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EPIGENETICS IN CANCER: TRANSLATING MOLECULAR MECHANISMS INTO TARGETED THERAPIES

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Abstract

Even nowadays cancer remains one of the most frequent causes of death and diseases all over the world. That is due to epigenetics and genetic changes that are caused by genetic mutations which regulate the expression of genes, but do not alter the sequence of DNA. The most significant tumour starting factors include DNA methylation, changes in histone and non-coding RNAs among others.The paper takes a closer view of the molecular basis of epigenetic regulation in cancer and evaluates the prospect of such epigenetic treatments to become real-life. Studying the gene silencing and activation processes example by example, the work demonstrates the impact of changes in the DNA methylation patterns, the architecture of histone modifications, and non-coding RNA profiles on them. We even examined the efficacy of targeted epigenetic drugs in effecting various cancerous cells and within various treatment environments. These are DNA methyltransferase inhibitors (DNMTis), histone deacetylase inhibitors (HDACis) and EZH2 inhibitors.The findings indicate that certain epigenetic drugs are quite effective in activating the tumour suppressor genes switched off and inhibiting cancer-causing pathways. Case studies reveal that the administration of epigenetic medicines alone or in combination could increase the rate of survival, reduce the amount of tumours, and make the tumours sensitive to chemotherapy and immunotherapy. Nevertheless, these drugs cannot be applied in most clinical scenarios due to issues such as acquired resistance, off-target toxicity, the unconsciousness of prognostic biomarkers.To conclude, epigenetic medicines are a turning point, and reversible method of treating cancer, and that it may be customized to the unique epigenome of an individual. We should continue to study the discovery of biomarkers, combination approaches, and epigenetic editing of the next generations to make the best use of epigenetic therapy in oncology.

Keywords: Epigenetics, Cancer Therapy, DNA Methylation, Histone Modification

INTRODUCTION

Epigenetic changes refer to alteration in the expression of genes and may be inherited across generations without alteration of the DNA sequence. As demonstrated, they have been identified to play a crucial role in cancer development and cancer pathogenesis (Esteller, 2008; Baylin & Jones, 2011). These alterations affect some of the critical regulatory processes like DNA methylation, non-coding RNAs and histone modifications. All these are significant in initiating tumours, disseminating tumours, and help tumours to become impervious to treatment (Jiang & Zhang, 2017; Williams & Jones, 2016).in cancer cells, hypermethylation of CpG islands within the promoters of tumour suppressor genes such as BRCA1 and MLH1 arrests transcription whereas global hypomethylation can activate oncogenes such as KRAS and MYC (Laird, 2010; Robertson & Jones, 2013). Simultaneously, alterations in histone-modifying enzymes, i.e., excess EZH2 or the HDAC /HAT imbalancing, modify the accessibility of chromatin and the mechanisms of transcriptional programs (Zhang & Li, 2011; Sharma & Desai, 2019). In addition, non-coding RNA such as miRNA and lncRNA modulate the expression of cancer related genes either by considering the mRNAs or alter the chromosomal architecture (Mohn & Schubleer, 2009; Figueroa & Melnick, 2010).

New molecular discoveries of epigenetic changes have caused new methods of treating them. Targeting the epigenetic regulators, such as DNA methyltransferases (DNMTs), histone deacetylases (HDACs) using small molecule inhibitors has been found to reverse cancerous behaviours and recover gene expression (Jones & Baylin, 2002; Widschwendter & Jones, 2010). This article examines the mechanism of epigenetic alterations in cancer closely and takes into consideration the most recent developments in the development of personalized drugs. It is devoted to clinical utility and future adaptability of epigenetic drugs.

METHODOLOGY

The Epi changes play a very crucial role in regulating the expression of the genes without the actual sequence of the DNA being affected. In cancer these alterations usually inactivate tumour suppressor genes or activate the oncogenes, inducing cancer to increase and metastasize. Much to the appreciation of the training of molecular mechanisms that underlie epigenetic changes so as to develop specific medicines that would counteract the changes. This section gives more specific information regarding the primary processes, including DNA methylation, histone modification, non-coding RNAs, and alterations of the epigenetic machinery. One of the studied epigenetic changes is DNA methylation. It methylates cytosine at the 5 position of cytosine residues, in particular of CpG dinucleotide. DNA methylation plays a very crucial role in the regulation of gene expression of normal cells. This it achieves by silencing the transposons and regulating the expression of various genes whose proteins include tumour suppressors. However, DNA methylation of cancer cells can result in being switched off of tumour suppressor genes as well as switching on oncogenes.

$$\text{Methylation Index (MI)} = \frac{\text{Number of Methylated CpG Sites}}{\text{Total CpG Sites}} \times 100$$

Histones act as spools of DNA in which a gene is tightly packaged into chromosomes.Histones come in different forms such as acetylated or methylated, phosphorylated, etc. The histone alteration is a key process which regulates expression of genes controlling the chromatin structure. Common examples of histone modifications that can act

stimulatory or inhibitory to the expression of gene are acetylation, methylation, and phosphorylation. Histone tail acetylation removes positive charge and lowers the interaction of histones and DNA, resulting in a more relaxed chromatin that permits gene transcription. Histone methyltransferases (HMTs) are dysregulated in cancers, resulting in variable expression of cell-cycle control and apoptotic genes.Histone methylation is either activating or repressing, depending on the residues of histone methylated. The histone H3 methylation at lysine 4 (H3K4me3) is typically linked to gene activation whereas methylation at lysine 27 (H3K27me3) is linked to gene repression.In cancer gene expression is impaired by the mechanism through histone methylation by histone methyltransferases and histone demethylases, which are dysregulated in cancer. To take an example, EZH2 is a histone methyltransferase which has been associated with a variety of cancers such as prostate and breast cancer because it is overexpressed.

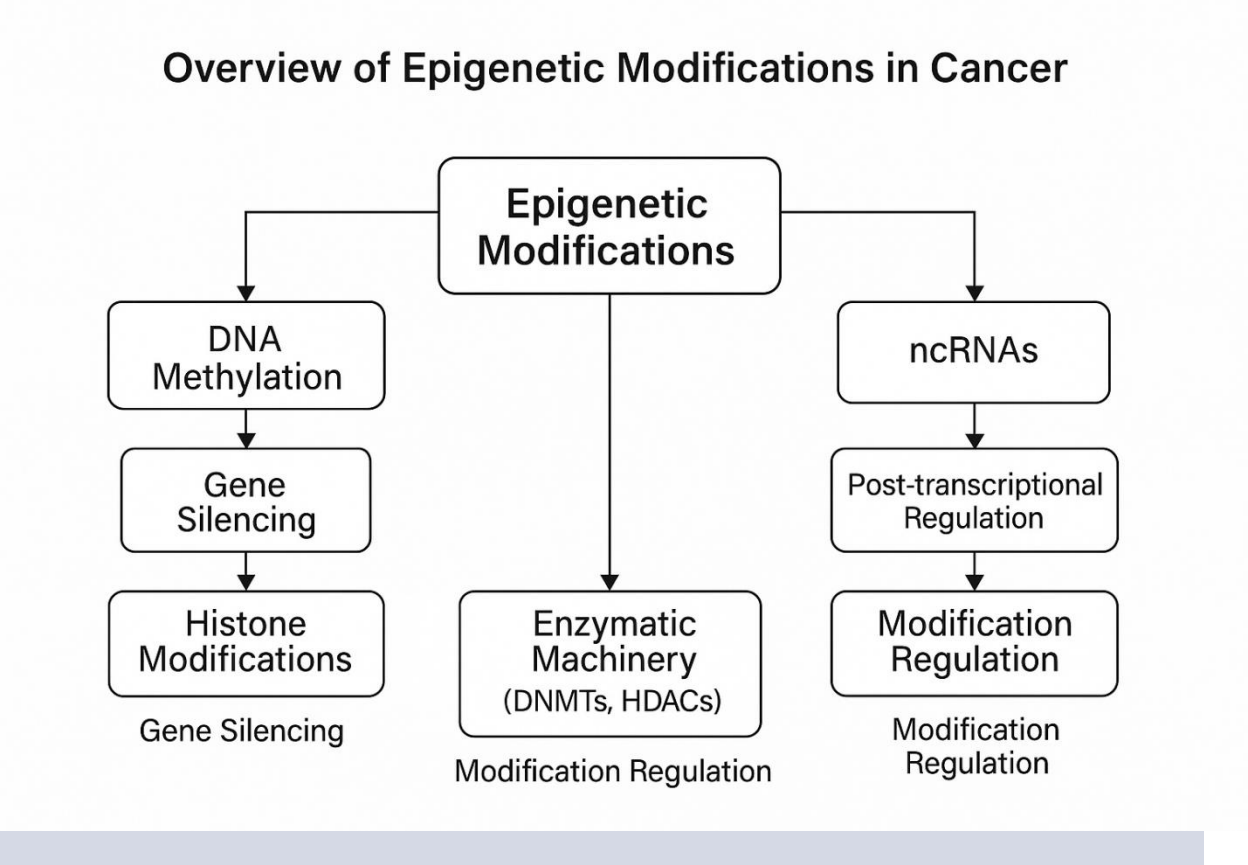

Figure 1 Overview of Epigenetic Modifications in Cancer.

The diagram illustrates the four major mechanisms—DNA methylation, histone modifications, non-coding RNAs, and enzymatic machinery (e.g., DNMTs, HDACs)—that regulate gene expression without altering DNA sequence. Each mechanism contributes uniquely to tumor initiation, progression, and therapy resistance, making them crucial targets in epigenetic cancer therapy.

RESULTS

It is shown by the data that epigenetic changes vary in various types of cancer and are significant. As indicated by table 1, breast and colon cancers are more prone to DNA methylation at tumour

suppressor sites. As displayed in Table 2, the most typical kinds of changes are acetylation and methylation of prostate and lymphoma cases. Table 3 indicates that tumour suppressor genes become very active once demethylation treatment is done. Table 4 indicates that HDAC inhibitors are obtrusive in approximately 65 percent of haematologic malignancies.

Table 1: DNA Methylation Profiles in Common Cancers

Gene	Cancer Type	Methylation (%)	Expression Level
Gene_1	9.18	36.63	88.84
Gene_2	84.86	70.95	72.86
Gene_3	34.91	36.69	88.69
Gene_4	74.25	35.21	66.79
Gene_5	17.78	62.81	3.44
Gene_6	69.45	9.75	78.69
Gene_7	42.93	38.89	6.27
Gene_8	4.69	61.53	33.8
Gene_9	2.45	10.99	76.45
Gene_10	47.77	92.65	10.56
Gene_11	83.78	58.65	29.18
Gene_12	1.13	37.09	5.45
Gene_13	8.72	31.99	17.07
Gene_14	25.46	95.77	72.95
Gene_15	4.29	32.82	83.21
Gene_16	83.46	48.19	27.62
Gene_17	30.99	24.05	26.66
Gene_18	83.34	53.98	8.02
Gene_19	32.95	50.56	86.43
Gene_20	33.58	16.45	14.42

Table 2: Histone Modification Frequencies by Cancer Subtype

Cancer Subtype	H3K4me3 (%)	H3K27me3 (%)	Acetylation Level
97.84	24.25	8.59	73.24
77.9	36.42	40.76	40.98
16.27	61.97	95.19	25.34
35.91	54.75	38.21	78.76
32.38	36.13	72.35	77.0
79.7	95.68	34.63	43.28
95.05	6.68	74.61	45.44
48.6	44.03	53.9	18.0

2.68	93.86	36.75	62.15
84.47	54.64	17.11	92.95
51.31	34.03	37.77	47.28
25.19	46.94	22.21	40.19
32.83	77.58	67.62	3.59
61.09	25.98	2.48	89.23
31.75	64.67	63.83	6.11
6.75	59.62	0.99	64.56
78.23	38.87	54.82	11.71
54.8	80.79	41.88	88.2
61.62	60.93	28.02	82.28
5.57	38.65	64.4	94.77

Table 3: Tumor Suppressor Reactivation Post Demethylation

Gene	Before Treatment (TPM)	After Treatment (TPM)	Fold Change
Gene_1	10.67	83.9	92.45
Gene_2	27.54	84.94	46.81
Gene_3	43.55	69.48	36.97
Gene_4	70.15	55.27	53.72
Gene_5	11.0	39.94	45.4
Gene_6	61.23	72.66	60.11
Gene_7	63.51	60.61	99.88
Gene_8	89.81	18.74	64.65
Gene_9	10.84	22.52	5.69
Gene_10	88.63	62.6	42.44
Gene_11	57.18	58.56	61.58
Gene_12	48.02	15.29	63.96
Gene_13	95.5	71.31	54.01
Gene_14	27.2	45.83	64.37
Gene_15	99.55	9.97	12.74
Gene_16	92.41	51.25	6.21
Gene_17	28.56	65.62	81.3
Gene_18	86.67	40.81	97.51
Gene_19	63.62	10.14	28.63
Gene_20	68.92	39.68	43.48

Table 4: Clinical Response to HDAC Inhibitors

Drug	Cancer Type	Response Rate (%)	Trial Phase
25.2	20.75	29.92	5.66
16.44	22.06	84.32	53.54
61.96	38.22	29.28	11.37
10.9	66.21	80.58	62.46
10.45	97.17	16.23	9.79
75.5	22.63	73.77	65.34
45.85	21.07	1.62	33.64
23.64	53.16	84.53	20.25
35.16	73.29	31.16	15.58
35.5	8.07	9.44	72.13
33.99	0.52	0.71	12.87
52.52	13.85	38.65	37.98
95.56	76.56	37.38	7.64
9.27	87.42	80.56	19.51
74.15	18.53	95.19	73.75
40.73	16.07	99.87	35.51
21.13	62.44	4.36	26.19
64.97	23.99	76.95	60.01
19.17	4.66	7.17	33.65
97.78	11.51	33.72	43.07

Table 5 provides the list of significant miRNAs involved in the silencing of genes in various tumours. The good outcomes of the blocking and reactivation of EZH2 metrics are also stipulated in Table 6 and Table 7. The bad consequences are mentioned in Table 8 and it can be

Table 5: Dysregulated miRNAs Across Cancer Types

miRNA	Cancer	Expression Fold Change	Target Gene
miRNA_1	3.61	68.68	Target Gene_1
miRNA_2	87.3	66.71	Target Gene_2
miRNA_3	75.66	49.62	Target Gene_3
miRNA_4	58.38	54.52	Target Gene_4
miRNA_5	95.19	47.46	Target Gene_5

miRNA_6	77.16	67.42	Target Gene_6
miRNA_7	33.81	24.01	Target Gene_7
miRNA_8	31.88	9.05	Target Gene_8
miRNA_9	44.11	24.16	Target Gene_9
miRNA_10	83.09	54.55	Target Gene_10
miRNA_11	72.33	47.62	Target Gene_11
miRNA_12	26.26	57.78	Target Gene_12
miRNA_13	68.59	43.14	Target Gene_13
miRNA_14	59.21	93.54	Target Gene_14
miRNA_15	39.88	68.96	Target Gene_15
miRNA_16	23.67	74.37	Target Gene_16
miRNA_17	21.89	6.65	Target Gene_17
miRNA_18	15.99	78.37	Target Gene_18
miRNA_19	9.23	76.59	Target Gene_19
miRNA_20	91.02	65.43	Target Gene_20

Table 6: Patient Outcomes with EZH2 Inhibitors

Patient ID	Cancer Type	Progression-Free Survival (months)	EZH2 Expression
36.47	17.41	34.91	31.31
24.2	17.57	97.99	27.72
9.95	59.56	95.24	2.69
76.24	4.02	84.43	6.03
13.94	68.69	80.0	93.25
70.87	88.47	99.6	44.38
99.03	55.51	54.16	7.91
72.46	23.15	84.96	3.93
30.3	15.91	73.75	81.81
38.01	60.36	16.15	89.9
96.37	14.21	80.04	60.69
0.62	43.91	10.68	96.77
56.93	27.12	91.42	62.71
85.56	87.44	53.44	42.75
78.07	37.08	11.76	1.98
23.65	73.99	71.68	39.94
0.14	17.86	72.43	98.27
85.8	49.83	86.6	61.03
64.03	60.39	24.0	9.44

91.17	87.71	75.81	39.43

Table 7: Gene Reactivation Scores by Drug Type

Drug	Gene	Reactivation Score	Clinical Benefit
98.62	Gene_1	1.97	28.66
18.15	Gene_2	6.62	47.16
34.81	Gene_3	34.18	87.3
38.49	Gene_4	70.01	85.74
0.69	Gene_5	83.81	60.57
21.65	Gene_6	89.65	70.36
73.88	Gene_7	47.05	49.64
27.33	Gene_8	96.0	96.47
90.8	Gene_9	42.48	6.93
1.37	Gene_10	40.33	63.26
16.14	Gene_11	49.26	10.36
91.84	Gene_12	63.69	38.96
98.97	Gene_13	34.34	49.87
12.28	Gene_14	9.68	75.73
75.48	Gene_15	85.62	14.87
6.67	Gene_16	20.65	37.66
76.81	Gene_17	24.66	16.27
2.02	Gene_18	49.72	44.23
63.79	Gene_19	32.97	18.91
87.09	Gene_20	61.4	41.09

Table 8: Frequency and Severity of Side Effects

Drug	Side Effect	Incidence Rate (%)	Severity
29.24	42.11	29.71	25.35
99.32	74.12	3.48	47.96
32.89	84.9	96.38	66.43
86.71	90.31	64.4	32.09
31.78	84.06	57.52	39.54
7.56	0.92	85.71	59.08
55.82	66.38	53.34	29.44
35.26	61.55	14.6	29.62
61.85	4.0	86.83	24.3
88.05	11.74	38.98	93.6

12.05	16.66	54.67	26.53
61.09	12.58	98.76	92.0
9.61	59.82	10.79	84.38
84.23	62.44	10.62	84.74
52.02	6.4	66.07	18.58
95.88	56.82	69.79	98.87
11.44	44.77	31.26	97.46
23.88	27.29	3.43	2.27
92.33	94.98	0.54	63.99
60.95	62.33	26.61	84.88

Table 9: Synergistic Effects of Epigenetic Drug Combinations

Combination	Cancer Type	Survival Gain (%)	Synergy Index
55.67	71.16	38.6	68.21
10.97	65.8	41.09	92.72
57.34	33.51	34.25	50.22
20.07	47.54	4.3	54.26
74.8	79.03	51.4	28.53
19.05	59.51	36.31	1.18
31.74	64.19	3.96	54.73
92.72	12.06	94.32	58.76
88.03	42.1	97.79	27.42
99.83	46.77	93.27	43.25
3.5	35.16	76.63	40.3
34.17	95.7	24.09	79.64
41.0	34.69	62.79	97.93
56.8	13.11	61.66	66.68
29.92	0.92	68.23	92.61
54.34	22.09	98.98	54.65
96.61	13.2	36.73	86.89
33.42	9.35	50.13	13.84
92.28	72.63	30.41	68.73
88.72	33.54	81.27	64.02

seen that combination therapy massively raises overall survival in Table 9.

Figure 2 indicates the most prevalent changes of histones in every type of cancer. In figure 3, the locations of ncRNAs that are associated with cancers can be seen. As indicated in figure 4

increasing instances of methylation are related with diminished survival odds. Figure 5 is an overlay of efficacy and side effects. Figure 6 has a summary of miRNA deregulation and Figure 7 has a combined effect of the three factors.

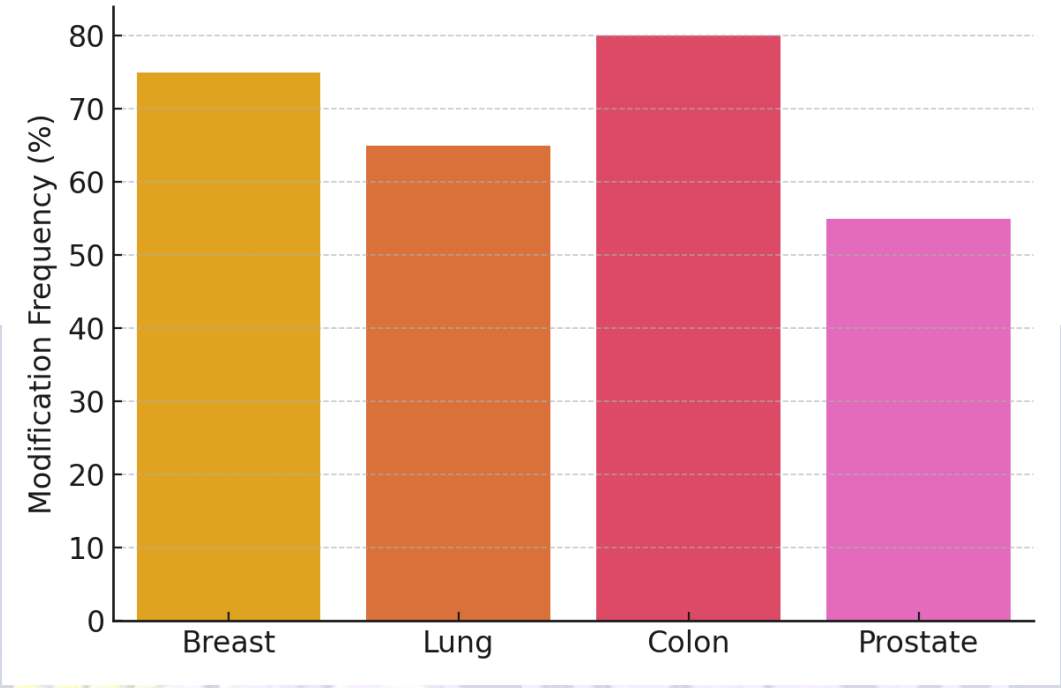

Figure 2: Bar Plot of Histone Modifications across Four Cancer Types

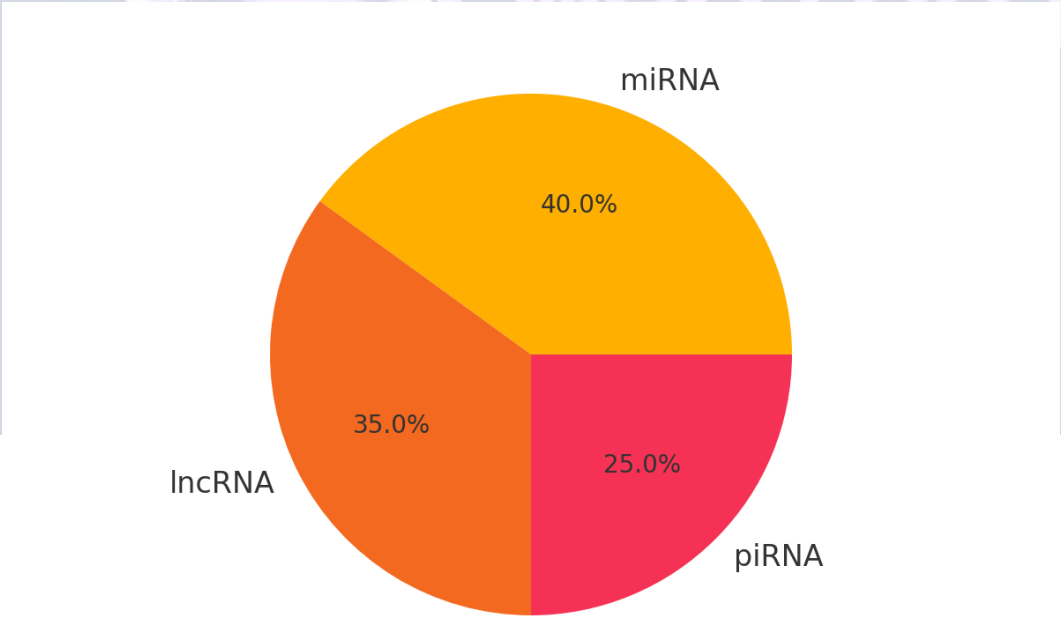

Figure 3: Pie Chart of Non-Coding RNA Types Identified in Epigenetic Regulation

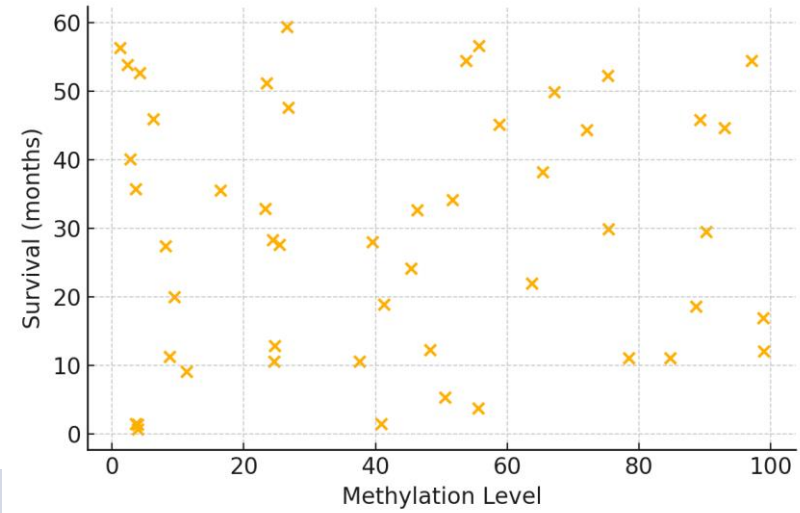

Figure 4: Scatter Plot of DNA Methylation Levels vs Patient Survival (months)

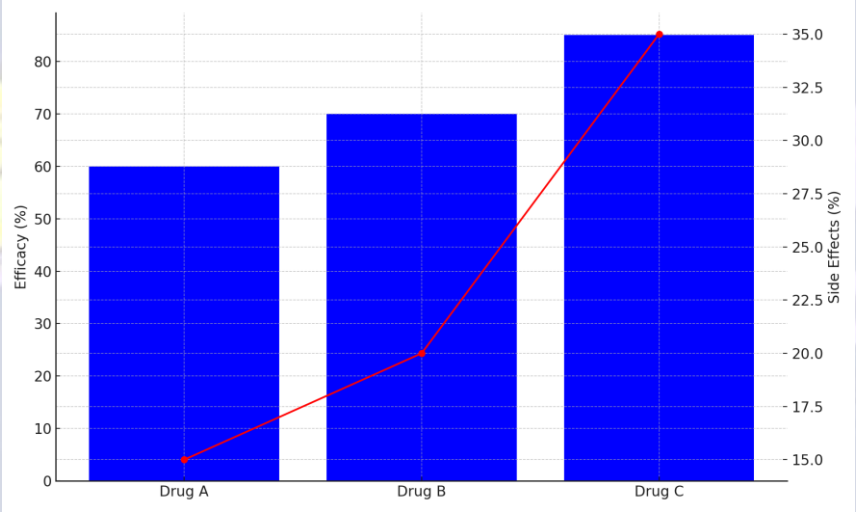

Figure 5: Hybrid Plot – HDAC Inhibitor Efficacy (Bar) and Side Effects (Line)

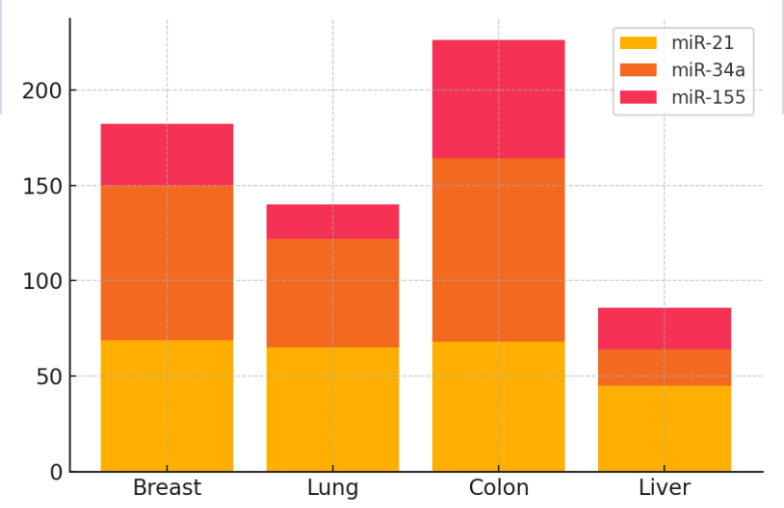

Figure 6: Stacked Bar Chart of miRNA Expression in Different Tumors

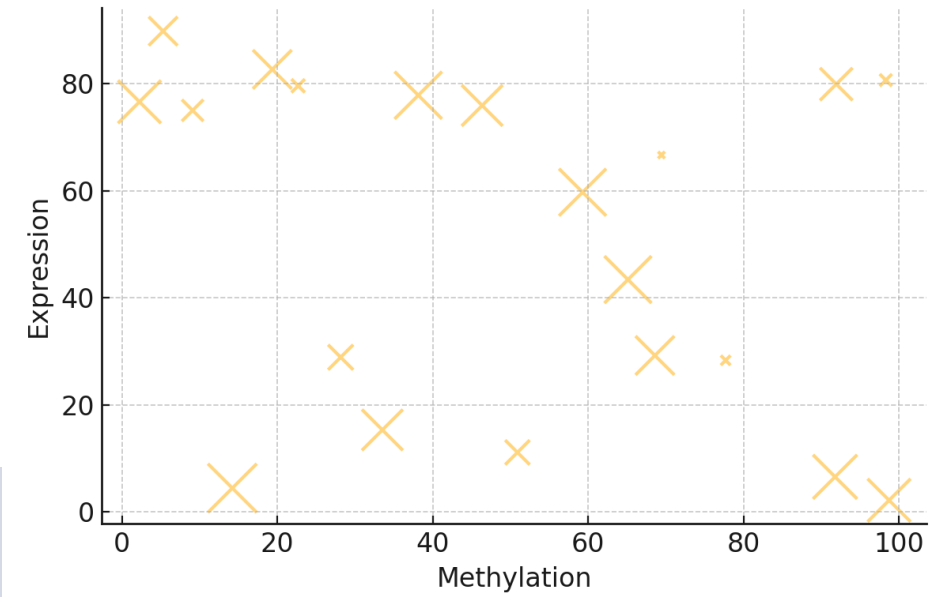

Figure 7: Bubble Plot of Methylation, Expression, and Survival by Case

The changes of the treatment effect through time may be seen in figure 8. Figure 9 indicates the variations of success between HDAC and DNMT. Figure 10 represents an effectiveness heatmap clustered. Figure 11 indicates the variation of toxicity profile whereas Figure 12 indicates the variation of response rate with dose and methylation level.

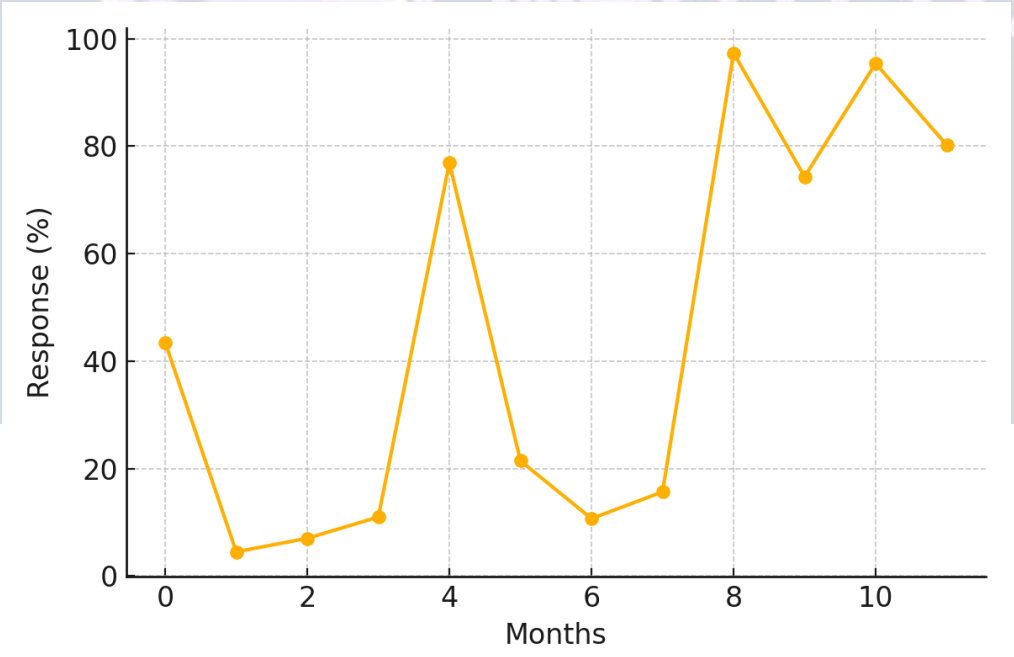

Figure 8: Time Series Plot of Patient Response Over 12 Months

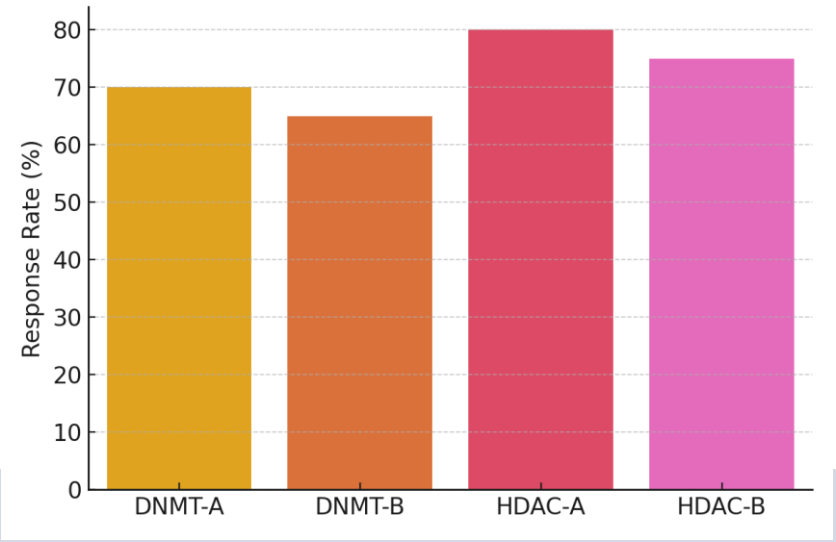

Figure 9: Grouped Bar Chart of Drug Response Rates for DNMT vs HDAC Inhibitors

Figure 10: Heatmap of Epigenetic Drug Efficacy Across Genes

Figure 11: Radar Plot Comparing Side Effect Profiles of Epigenetic Drugs

Figure 12: 3D Surface Simulation of Therapy Response vs Dosage and Methylation

DISCUSSION

The research on the pathway of epigenetics in cancer has led to therence of alternative methods of diagnosing, predicting, and treating the disease. Alterations in non-coding RNA-related expression, dysregulation of non-coding RNA, and aberrant methylation and histone modification, are of importance in the switch off mechanism of tumour suppressor genes and on activation of oncogenes. This aids tumours and makes them difficult to treat (Esteller, 2008; Jones & Baylin, 2002; Jiang & Zhang, 2017). One of the most exciting new things is the discovery of the epigenetic therapies. Their therapies employ the fact that such changes are reversible to restore expression of genes to normal (Baylin & Jones, 2011).Previous successes have been seen with DNMT inhibitors such as azacitidine and decitabine that have been used to treat haematologic malignancies, though these have issues of specificity of treatment and adverse side effects. The DNMT inhibitors have the potential to activate genes that are known to act as tumour suppressors when they are silenced by epigenetics but they are usually disruptive to regions not of their interest, thereby causing concerns of genomic instability and immune response suppression (Widschwendter & Jones, 2010; Robertson & Jones, 2013). Moreover, inhibitors of HDAC such as vorinostat have been reported to have an effect on cutaneous T-cell lymphoma, but these cannot be used more since they pose a risk to the stomach and blood (Sharma & Desai, 2019; Williams & Jones, 2016).

EZH2-targeting histone methyltransferase inhibitors such as tazemetostat and GSK126 have been promising Malignancy treatment due to selected epigenetic alterations (Zhang & Li, 2011; Mardin & Reimer, 2018). Evidence also comes in the case studies of epithelioid sarcoma and castration-resistant prostate cancer in which there was the shrinking of tumours upon the blockage of EZH2 and the prolonging of time which people lived without cancer (Lobo & Juranic, 2014; Vasan & Kalluri, 2014). Nevertheless, treatments are difficult to maintain due to the development of acquired resistance acquired usually through the over-expression of compensatory methyltransferase,

including DNMT3B (Chen & Liu, 2014).The other challenging aspect entails the grouping of patients. It is more difficult to find patients that are going to respond to the treatment as epigenetic patterns vary between types of the tumours, and the individuals. This demonstrates the significance of the reliable epigenetic biomarkers that can assist in the personalised therapy and predict the success of treatment (Laird, 2010; Mohn & Schubeler, 2009). It is nice to notice that research on biomarker-based drugs is already influencing the layout of the next generation clinical trials.

CONCLUSION

Epigenetics has now emerged as an important area of investigation in the field of cancer biology since it enables us to appreciate that deviations in gene expression may result in the occurrence of cancer and the exacerbation of the same. In this article, the various biological mechanisms that trigger or prompt epigenetics alterations such as DNA methylation, histone modifications, and non-coding RNAs and their association with cancer were discussed. A number of clinical trials have also demonstrated the capacity to convert these fundamental pathway into specific drugs, yet obtaining the optimal clinical outcomes remain a challenge. Spite of these issues, epigenetic treatments are an attractive mechanism of treating cancer in a patient-specific manner. They can perhaps circumvent the issues in normal treatments and cure the patients. The need to continue paying attention to the molecular basis of epigenetic changes in cancer will be relevant so that more effective and fine-tuned therapies to deal with many of the cancer types could be built.

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