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How Does Epigenetics Affect Antigen Presentation in Cancer Cells?

[1] Lisa Li

[1] Magdalen College School, Oxford, England
Corresponding Author Email: [1] li.xiao.tong@hotmail.com

***Abstract*— Epigenetics involves changes in the expression of genes but does not alter the DNA sequence itself. The importance of these key mechanisms such as DNA methylation, histone modifications, and non-coding RNAs on the downregulation of major histocompatibility complex (MHC) molecules, are examined, which are essential for the recognition of tumour-associated antigens by the immune system. Inhibition of MHC molecule expression due to aberrant epigenetic modifications causes cancer cells to evade the immune system, thereby promoting tumour growth and metastasis.**

The difficulty in diagnosing cancers based on epigenetic markers are explored, particularly the variability of epigenetic modifications across different cancer types and individuals. The effectiveness of techniques such as bisulfite sequencing and chromatin immunoprecipitation sequencing (ChIP-seq) in detecting these epigenetic modifications is discussed, despite the complexities posed by the heterogeneity of these changes. The need for personalised diagnostic approaches is emphasised. The potential benefits of combining epigenetic therapies with immunotherapy, such as immune checkpoint inhibitors and chimeric antigen receptor (CAR)-T cell therapies, are highlighted as promising strategies to counteract immune evasion by cancer cells. This study investigated peer reviewed published articles to provide an overview on the critical effects of epigenetic modifications on cancer cell expression and their role in immune evasion and tumour progression. Furthermore, the importance of epigenetic regulation in developing personalised cancer therapies that could significantly enhance patient outcomes is underlined.

***Index Terms*— Antigen Presentation, Cancer Immunotherapy, Epigenetics, Immune Evasion.**

I. INTRODUCTION

Epigenetics refers to the changes in gene expression that do not involve alteration to the underlying DNA sequence. These changes play a vital role in many different biological processes, such as cancer development and progression. The primary mechanisms are regulated by: DNA methylation, histone modification and non-coding RNAs (Yu et al., 2024). DNA methylation is the process of adding a methyl group to the DNA molecule, often leading to gene silencing, which can contribute to uncontrolled cell growth in cancer (Gayatri & Bedford, 2014). Histone modifications, such as acetylation, phosphorylation and ubiquitination, alter the chromatin structure, affecting gene accessibility and transcription (Denis et al., 2009). These modifications can either inhibit or promote the expression of genes involved in cancer cell survival and proliferation, depending on the corresponding gene (Webby et al., 2009). Non-coding RNAs, including microRNAs, play a role in post-transcriptional regulation of gene expression and cancer development and progression. This adds another step of control over the complexity of cancer epigenetics (Yu et al., 2024).

Epigenetic mechanisms are essential in normal cellular functions and the pathogenesis of cancer. Cancer emerges from a combination of epigenetics alterations and genetic mutations that leads to uncontrolled growth of cells. Epigenetics has the ability to affect the immune system to recognise and eliminate cancer cells, known as immune surveillance (Yu et al., 2024). Epigenetics alterations significantly impact antigen presentation on cancer cells. Abnormal epigenetic expression can lead to the downregulation of genes involved in antigen presentation to enable cancer cells evading immune surveillance.

This issue is particularly important when considering high mortality rates and incidence of cancers such as lung, breast and colorectal cancers, with lung cancer alone accounting for around 2.2 million new cases and 1.8 million deaths globally in 2020 (Yu et al., 2024). Late-stage diagnosis and subsequent challenges in treatment are often due to the cancer cell's ability to escape immune surveillance, emphasising the crucial role of epigenetics in antigen presentation and immune evasion (Ota et al., 2002).

Current therapeutic approaches targeting epigenetic modifications in cancer include the use of epigenetic drugs such as DNA methyltransferase inhibitors (e.g., azacitidine and decitabine) and histone deacetylase inhibitors (e.g., vorinostat and romidepsin) (Yoshimatsu et al., 2011). These therapies aim to reverse aberrant epigenetic markers, restore normal gene expression, and enhance antigen presentation to improve immune recognition and targeting of cancer cells (Zou et al., 2012). However, the heterogeneity of epigenetic marks within tumours still presents a significant challenge (Yu et al., 2024).

The heterogeneity of epigenetic marks in tumour cells complicates the effectiveness of epigenetic therapies, which can lead to variable responses to treatment, with some cells within a tumour being resistant to medications (Gayatri, 2024). Therefore, understanding and mapping the epigenetic heterogeneity within tumours is important for developing

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more effective and personalised and precise treatment strategies (Yu et al., 2024).

Traditional cancer treatments such as chemotherapy and radiation therapy often fail to achieve long-term remission due to their inability to specifically target cancer cells, leading to significant toxicity and adverse effects. Moreover, these treatments do not address the underlying epigenetic alterations that contribute to tumour progression and immune evasion (Hanhan, 2011). Also, cancer cells can develop resistance to these therapies which highlights the necessity for other treatment strategies (Holohan et al., 2013).

In recent years, immunotherapies, including immune checkpoint inhibitors and chimeric antigen receptor (CAR)-T cell therapies, have shown success in treating certain cancer types. These therapies work by enhancing the immune system's ability to recognise and attack cancer cells (Denis et al., 2009). Combining epigenetic therapies with immunotherapies holds potential for improving treatment outcomes by targeting epigenetic alterations that impair antigen presentation and boosting the immune response (Chen et al., 2017).

The primary aim of this paper is to explore how epigenetic modifications affect antigen presentation in cancer cells and to evaluate the implications for immune evasion and cancer progression. The objectives include reviewing the mechanisms of DNA methylation, histone modifications, and non-coding RNAs in regulating antigen presentation, analysing the impact of these changes on the expression of MHC molecules, assessing the different cancer treatments and the potential of combining epigenetic therapies with immunotherapeutic approaches to achieve personalised medicine.

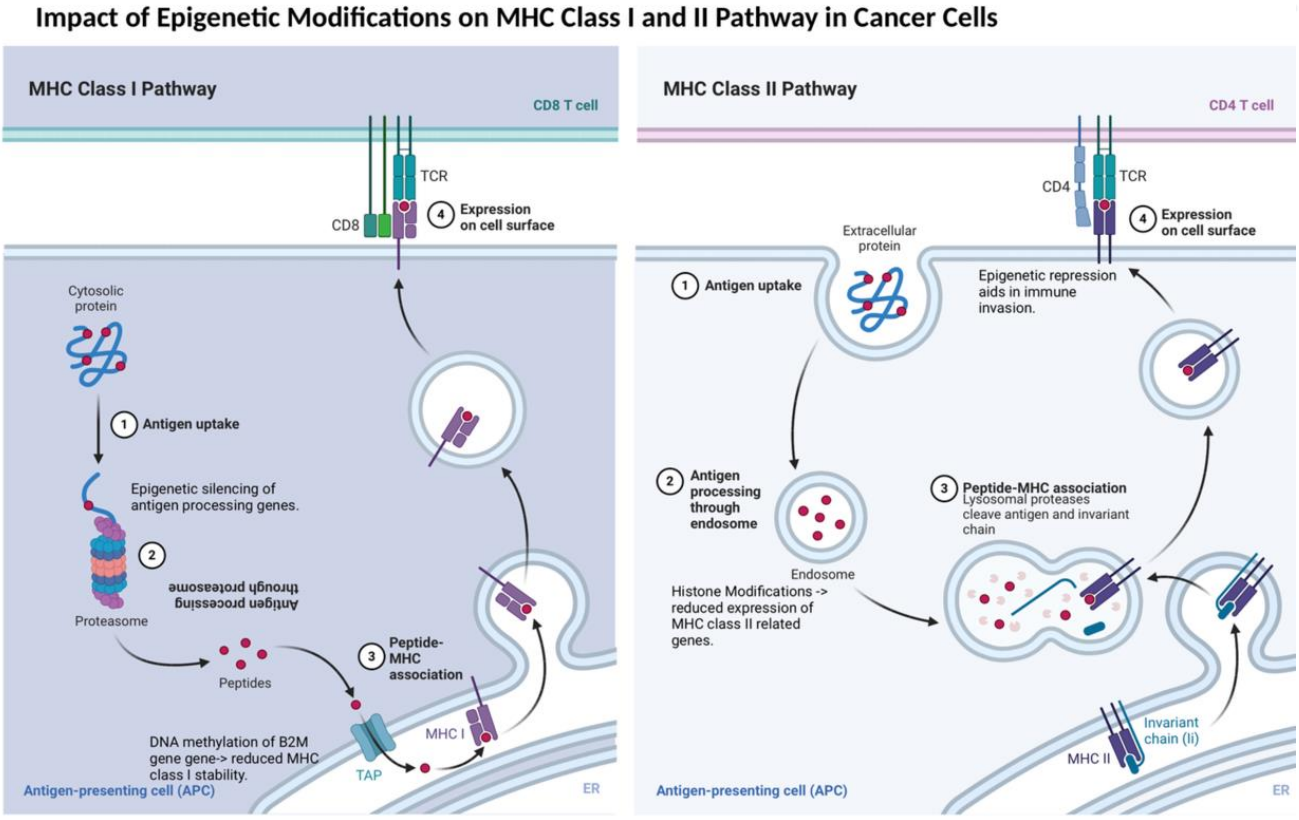

Figure 1

Figure 1. illustrates the MHC class I and class II pathways, which are essential for antigen presentation and immune surveillance. In the MHC class I pathway, cytotoxic proteins, often derived from intracellular pathogens or tumour cells, are ubiquitinated and degraded by the proteasome into smaller peptides. These peptides are transported into the endoplasmic reticulum (ER) by the Transporter Associated with Antigen Processing (TAP), where they bind to MHC class I molecules. Then, the peptide-MHC class I complexes are transported to the cell surface for presentation to CD8+ cytotoxic T cells. The figure was created using Biorender.

In contrast, the MHC class II pathway involves the uptake of extracellular proteins by antigen-presenting cells (APCs) through endocytosis. After processing in endosomes, where they are degraded into peptides, the peptides bind to MHC class II molecules with the endosome, and the resulting peptide-MHC class II complexes are transported to the cell surface to be recognised by CD4 + helper T cells (Blum et al., 2013). This interaction is essential for activating the broader immune response. Epigenetic modifications can down-regulate the expression of MHC molecules on cancer

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cells, leading to reduced antigen presentation and allowing cancer cells to evade immune detection (Schumacher, 2015).

II. METHODS

The research was conducted from scholarly sources including Google scholars, the National Center for Biotechnology Information (NCBI), the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the National Institutes of Health (NIH). The search was limited to papers published in English over the past 20 years that were focused on the following keywords for research: "Cancer", "Epigenetics", "Gene expression", "Acetylation", "Methylation", "Non-coding RNA", "MHC". Studies were included within the following criteria: (a) focused on cancer gene expression and epigenetics in human, (b) were published in peer-reviewed journals. Non-English studies and studies mainly focused on animals were excluded. The figures were created using Biorender.

III. MECHANISM

Epigenetic modifications play a vital role in the regulation of gene expression and significantly impact the presentation of antigens on cancer cells. These mechanisms include DNA methylation, histone modifications, and non-coding RNAs each contributing to the downregulation of genes involved in antigen presentation, thus enabling cancer cells to evade immune surveillance.

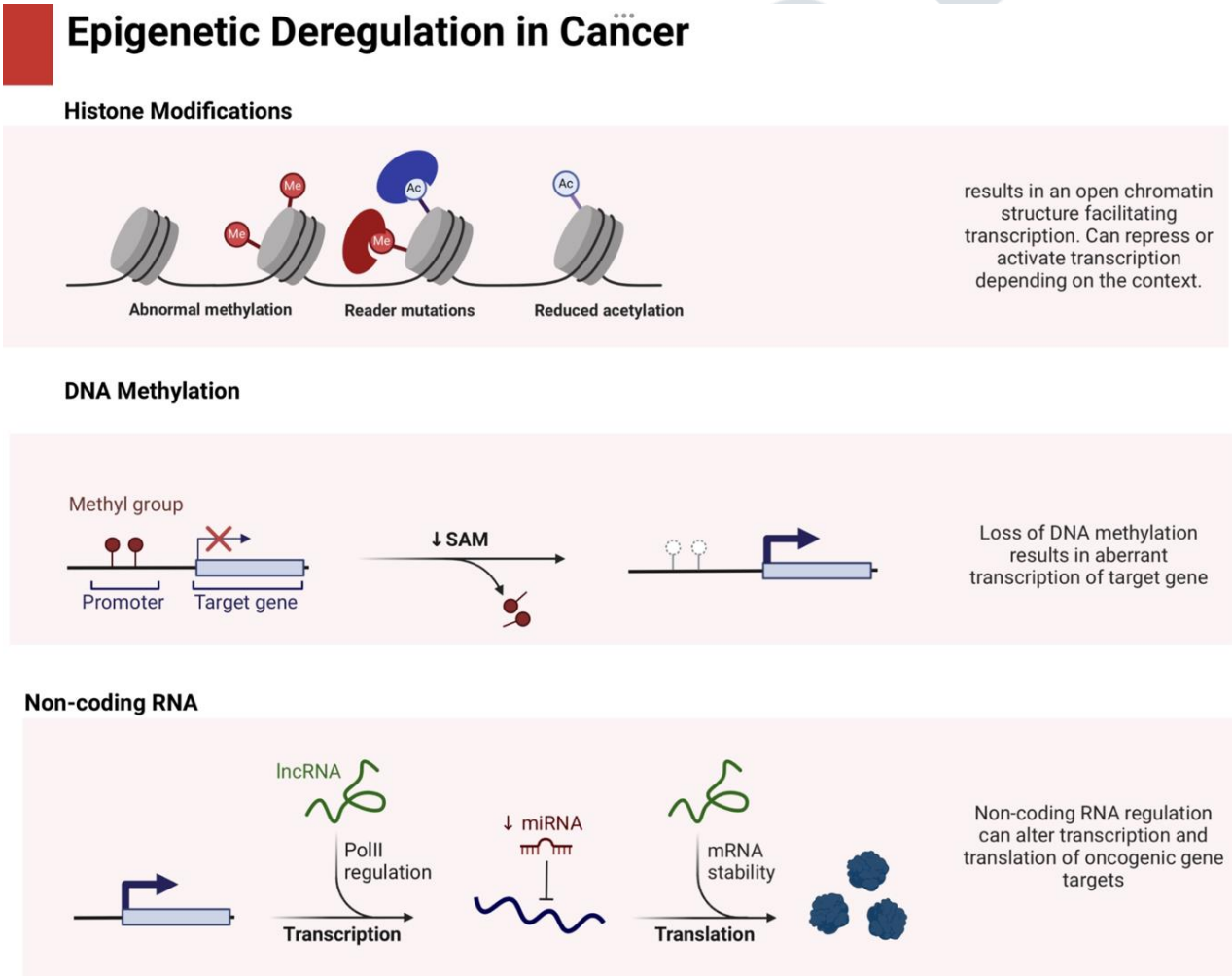

Figure 2

Figure 2. The mechanisms by which epigenetic modifications affect antigen presentation in cancer cells. The mechanism of DNA methylation, histone modifications, and non-coding RNAs contribute to the downregulation of genes involved in antigen presentation, thus enabling cancer cells to evade immune surveillance. The figure was created using BioRender.

DNA methylation involves the addition of a methyl group to the 5-position of cytosine rings in CpG dinucleotides, often leading to gene silencing. This modification typically occurs in the promoter regions of genes, where it can block the binding of transcription factors, thereby preventing gene expression. In cancer cells, aberrant DNA methylation is a common occurrence and can lead to the silencing of tumour

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suppressor genes and genes involved in antigen presentation, such as those encoding MHC molecules (Jones et al., 2002). For instance, the hypermethylation of the beta-2-micro-globulin (B2M) gene, essential for MHC class I stability and surface expression, has been observed in various cancers, including colorectal cancer, breast cancer, and hepatocellular carcinoma leading to reduced antigen presentation and impaired immune recognition (Georgoulis et al., 2017)

Histone modifications, including acetylation and methylation, are crucial in regulating chromatin structure and gene expression. These modifications can either promote or inhibit the expression of genes depending on the specific residues modified and the context of the modification. Histone acetylation is mediated by histone acetyltrasnferases (HATs), generally results in an open chromatin structure, facilitating transcription. In contrast, histone deacetylases (HDACs) remove acetyl groups, leading to chromatin condensation and gene repression. In cancer cells, over expression of HDACs can lead to the deacetylation and repression of genes involved in antigen processing and presentation, including those encoding MHC molecules and antigen-processing machinery components such as transporter associated with antigen processing (TAP1 and TAP2) (Grohmann et al,. 2013).

HOTAIR (HOX Transcript Antisense RNA) is a long non-coding RNA that modulates chromatin structure and gene expression by recruiting the Polycomb Repressive Complex 2 (PCR2). By binding to PRC2, HOTAIR guides the complex to specific genomic loci, leading to histone modification and gene silencing (Tsai et al., 2010). One of the key modifications mediated by PRC2 is the trimethylation of histone H3 at lysine 27 (H3K27me3), a mark associated with transcriptional repression. H3K27me3 alters the chromatin structure, making it more compact and less accessible to transcription factors, thereby inhibiting gene expression (Cao et al., 2002). In cancer, HOTAIR overexpression and subsequent H3K27me3 deposition led to the silencing of tumour suppressor genes, including those bestial for MHC class I expression (Gupta et al., 2010).

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (IncRNAs), regulate gene expression post-transcriptionally and play significant roles in cancer progression and immune evasion. miRNAs can bind to the 3' untranslated regions (UTRs) of target mRNAs, leading to their degradation or inhibition of translation. In cancer, certain miRNAs are unregulated and can target mRNAS encoding components of the antigen presentation machinery, such as MHC molecules. For instance, Mir-27a down regulates TAP1 expression, reducing antigen presentation and aiding in immune evasion (He et al., 2014). Similarly, IncRNAs like HOTAIR can recruit polycomb repressive complex to the promoters of target genes, leading to increased H3K27me3 and gene repression, including genes essential for MHC class I expression (Gupta et al., 2010). The following table summarise various types of ncRNAs, their lengths, functions, examples, mechanisms of action, and reference, illustrating their impact on antigen presentation in cancer cells.

Table 1: An overview of non-coding RNAs in cancer

Name	Abbreviation	Length (nt)	Function	Example	Mechanism	Reference
Long non-coding RNAs	IncRNA	>200	Involved in epigenetic modifications and post-transcriptional processing	HOTAIR	Recruits Polycomb Repressive Complex 2 (PCR2) to promoters, leading to increased H3K27me3 and gene repression	Gupta et al., 2010
Micro-RNA	miRNA; miR	21-24	Function in RNA silencing and post-transcriptional regulation of gene expression	miR-27a	Downregulates TAP1 expression, reducing antigen presentation and aiding in immune evasion	He et al., 2014
Small interfering RNA	siRNA	20-25	RNA silencing, defense against viruses and transposed activity	siRNA	Promotes mRNA degradation	Voglova et al., 2016
Circular RNA	circRNA	100-1600	Covalently closed RNA rings; potential gene regulators and miR 'traps'	circRNA	May function as miRNA sponges, thus regulating miRNA availability and activity	Catrina et al., 2017
Transcribed UCR	T-UCR	50-570	Frequently located at fragile sites and cancer-associated genomic regions	T-UCR	Possibly regulated by miR	Catrina et al., 2017
Small nucleollarRNA	snoRNAs	60-300	Guide chemical modifications of other RNAs	snoRNAs	RNA modification	Voglova et al., 2016

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Abnormal epigenetics changes can lead to the downregulation of genes involved in antigen presentation, therefore enabling cancer cells to escape immune surveillance. The immune system relies on the detection of tumour-associated antigens (TAAs) presented by major histocompatibility complex (MHC) molecules on the surface of cancer cells (Denis et al., 2009). Effective antigen presentation is crucial for the activation of cytotoxic T cells, which destroy cancer cells (Chen et al., 2017). Fewer antigen presentation is a main mechanism by which cancer cells escape the immune system.

Genetic predispositions play a crucial role in determining an individual's susceptibility to cancer and the associated epigenetic alterations that affect antigen presentation. Certain inherited mutations can predispose individuals to aberrant epigenetic modifications, such as those affecting the enzymes involved in DNA methylation or histone modification processes. For instance, mutations in genes encoding for DNA methyltransferases or histone deacetylases can lead to widespread changes in gene expression, including the downregulation of MHC molecules critical for antigen presentation (Estelle's, 2008). These genetic predispositions can compromise the immune system's ability to recognise and destroy cancer cells effectively, facilitating immune evasion and tumour progression.

Similarly, environmental factors significantly contribute to epigenetic changes that impact antigen presentation in cancer cells. Exposure to environmental toxin, such as tobacco smoke, heavy metals, and industrial pollutants, can induce epigenetic alterations, including DNA methylation and histone modifications (Zhang et al., 2011). For example, benzene is a carcinogenic component of tobacco smoke, which has been shown to cause hypermethylation of tumour suppressor genes, leading to decreased expression of these genes and impaired antigen presentation (Siegfried et al., 1997). Similarly, exposure to heavy metals, such as arsenic and cadmium can result in histone modifications that repress gene expression, including genes involved in the MHC pathway (Chervona et al., 2012). Such environmental factors exacerbate the ability of cancer cells to evade. Immune detection by altering the normal patterns of antigen presentation, thus promoting tumour growth and metastasis.

Epigenetic changes have a profound impact on the expression of MHC molecules, which are pivotal for effective antigen presentation. DNA methylation, histone modifications, and non-coding RNAs can all contribute to the downregulation of MHC gene expression. For instance, hypermethylation of the promoters of MHC class I genes can prevent transcription factor binding, leading to reduced expression of MHC molecules on the cell surface (Jones et al., 2002). This downregulation hampers the ability of cytotoxic T cells to recognise and eliminate cancer cells. Similarly, histone deacetylation by HDACs result in a closed chromatin conformation that restricts access to transcriptional machinery, thereby reducing MHC gene expression (Grohmann et al., 2013). Non-coding RNAs, such as miRNAs, further modulate MHC expression by targeting mRNAs for degradation or inhibiting their translation. For example, miR-27a directly targets TAP1 mRNA, reducing the availability of TAP1, which is essential for peptide loading onto MHC class I molecules, thereby diminishing antigen presentation (He et al., 2014)

Such alterations of MHC expression and antigen presentation have significant consequences for immune recognition and evasion by cancer cells. The downregulation of MHC molecules due to epigenetic changes has significant consequences for immune recognition and evasion by cancer cells. MHC class I molecules present endogenous peptides, including tumour-associated antigens to CD8+ cytotoxic T cells. When MHC class I expression is reduced, these antigens are not effectively presented, leading to a silure in the activation of cytotoxic T cells. Consequently, cancer cells can proliferate and metastasise without being targeted by the immune system (Schumacher et al., 2015). Similarly, reduced expression of MHC class II molecules on APCs impairs the activation of CD4+ helper T cells, which are crucial for coordinating the immune response. This impairment further weakens the immune system's ability to mount an effective anti-tumour response.

IV. DIAGNOSIS, AND TREATMENT

The identification of epigenetic changes that affect antigen presentation in cancer cells is crucial for improving diagnostic accuracy and developing targeted treatments. Advanced methods have been developed to detect epigenetic modifications. One widely used method is bisulfite sequencing, which involves treating DNA with bisulfite to convert unmethylated cotosines to uracil's while living methylated cytosines unchanged. This allows for precise mapping of methylation patterns across the genome (Eckhardt et al., 2006). Bisulfite sequencing is particularly effective in identifying hypermethylation in promoters of MHC genes, which can lead to reduced antigen presentation and enable immune evasion by cancer cells (Li et al., 2002).

Another technique is chromatin immunoprecipitation followed by sequencing (ChiP-seq). This method maps histone modifications across the genome by using specific antibodies to precipitate DNA-protein complexes, followed by sequencing of the precipitated DNA (Barski et al., 2007). ChiP-seq can reveal regions of chromatin that are epigenetically silenced through histone modifications such as deacetylation and methylation, which downregulate genes involved in antigen presentation (Barski et al., 2007).

Despite advancements in techniques for identifying epigenetic changes, several challenges remain in diagnosing cancer based on these modifications. One major challenge is the variability in epigenetic changes across different cancers and individuals. Epigenetic modifications can vary significantly not only between different types of cancers but

also among patients with the same type of cancer. This heterogeneity complicated the development of standardised diagnostic criteria based on epigenetic markers (Scherf et al., 2000). Additionally, the dynamic nature of epigenetic changes, which can occur in response to environmental factors and treatment, further complicates diagnosis.

Integration epigenetic data with other genomic and clinical information is also challenging. While techniques like bisulfite sequencing and ChIP-seq provide detailed maps of epigenetic modifications, interpreting these data in the context of patient-specific factors and other molecular characteristics of the tumour requires computational tools and bioinformatics expertise. This can hinder the translation of epigenetic findings into clinical practice (Jones et al., Baylin, 2007).

The variability of epigenetic changes across different cancers and individuals poses significant challenges for both diagnosis and treatment. Epigenetic modifications are highly context-dependent, epigenetic modifications are highly context-dependent, influenced by the type of cancer, its stage, and individual patient factors. For instance, the same epigenetic modification might have different effects on antigen presentation in different cancer types. For example, in colorectal cancer, hypermethylation of the beta-2-microglobulin (B2M) gene leads to reduced MHC class I expression and impaired immune recognition (Georgoulis et al., 2017). However, the same modifications might not have a similar impact in breast cancer or hepatocellular carcinoma due to differences in the tumour microenvironment and genetic background (Hadley et al., 2014).

This variability also extends to individual patients, where genetic predispositions and environmental exposures can result in unique epigenetic changes. For example, exposure to tobacco smoke or heavy metals can induce specific epigenetic changes that are not present in individuals without such exposures (Zhang et al., 2011). These personalised epigenetic signatures mean that a general approach to diagnosis and treatment is not feasible, which highlights the necessity of personalised medicine strategies that account for individual variability (Feinberg et al., 2016).

V. CONCLUSION

Epigenetic modifications have emerged as crucial factors influencing antigen presentation in cancer cells, significantly impacting the ability of the immune system to recognise and eliminate malignancies. The processes of DNA methylation, histone modifications, and non-coding RNAs are central to the regulation of gene expression, including those genes involved in the antigen presentation machinery. Aberrant epigenetic changes, such as the hypermethylation of MHC gene promoters or the dysregulation of non-coding RNAs, can lead to the downregulation of MHC molecules on the surface of cancer cells. This downregulation impairs the presentation of tumour-associated antigens to T cells, thereby enabling cancer cells to evade immune surveillance and contributing to tumour progression and metastasis.

Targeting epigenetic modifications through the use of DNA methyltransferase inhibitors, histone deacetylase inhibitors, and other epigenetic drugs holds promise for restoring the expression of MHC molecules and enhancing the immune system's ability to recognise and attack cancer cells. Moreover, the combination of epigenetic therapies with immunotherapies, such as immune checkpoint inhibitors or CAR-T cell therapy, may offer synergistic effects, leading to more effective and durable cancer treatment outcomes.

However, the heterogeneity of epigenetic changes across different cancers and among individual patients presents significant challenges. This variability underscores the importance of personalised medicine approaches that tailor treatments based on the specific epigenetic landscape of each patient's tumour.

In conclusion, the impact of epigenetics on antigen presentation in cancer cells is a pivotal area of study with significant implications for cancer diagnosis and treatment. By targeting the epigenetic alterations that enable immune evasion, there is potential to significantly improve cancer treatment outcomes, offering hope for more effective and personalised therapeutic strategies in the fight against cancer.

REFERENCES

[1] Barski, A., Cuddapah, S., Cui, K., Roy, T. Y., Schones, D. E., Wang, Z., … & Zhao, K. (2007). High-resolution profiling of histone methylations in the human genome. Cell, 129(4), pp. 823-837.

[2] Blum, J. S., Wearsch, P. A., & Cresswell, P. (2013). Pathways of antigen processing. Annual Review of Immunology, 31(1), pp. 443-473. doi:10.1146/annurev-immunol-032712-095910.

[3] Cao, R., Wang, L., Wang, H., Xia, L., Erdjument-Bromage, H., Tempst, P., & Zhang, Y. (2002). Role of histone H3 lysine 27 methylation in Polycomb-group silencing. Science, 298(5595), pp. 1039-1043.

[4] Chen, H., Li, S., Liu, S., & Guo, X. (2017). Combination of epigenetic therapies with immunotherapy for cancer treatment. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 1868(1), pp. 230-239.

[5] Eckhardt, F., Lewin, J., Cortese, R., Rakyan, V. K., Attwood, J., Burger, M., … & Beck, S. (2006). DNA methylation profiling of human chromosomes 6, 20 and 22. Nature Genetics, 38(12), pp. 1378-1385. doi:10.1038/ng1909.

[6] Esteller, M. (2008). Epigenetics in cancer. New England Journal of Medicine, 358(11), pp. 1148-1159.

[7] Feinberg, A. P., Koldobskiy, M. A., & Gopalakrishnan, S. (2016). Epigenetic mechanisms in human disease. Cell, 128(4), pp. 681-694.

[8] Georgoulis, A., Vogt, M., Blatsios, G., Kruger, R., Wang, Y., Papatheodorou, I., & Muller, F. (2017). Epigenetic silencing of the B2M gene impairs immunorecognition of colorectal cancer cells. Journal of Molecular Medicine, 95(7), pp. 757-767.

[9] Grohmann, U., Bronte, V., & De Santo, C. (2013).

Immunosuppressive properties of IDO and tryptophan metabolism: From bench to bedside. Nature Reviews Immunology, 13(12), pp. 812-823.

[10] Gupta, R.A., Shah, N., Wang, K.C., Kim, J., Horlings, H.M., Wong, D.J., … & Chang, H.Y. (2010). Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature, 463(7291), pp. 1071-1076.

[11] Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. Cell, 144(5), pp. 646-674.

[12] He, Y., Meng, L., Huang, J., & Li, J. (2014). miR-27a regulates the growth, colony formation, and migration of HCC cells by targeting HSP90AA1 and stanniocalcin 2. Cancer Letters, 34(2), pp. 616-626.

[13] Jones, P. A., & Baylin, S. B. (2002). The fundamental role of epigenetic events in cancer. Nature Reviews Genetics, 3(6), pp. 415-428.

[14] Jones, P.A., & Baylin, S.B. (2007). The epigenomics of cancer. Cell, 128(4), pp. 683-692.

[15] Kondo, Y., Shen, L., Ahmed, S., Boumber, Y., Sekido, Y., Issa, J.-P. J., & Rowley, J. D. (2008). Polycomb repressive complex 2 is a key mediator of epigenetic silencing in cancer. Cell Research, 18(7), pp. 797-803.

[16] Li, L. C., & Dahiya, R. (2002). MethPrimer: designing primers for methylation PCRs. Bioinformatics, 18(11), pp. 1427-1431.

[17] Neefjes, J., Jongsma, M. L., Paul, P., & Bakke, O. (2011). Towards a systems understanding of MHC class I and MHC class II antigen presentation. Nature Reviews Immunology, 11(12), pp. 823-836.

[18] Scherf, U., Ross, D. T., Waltham, M., Smith, L. H., Lee, J. K., Tanabe, L., … & Weinstein, J. N. (2000). A gene expression database for the molecular pharmacology of cancer. Nature Genetics, 24(3), pp. 236-244.

[19] Schumacher, T. N., & Schreiber, R. D. (2015). Neoantigens in cancer immunotherapy. Science, 348(6230), pp. 69-74.

[20] Voglova, K., Bezakova, J., & Herichova, I. (2016). Role of non-coding RNAs in the etiology of bladder cancer. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 1868(1), pp. 230-239.

[21] Yu, X., Li, Y., Li, M., Wang, Y., Zhou, C., Zhao, F., … & Fan, X. (2024). Cancer epigenetics: from laboratory studies and clinical trials to precision medicine. Cell Death Discovery, 10(1), pp. 1-12.

[22] Yoshimatsu, S., Ono, Y., Fujimori, T., & Sasaki, H. (2011). DNA methyltransferase inhibitors and histone deacetylase inhibitors in cancer therapy. Current Cancer Drug Targets, 11(5), pp. 546-570.

[23] Zhang, Y., Wilson, R., Block, M. L., Miller, D. B., Hong, J. S., & Cunningham, J. M. (2011). Environmental particulate matter (PM) activates inflammatory signalling and suppresses p52 expression in human macrophages. Environmental Health Perspectives, 119(1), pp. 92-98.

[24] Zou, J., Li, J., Ge, Z., Wang, Z., Liu, Z., Zhu, H., & Liu, X. (2012). DNA methyltransferase inhibitors in cancer therapy. Oncotarget, 3(6), pp. 735-746.