livant D, Weiss SJ, Rubin MA, Chinnaiyan AM. EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. Proc Natl Acad Sci USA. 2003;100:11606–11611.
100 Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, Ghosh D, Pienta KJ, Sewalt RG, Otte AP, Rubin MA, Chinnaiyan AM. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature. 2002;419:624–629.
101 Neganova ME, Klochkov SG, Aleksandrova YR, Aliev G. Histone modifications in epigenetic regulation of cancer: Perspectives and achieved progress. InSeminars in Cancer Biology 2022;(Vol. 83, pp. 452–471).
102 Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, Liu W, Kim S, Lee S, Perez- Neut M, Ding J. Metabolic regulation of gene expression by histone lactylation. Nature. 2019;574(7779):575–80.
103 Ghecham A, Senator A, Pawlowska E, Bouafia W, Błasiak J. Epigenetic modifiers 5-aza-2′-deoxycytidine and valproic acid differentially change viability, DNA damage and gene expression in metastatic and non-metastatic colon cancer cell lines. Acta Biochimica Polonica, 2019;66(3), pp.355–360.
104 Huang S, Wang Z, Zhou J, Huang J, Zhou L, Luo J, Wan YY, Long H, Zhu B. EZH2 inhibitor GSK126 suppresses antitumor immunity by driving production of myeloid-derived suppressor cells. Cancer Research. 2019;79(8):2009–20.
105 Kimura T. Non-coding natural antisense RNA: mechanisms of action in the regulation of target gene expression and its clinical implications. Yakugaku zasshi: Journal of the Pharmaceutical Society of Japan. 2020;140(5):687–700.
106 Coan M, Haefliger S, Ounzain S, Johnson R. Targeting and engineering long non-coding RNAs for cancer therapy. Nature Reviews Genetics. 2024;29:1–8.
107 Ebrahimi F, Gopalan V, Wahab R, Lu CT, Smith RA, Lam AK. Deregulation of miR-126 expression in colorectal cancer pathogenesis and its clinical significance. Experimental cell research. 2015;339(2):333–41.
108 Li F. Expression and correlation of miR-124 and miR-126 in breast cancer. Oncology letters. 2019;17(6):5115–9.
109 Lechman ER, Gentner B, Ng SW, Schoof EM, van Galen P, Kennedy JA, Nucera S, Ciceri F, Kaufmann KB, Takayama N, Dobson SM. miR-126 regulates distinct self-renewal outcomes in normal and malignant hematopoietic stem cells. Cancer cell. 2016;29(2): 214–28.
110 Chen SR, Cai WP, Dai XJ, Guo AS, Chen HP, Lin GS, Lin RS. Research on miR-126 in glioma targeted regulation of PTEN/PI3K/Akt and MDM2-p53 pathways. European Review for Medical & Pharmacological Sciences. 2019;23(8).
111 Luo H, Zhu G, Xu J, Lai Q, Yan B, Guo Y, Fung TK, Zeisig BB, Cui Y, Zha J, Cogle C. HOTTIP lncRNA promotes hematopoietic stem cell self-renewal leading to AML-like disease in mice. Cancer cell. 2019;36(6):645–59.