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Herbal used as Epigenetic for Cancer Treatment

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ABSTRACT

Patterns of chromatin accessibility, which are in turn altered by epigenetic mechanisms, are responsible for determining the interactions that take place between transcription machinery, genes, and the cis-regulatory elements of those genes. Mutations that interfere with epigenetic processes frequently have the unfortunate side effect of causing cancer. Since these mutations can be undone, numerous anticancer treatments that target epigenetic pathways are now being developed and evaluated. (Cancer) is becoming more and more common everywhere. This decline in clinical outcomes is a result of a number of factors, including late diagnosis, a lack of efficient treatments for particular cancer subtypes, and drug resistance. Treatment resistance and stemness traits have been recognised as markers of this disease, and it has been demonstrated that epigenetic changes play a role in the process of cancer growth. Understanding these alterations and how they impact cancer carcinogenesis treatment is challenging but crucial. However, it may be able to provide the special knowledge needed to use these alterations as potential diagnostic, prognostic, therapeutic agents, and predictors of treatment efficacy. This underlines the importance of continued research to advance our knowledge of cancer carcinogenesis and epigenetics and help us overcome these challenges. This review aims to provide an overview of the state of the art in epigenetics research for cancer detection and treatment and to stimulate discussion on this subject.

Keywords- Cancer, Epigenetics, Treatment, Diagnosis, Chronic.

I. INTRODUCTION

Immunotherapy has recently been recognised as a potentially useful therapeutic approach for the treatment of cancer [1]. This is mostly attributable to immunotherapy's ability to recruit the body's immune system in the fight against cancer cells. This innovation in conventional cancer treatment has increased survival rates, particularly for patients with metastatic tumours [2]. Depending on the type of cancer involved, the immune system either helps or hinders the development of tumours. It is generally agreed that the three stages of immunoediting eradication, equilibrium, and escape make up its natural progression [3]. Both the innate and adaptive systems are responsible for the early detection and eradication of the growing number of tumour cells as part of the process of elimination. A rare tumour variant that survives the elimination stage, though, advances to the equilibrium stage, where the adaptive system slows tumour growth and changes the immunogenicity of the tumour. Cancer cells then develop suppressive factors to evade the immune system

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and stop expressing the target antigen [3,4,5]. This occurs as a result of the continual exposure of equilibrium-stage tumours to immunological stress. Cancer cells are able to avoid being destroyed by the immune system of the body in a variety of different ways. There is a correlation between increased expression of immune checkpoint molecules on T cells and evasion of the immune system by tumours [6]. The following molecules are considered to be part of this category: programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and mucin domain 3 (TIM3), and lymphocyte-activation gene 3 (LAG3).

By concentrating on particular immunological processes, numerous efforts have been made over the past ten years to strengthen the immune response against cancer cells. The goal of immunotherapy is to influence the body's built-in defences against cancer cells by concentrating on specific immunological elements that have an impact on the immune system [7]. Recent developments in cancer immunotherapy have shown great promise, including immune checkpoint inhibition, T-cell transfer therapy, and cancer vaccines [6].

Immunological checkpoints, which inhibit signalling, are essential for preserving immune balance and preventing autoimmune diseases [8]. Cancer cells are able to circumvent the functions of the immune system and grow as a result of their ability to upregulate immunological checkpoints. Antibodies that target PD1, PD-L1, and CTLA-4 are examples of the immune checkpoint blocks (ICBs) that have been given FDA approval. They restore a weakened anticancer immune response by preventing immunological checkpoints from attaching to their equivalent receptor expressed on T cells [8]. Similar to interferon-releasing chemotherapeutics (ICBs), chimeric antigen receptor engineered T (CAR-T) cells have been proven to be effective in treating haematological cancers. CAR-T cells precisely target cancer cells rather than relying on a response from the body's normal T cells. Nevertheless, despite the favourable results, many patients either only partially respond or acquire resistance to these immunotherapies. The T cell state affects immunotherapy effectiveness, and different cancer types respond to checkpoint inhibitors and adoptive T-cell therapy in very different ways [10]. There are two types of immunotherapy resistance: primary and acquired [11,12]. Primary resistance may emerge from both intrinsic and extrinsic factors, including the tumour cell itself (intrinsic resistance) and the tumour microenvironment (extrinsic resistance) [10]. Cancer immunoediting has some connection to immunotherapy-resistant tumours. The pathway that results in a subpar immune response or resistance to immunotherapy is depicted below (Figure 1).

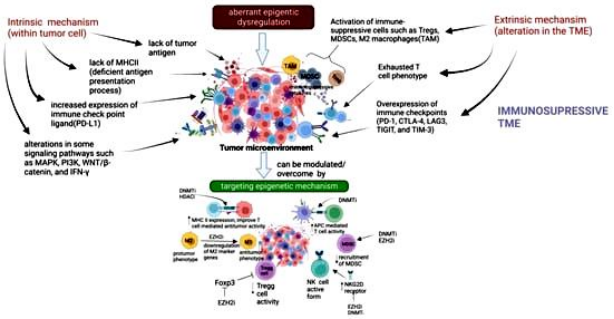

Fig. 1: The mechanism of immunotherapy resistance and epigenetic combination therapy for improving immunotherapy efficacy: The vitality of T cells is essential for immunotherapy to be effective. Extrinsic mechanisms, such as the activation of immunosuppressive cells (such Tregs, MDSCs, and M2 macrophage (TAM) generating an immunosuppressive TME, emerge as a result of TME modification. Lack of tumour antigen, enhanced immunological checkpoint expression, absence of the MHCII complex, and changes to the signalling cascade are some intrinsic causes. Both the underlying cause of cancer as well as the key factor that contributes to its development are faulty transcriptional pathways. These pathways are driven in turn by epigenome dysregulation. Epigenetic changes have been observed to affect immune cells that fight tumours and their immunogenicity. As a result, it's conceivable to combat immunotherapy resistance by focusing on epigenetic mechanisms.

The possible relevance of epi-drug in cancer therapy based on epigenetic regulation in human cancer

The epigenetic alterations can be divided into three broad groups using histone modifications, non-coding RNAs, DNA, and RNA methylations, which are believed to be the fundamental regulatory mechanisms throughout the course of cancer.

II. DNA AND RNA METHYLATIONS

DNA methylation and demethylation

It has been demonstrated that DNA methylation can be found in the 5' promoter region of more than half of all human genes [13]. Because it is so common on CpG islands, this epigenetic process has received probably the greatest amount of attention and research over the years (CGIs). X chromosome inactivation, embryonic development, genomic imprinting, epigenetic reprogramming, cell identity establishment, and lineage specification are some of the important biological processes and diseases that depend on it [14]. Gene silencing occurs as a consequence of the attachment of S-adenosylmethionine (SAM) methyl groups, which are covalently linked to the 5 position of the cytosine pyrimidine ring. Repression of gene expression can be brought on by the 5-methylcytosine (m5C) structure in one of two different ways: either by preventing

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transcription factors (TFs) from accessing DNA binding sites or by recruiting methyl-binding domain proteins (MBDs) to reorganise chromatin in conjunction with histone modifications. Both of these methods are described in more detail below.

It takes the combined efforts of three different DNA methyltransferases (DNMTs) in order to successfully methylate DNA. These enzymes are DNMT1, DNMT3a, and DNMT3b. Maintenance Due to its increased catalytic activity and preference for preferentially methylating hemimethylated DNA during replication, DNA methyltransferase 1 (DNMT1) is primarily responsible for maintaining the DNA methylation state [15]. This is because DNMT1 preferentially methylates hemimethylated DNA. On the other hand, DNA demethylation is a process that restores repressed genes by reactivating them after DNMT has silenced them in the past. "de novo" methyltransferases, such as DNMT3a and DNMTb, generate and maintain the correct DNA methylation state in the genome by preferentially binding to the previously unmethylated DNA [16]. This occurs independently of whether the DNA is being replicated or not. The ten-eleven translocation methylcytosine dioxygenases TET1, TET2, and TET3 are responsible for the oxidation of 5-hydroxymethylcytosine (5-hmC) to 5-formylcytosine (fC) and 5-carboxylcytosine (caC) [17]. The process of gene expression is a dynamic one that calls for numerous distinct types of cells to perform a delicate balancing act between the methylation and demethylation of their respective DNA.

RNA methylation

Since the 1970s, the methylation of the N-6 position of the adenine residue, also known as N6-methyladenosine (m6A), has been the subject of research in relation to epigenetic mechanisms and cancer biology. M6A mutations seem to favour the presence of a stop codon, a 3'-untranslated region, and internal long exon enrichment [18]. It has an effect on the entirety of the pathway that RNA takes to be processed [19], from transcription to degradation to splicing to translation.

Recent study has demonstrated that alterations to m6A can be both dynamic and reversible. RNA m6A is produced by the methyltransferases known as Methyltransferase-like 3 (METTL3) and Methyltransferase-like 14 (METTL14), as well as the Wilms tumour 1-associated protein (WTAP), RNA binding motif protein (RMB15/15B), zinc finger CCCH-type containing 13 (ZC3H13), and KIAA14.

Histone modifications

When DNA is bundled into chromatin and coated with histone octamer, which enables precise regulation of DNA sequence accessibility, nucleosomes and the "beads on a string" structure are generated. Nucleosomes are the building blocks of nucleosomes. A core containing tetramers of histones 2A (H2A) and 2B (H2B) can be found in the centre of each histone octamer, with histones 3 (H3) and 4 (H4) on each side of the core (H4). Histone proteins can have their C-terminal globular domains and their N-terminal tails modified by post-translational modifications (PTMs) such as methylation, acetylation, ubiquitylation, phosphorylation, SUMOylation, ADP ribosylation, citrullination, and biotinylation. Other PTMs include phosphorylation, SUMOylation, and ADP ribosylation.

A significant amount of research has been conducted on the methylation of histone H3 and the acetylation of lysine in histone H3, respectively. According to the "charge neutralisation model" that describes how the process of histone acetylation works, the positively charged lysine residues on histones H3 and H4 make it possible for negatively charged DNA to be packed in close proximity to histones. However, the introduction of an acetyl group might loosen the compacted structure of chromatin, making it possible for transcription factors (TFs) to enter the chromatin and start the transcription process [28]. Histone acetyltransferases (HATs) and histone deacetylases are two distinct enzymes that are responsible for catalysing the addition and removal of acetyl groups, respectively (HDACs).

Compared to the effects of histone acetylation, the effects of histone methylation are more complex and depending on the specific region. Methylation at lysine H3:9, H3:27, or H4:20 are all examples of restrictive epigenetic markers, whereas methylation at lysine 4/36/79 (H3K4/36/79) is typically linked with an active transcriptional status [29,30,31,32]. These modifications are only able to be generated by specialised enzymes that are referred to as histone methyltransferases (HMTs). The great majority of HMTs have a domain that is referred to be SET. For example, the process of H3K27 trimethylation (H3K27me3) leads to the induction of transcriptional silence via the enhancer of zeste 2 (EZH2) [21]. SET7/9 is responsible for the catalysis of the H3K4me activation of inflammatory gene expression [22]. Histone demethylases are enzymes that remove methyl groups from certain marks on histones, thereby altering the state of transcriptional activity (HDMTs).

Non-coding RNAs

At least 70% of the human genome is composed of non-coding RNAs, also known as ncRNAs [23]. The majority of these ncRNAs are involved in regulatory processes. Longer noncoding RNAs are typically defined as having a length of more than 200 nucleotides, whilst shorter noncoding RNAs are typically defined as having a length of fewer than 200 nucleotides. The sncRNA that has been the subject of the most investigation is known as miRNA. It is a single-stranded RNA with 20 nucleotides and is highly conserved. After being written off as "junk transcripts" at first, it was subsequently discovered that they play a crucial part as mediators in biological resilience by

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reducing the effect of very minor disruptions and ensuring that animals remain in a state of equilibrium. MiRNAs are responsible for controlling nearly 60 percent of human genes that code for proteins [24]. They accomplish this through complementary binding to the 3' untranslated region of the target messenger RNA, which in turn inhibits gene expression. There are two distinct roles that microRNAs can play in the body depending on the function of the genes that they target: onco-miRNAs and tumour suppressor miRNAs. More than half of all miRNA genes are situated in close proximity to CGIs, which renders them amenable to epigenetic control [25]. Recent research has shed light on how miRNAs work in virtually every subtype of cancer, which was previously unknown.

Long noncoding RNAs, often known as LncRNAs, come from a genetic background that is equally as diverse as the transcripts themselves. The effects of lncRNAs can be observed in both the nucleus and the cytoplasm, and they perform a variety of functions, such as those of chromatin regulators, enhancers, sponges for noncoding RNAs, molecular scaffolds, and so on [26]. These effects can be observed in both the nucleus and the cytoplasm. It was previously believed that the activities of lncRNAs and circRNAs were more complicated than they actually are. This was due to the fact that they allow for the encoding of functional peptides with short open reading frames (sORFs) [27]. Recent developments, on the other hand, have made this defect obsolete.

III. ANTIGEN PRESENTATION AND HLA EXPRESSION

Since cancer cells contain antigenic peptides that are expressed on major histocompatibility complex (MHC) class I molecules, tumor-specific T lymphocytes are able to recognise cancer cells and target them for destruction. A combination of mutations, alternative splicing that is particular to cancer cells, and the re-expression of embryonic antigens that are normally silenced in healthy adult tissues could be the source of cancer-specific antigens. It is common practise for genes that code for tumor-associated antigen and major histocompatibility complex class I antigen to be suppressed in order for cancer cells to elude the immune system. Upregulation of MHC class I genes and cancer testis antigens (CTAs) is caused by anti-DNA methyltransferase (DNMT) inhibitors [36,37]. These genes are only produced in the placenta and testis and not in any other adult healthy tissues. This points to DNA methylation playing a part in the development of cancer. It has been demonstrated that AZA and HDAC inhibitors can revive dormant repetitive elements, such as endogenous retroviruses and transposable elements [28,29]. This can then potentially introduce mutations and produce novel antigens that the immune system can later target. In lung cancer cell lines that only generate small amounts of the genes in question, the restrictive chromatin mark H3K27me3 is found to be abundant in the promoters of numerous CTAs. Therefore, inhibiting EZH2, the enzyme that is responsible for the deposition of H3K27me3, results in an improvement in DAC-induced CTLAs in these cell lines [30]. Increased DAC-mediated activation of these cancer-testis genes was also produced as a consequence of the suppression of the demethylases KDM1 or KDM5B [31]. Even though the inhibition of these demethylases resulted in significantly increased levels of H3K4me2 at a number of CTAs, the activation of these genes was only observed when DAC was present. This is despite the fact that the activation of these genes was caused by the inhibition of these demethylases. There is a connection between the alteration of H3K4 methylation and the activation of genes. These findings shed light on the delicate nature of the interplay that exists between alterations to histones and DNA in the process of regulating gene expression in vivo. Recently, KDM5 inhibitors have been discovered [32], and studies conducted on animal models have indicated that these inhibitors can reduce the growth of tumours. Researchers have been granted the go-ahead to investigate whether or not the use of KDM1 and KDM5 inhibitors increases the antigenicity of tumours. This comes as more data is obtained from preclinical models, and as KDM1 and KDM5 inhibitors make their way into clinical trials. There is evidence to suggest that HDAC inhibitors, similar to DNMT inhibitors, can increase the expression of cancer-specific antigens and components of the system that processes tumour antigens and presents them to MHC [33].

Although tumour cells are efficient at transmitting antigens, they can only activate T cells to a limited amount due to their size and structure. Antigen-presenting cells known as dendritic cells (DCs) are essential for the activation of T lymphocytes by cancer-associated antigens. Dendritic cells play an important role in the immune system (fig 2). T cell activation cannot occur without the correct antigen being presented by the MHC; however, in addition to this, the co-stimulatory surface components B7 on DCs and CD28 on T cells are also necessary. DCs use a mechanism called phagocytosis in conjunction with the capture of dead tumour cells in order to collect samples of tumour antigens [34]. This is done in order to ensure that sufficient amounts of tumour antigens are collected. As a consequence of this, epigenetic inhibitors that promote apoptosis in malignancies may also improve antigen presentation by DCs, which ultimately results in increased T cell activation. It is not well understood whether or how epigenetic medicines alter the expression of key molecules that are involved in antigen presentation and the activation of T cells by DCs.

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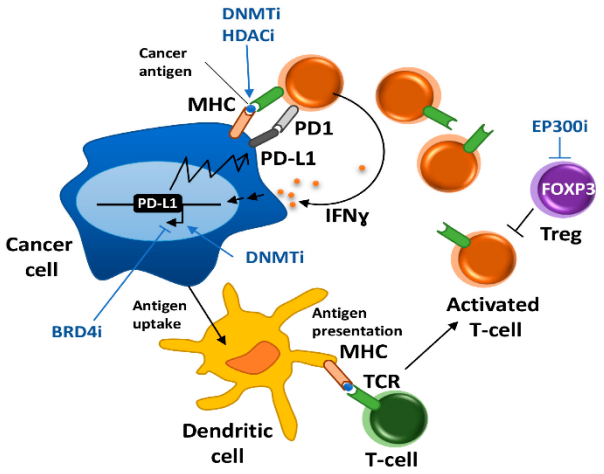

Fig. 2: By binding to sensitive areas in the DNA and so boosting transcription, FOXP3 activates histone acetyltransferases like EP300. EP300 links the bromodomain to acetylated histones at FOXP3-regulated promoters, and the HAT domain acetylates FOXP3 and histone tails in response to this interaction (red arrows). EP300 bromodomain inhibitors (blue arrows) are the culprits behind the downregulation of gene expression. These inhibitors stop EP300 from being appropriately recruited to chromatin and stop histones from being acetylated.

Pancreatic ductal adenocarcinoma: the emerging role of epigenetic alterations as biomarkers and novel targets for treatments

Despite the fact that epigenetic biomarkers have demonstrated a high level of potential for use in cancer diagnosis and prognosis, none of them are currently being employed frequently in PDAC (Figure 3). Alterations in the DNA methylation profile cause the genesis and progression of tumours during the premalignant phases of pancreatic cancer [35-39].

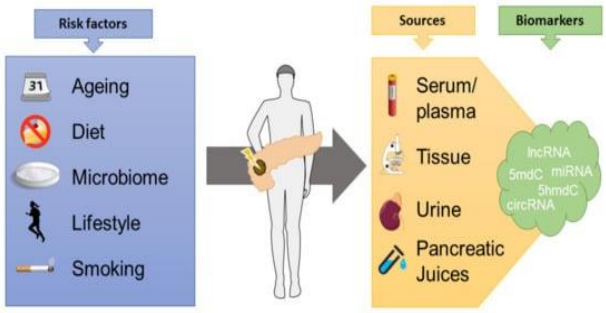

Fig. 3: The diagnostic and prognostic aspects of cancers are influenced by both modifiable and non-modifiable factors. Epigenetic biomarkers (lncRNA = long non-coding RNAs, 5mdC/5hmdC = 5-methyl or 5-hydroxymethyldeoxycytidine, miRNA = microRNA, circRNA = circular RNA) can be measured from tissue specimens or bodily fluids to determine these aspects. Epigenetic biomarkers can be measured from

Validation of particular methylated DNA markers (MDM) as early-stage diagnostic biomarkers can be carried out with a wide range of different biological materials, such as tissue samples from resected tumours or body fluids [40]. This is because MDMs are unique in that they are methylated only in specific locations. In one study (41), patients with biopsy-confirmed pancreatic ductal adenocarcinoma (PDAC) and healthy controls had their pancreatic fluids extracted endoscopically. It demonstrated the usefulness of three classes of MDMs as biomarkers, with a sensitivity of 83% for distinguishing PDAC patients from controls and a sensitivity of 80% for identifying patients with stage I and II PDAC or intraductal papillary mucinous neoplasms (IPMN) with high-grade dysplasia. The study was conducted on patients with pancreatic ductal adenocarcinoma of the colon (PDAC).

In pancreatic fluids, the methylation status of mucin gene promoter regions has been proven as both a diagnostic and prognostic indication. In pancreatic malignancies, the process of DNA methylation regulates the expression of the gene that codes for mucins, which are large membrane-bound glycoproteins that play an important part in both the carcinogenesis process and the invasion of tumours. Analysis of methylation patterns in the MUC1, MUC2, and MUC4 genes was used in the methylation-specific electrophoresis of pancreatic secretions [42]. This allowed for the differentiation of precancerous stages from neoplastic stages. According to the findings of a machine learning analysis of the methylation state of mucin genes [43], higher hypomethylation levels of MUC1 and MUC4 are associated with a poor prognosis. [Citation needed]

Recent developments in the technology used to sequence DNA have made it possible to sensitively identify epigenetic alterations in circulating cell-free DNA [44,45]. This could pave the way for diagnostic methods that are less invasive. Combining two different approaches for identifying 5-methylcytosine and 5-hydroxymethylcytosine enhanced the sensitivity of the test [46]. This allowed researchers to more accurately differentiate between individuals whose pancreatic cancer was in stage I or stage II.

Examples of non-coding, persistent, and functional components that can be found in the circulating transcriptome include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). Because they are resistant to RNase activity and can be quickly detected in the bodily fluids of cancer patients, they have the potential to be employed as biomarkers in PDAC. This is because PDAC is one of the most common types of cancer. The profiling of miRNA expression, which links to the course of disease [47], can yield information that can be used as potential diagnostic and prognostic markers for malignant pancreatic illness. According to the findings of a retrospective study that screened 2549 human miRNAs in patient serum [48], patients who had shorter

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survival periods had lower levels of survival-related differentially expressed miRNAs compared to those who had longer survival times. [Citation needed] In addition, high levels of hsa-miR-486-5p and hsa-miR-6126 expression were associated with long-term survival, but high levels of hsa-miR-3135b expression were associated with poor outcomes. In addition, early-stage pancreatic ductal adenocarcinoma was linked to an increase in the ratio of mIR-3940-5p to miR-8069 that was observed in urine exosomes [49]. Cancer Antigen 19-9 (CA 19-9) is the current biomarker gold standard for PDAC, and when it was combined with the ratio, it exhibited a sensitivity of 93.0% and a positive predictive value (PPV) of 78.4%. This PPV increased to 100% when all of the markers were positive.

Because of their documented participation in the growth of tumours in PDAC, the detection of long non-coding RNAs (lncRNAs) in plasma or serum has been studied as a potential biomarker [50]. When compared to healthy controls, the serum expression of hexokinase-2 (HK2) and Hox transcript antisense RNA (HOTAIR) is higher in PDAC patients [51]. Patients who had been diagnosed with PDAC and exhibited high levels of expression for HOTAIR and HK2 had a much worse likelihood of surviving the disease when compared to patients whose expression levels were lower. In addition, LINC01111 is a tumour suppressor lncRNA, and research has shown a correlation between low levels of expression and a bad prognosis [52].

Circular RNAs, also known as circRNAs, are non-coding RNAs that are formed in the form of covalently closed loops. Because of their effect on the transcriptome, circular RNAs (circRNAs) may have therapeutic utility in PDAC as biomarkers [54]. Throughout the evolution of PDAC tumours, the cBFAR/miR-34b-5p/MET axis, which is regulated by the circRNA circBFAR, contributes to the proliferation and invasiveness of PDAC tumours. CircBFAR's function as a molecular sponge for miR-34b-5p, which in turn upregulates mesenchymal-epithelial transition factor, has been linked to the development of tumours in patients with PDAC. This link can be found by looking at the literature (MET). Overexpression of circBFAR was linked to a worse prognosis [53] in 208 patients with PDAC.

The extracellular vesicles (EV) found in the blood contain a wide variety of RNA species, including messenger RNA (mRNA), circular RNA (circRNA), and long noncoding RNA (lncRNA) (exLRs). EV-associated exLRs exhibit unique patterns between PDAC patients and healthy individuals [55], which suggests that they could be used as a diagnostic tool. A diagnostic profile that included eight EV-associated exLRs in the plasma of PDAC patients correctly diagnosed patients at stage I and stage II, according to case-control investigation. This suggests that PDAC can be diagnosed by exLR profiles at an early, resectable stage, and more importantly, in patients who do not have high levels of the tumour marker CA 19-9, allowing them to be differentiated from healthy controls [56].

IV. CHALLENGES & FUTURE PROSPECTIVES

Epigenetic medications, such as those that inhibit DNA methyltransferases, histone methyltransferases, and histone acetylases/deacetylases, are all capable of modifying the transcription of the entire genome. Because of their potential to globally activate or inhibit DDR-associated genes, tumour suppressors/oncogenes, or activating pathways that have detrimental effects on other pharmacological agents, they may be a double-edged sword in this sense. This is because of their potential to activate or inhibit DDR-associated genes globally. There is a possibility that treatment with medications like PARP inhibitors, which target specific biomarkers, could have a domino effect on gene expression all over the world. In light of the fact that PARP1 is capable of regulating chromatin confirmation and epigenetic regulation [57], PARPi may have off-target effects that are not entirely understood at this time. Patients who have germline mutations of the BRCA gene may have a favourable response to PARPi [58], but there is evidence to suggest that these individuals also have an increased risk of developing myelodysplastic syndrome and acute myeloid leukaemia [59]. Because HR or BRCA restoration may also invalidate any benefits of PARPi use [60], it is essential to plan treatment and create biomarkers that can predict not only the response but also the risk of HR restoration while receiving treatment. This emphasises the significance of developing biomarkers.

Cancer's defining characteristic is its ability to evade attack by the body's immune system, which is a task made easier by epigenetic changes. In preclinical models, inhibiting DNMT1 and EZH2 results in an increase in the synthesis of TH1-cytokines, a delay in the formation of tumours, and an improvement in the effectiveness of immune checkpoint inhibitor therapy [61]. The natural defences that the body has against viruses are an essential part of this system. Inhibition of DNMT1 leads to cytosolic sensing of double-stranded RNA (dsRNA), which in turn induces type I interferon responses. The reactivation of extensively methylated endogenous retroviruses is responsible for the production of many of the different species of dsRNA [62]. In light of these findings, combining immune checkpoint inhibitors with medicines that demethylate DNA might result in improved response rates. In 2017, the Food and Drug Administration (FDA) gave the go-ahead for the use of pembrolizumab to treat malignancies in which microsatellite instability (MSI-H) or mismatch repair failure was present (dMMR). It has been hypothesised that the emergence of neoepitopes mediates the immune response to therapy in MSI-H tumours. It has also been hypothesised that a larger

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somatic mutational load results in better responses to immunotherapy. MSI-H tumours in colorectal cancer may generate gene expression alterations (immunoediting) that give resistance to detection by the immune system and, by extension, resistance to pembrolizumab. This is despite the fact that MSI-H tumours in colorectal cancer have a high mutational load and frequently have lymphocytic infiltration. In addition to this, these malignancies have genomic and DNA methylation events that are connected with enhanced WNT signalling and the exclusion of T cells [63]. It is possible that the epigenetic mechanisms that underlie immunoediting will cause tumours with dMMR that are undergoing treatment to be resistant to checkpoint inhibitors. Therefore, patients who have lost the expression of MMR genes as a result of DNA methylation may benefit significantly from the combination of pembrolizumab with a medication that demethylates DNA.

Identification of patients who are most likely to benefit from epigenetic therapies will play a significant role in the clinical evaluation of these treatments, whether they are administered on their own or in combination with DNA-damaging medications. Although a large number of potential predictive biomarkers of drug sensitivity have been postulated in preclinical models, very few of these biomarkers have been validated in clinical trials of epigenetic treatments, and none of these biomarkers have yet been used as companion biomarkers during the clinical application of epigenetic treatments. This is partially attributable to the fact that the overwhelming majority of the biomarkers identified in the course of preclinical research have been evaluated as prognostic biomarkers rather than predictive biomarkers. This can be partially explained by the ease with which prognostic studies can be carried out, as compared to diagnostic studies, they call for a significantly less number of patient samples to be analysed. To give you an example, a study project on the prognosis of ovarian cancer would require approximately 110 tumour samples in order to have 80% power at $p = 0.05$ and be able to identify a hazard ratio of 2. In order to have sufficient statistical power for a prediction study that compares a biomarker between two treatment groups, the number of tumours that need to be analysed needs to be more than 1200. Previous work has been done to evaluate how difficult it is to build predictive biomarkers and to design possible roadmaps for how to test them [88,89]. These efforts have been documented. On the other hand, the predictive biomarker is often integrated into the designs of clinical trials at a late stage in the clinical review process. For instance, in phase II research of combinations with DNA-damaging cytotoxics[64], it may be more acceptable to choose patients based on an epigenomic subtype of DDR genes as opposed to a histological subtype.

Because of the potential for DNA-damaging therapies and epigenetic agents to have a synergistic effect, trial designs that include stratification biomarker screening will need to be carefully considered. Demethylation of genes such as MGMT and BRCA1 can result in resistance to cytotoxics and treatment failure; however, demethylation of MMR genes and other pro-apoptotic genes can increase efficacy in response to cytotoxics that induce DNA damage [65]. DNA-demethylating agents are a clear illustration of this phenomenon. When putting an epigenetic intervention into practise in a therapeutic environment will be extremely important. As a direct result of the process of carcinogenesis, which is characterised by a lack of DNA damage responses and genomic instability, tumours will already contain genetic and epigenetic abnormalities at the time of their initial manifestation. On the other hand, recurrent tumours will be different due to the adaptation of the tumour during therapy as well as the progression of the tumorigenic process. Additionally, DDR-associated genes have the potential to be actively regulated by many epigenetic mechanisms simultaneously. In spite of the fact that the MGMT promoter DNA is hypermethylated, robust MGMT expression can be enabled by histone acetylation in active enhancer sites [66-70]. As a result, it is possible to envision a scenario in which a patient who possesses a methylated gene associated with drug resistance may look as if they are a candidate who could benefit from therapy with a DNMT inhibitor; however, this may fail due to the fact that histone modification has a greater effect on expression. One could therefore foresee this scenario. An further hypothesis that is particularly intriguing is the question of whether or not epigenetic therapies could be used during remission as a method to prevent the development of epigenetic adaptation and resistance. If it were possible to delay the occurrence of recurrence or to maintain tumours in a state where they were responsive to chemotherapy, the overall survival rate of cancer patients would see a significant improvement. This, however, is based on the assumption that epigenetic drugs do not have any unwanted side effects, such as promoting the formation of tumours or causing normal cells to become toxic.

V. CONCLUSION

Epigenetic treatments have generated significant clinical responses in hematologic malignancies, according to the most recent clinical data. However, their performance as monotherapies has been less hopeful in various solid tumours due to limited efficacy and/or severe effects. Because these solid tumours arise from cells that have more fully differentiated into their final forms, they are essentially less susceptible to epigenetic disruption. Prolonged suppression of the epigenetic targets and altering dosing regimens are two potential ways to improve efficacy. On the other hand, as a result of the narrow therapeutic window, it has been challenging to achieve and maintain

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therapeutic efficacy up until this point. It will be difficult to determine the best treatment window if there are adverse effects, whether they are short-term or long-term. The fact that several epigenetic medicines, such as DNMT and EZH2 inhibitors, can elicit powerful therapeutic responses at doses that are well below the maximum-tolerated level suggests that it may be possible to apply lower dosages or intermittent dosing in order to decrease the likelihood of adverse effects occurring. When combining epigenetic drugs with other types of treatment, it is particularly essential to give some thought to alternative dosing and administration tactics. When designing the sequence and timing of a combination treatment with precision, one can achieve a number of desirable effects, including synergy, alternating selective pressure, prevention of initial resistance, and reversal of acquired resistance.

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