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REVIEW: ABERRANT EPIGENETIC MECHANISMS IN CANCER

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ABSTRACT: Tumours are extensively driven by both genetic and epigenetic lesions. Although cancers are induced by genetic mutations more often, progressive carcinogenesis is difficult if not impossible to sustain without an extra helping hand of aberrant epigenetic behaviour. Epigenetic regulatory mechanisms that look over the stability, expression, and maintenance of the genome without altering DNA sequence are susceptible to dysfunctioning and mutations in all cancer types but partially remain in the framework of modifiable machinery, intensifying the necessity of learning their contribution and course of action in carcinogenesis. Despite the fact that the DNA methylation is the most acknowledged and therapeutically approached epigenetic mechanism, compelling functionalism of hypomethylation, post-translational histone modifications, non-coding RNAs and chromatin remodellers have a somewhat equally dynamic role in facilitating oncogenesis in mutation-susceptible conditions. Over the last decade aberrant epigenetic mechanisms have found applications in designing prognostic, diagnostic and monitory techniques of cancer management. It's of immense importance to quest inside the genome and comprehend the underlying patterns of epigenetic mechanisms that allow cancers to invade, metastasize and progress towards the destruction of healthy well-being to enable a wider and more accessible advance in adopting epigenetic mechanisms to tackle tumors.

KEYWORDS: Epigenetic lesions, carcinogenesis, DNA methylation

INTRODUCTION:

Cancer is a disease induced by aberrant genetic and epigenetic alterations.[1] From the establishment of a single genetic mutation to a series of progressive genetic and epigenetic mutations lead healthy tissues to endure accumulated state of genomic abnormalities followed by metastasis, invasion, infiltration and destruction that exhibit uncontrolled proliferation of dominant tumour cells eventually setting off cancer.[2]

Aberrant genetic mutations are difficult if not impossible to reversibly manipulate. The immense stability of these altered nucleotide sequences stands on the ground of one of the biggest challenges lurking above the non-invasive treatments of cancer. On the flip side, epigenetic mutations that manifest over-expression or silencing of vital genes do so by recruiting epigenetic machinery to stimulate anticipated action by altering gene expression, strictly limiting their activities out of the bounds of direct DNA sequence manipulation.[3] This is an incredible phenomenon considering their relatively weak stability facilitating the achievement of practicable handling and management.

All cancer types demonstrate significant epigenetic lesions when compared with genetic abnormalities, the sole distinction of one over another being epigenetic aberrations remain widely available for externally induced reversibility in contrast to altered genetic sequences that once laid down are highly stable and remain beyond the therapeutic capabilities for reversion.[4] Transformability of epigenetic changes presents a bigger motivation in cancer management extending from serving diagnostic, interpretative, prognostic, and predictive purposes to delivering appreciable therapeutic value. Subsequently, studying epigenetic modifications in cancerous cells has become an emerging and promising field in oncology that aims to address and alter aberrant epigenetic lesions to predict progression of cancer, develop competent biomarkers, subcategorize patients bearing similar tumours and thereby selectively utilize relevant therapeutics to increase the life expectancy of cancer patients.[5,6]

DNA methylation-driven gene silencing is by far the most extensively studied epigenetic modification.[7] Relatively attainable screening, well-developed methodology and thorough

interpretation make it the most preferred and widely acknowledged but not the sole important aberrant epigenetic modification prevailing throughout tumorigenesis. Histone modifications also play a striking role in cancer development via three core mechanisms including histone tail modifications mediated expression or repression of genes, on-boarding chromatin remodelling complexes, and replacement of conventional histones with their specialized variants.[8,9] Chromatin remodelling complexes that are responsible for sustaining dynamism of chromatin and can drive nuclear architecture either close to idealism as they do in healthy cells or instability with reference to harboured malformed functionalities amid unnatural entanglement of euchromatin and heterochromatin as in the majority of tumours.[10,11,12] Another groundbreaking phenomenon that addresses non-coding RNAs' role in oncogenesis has had the backfoot of shortest history amongst other epigenetic modifications and yet their spectrum of roles in divergent types, stages and applications in cancer has secured them a pivotal position as a remarkable epigenetic persuader in tumorigenesis.[13] Broad range of piRNAs (piwi interacting RNAs), siRNAs (small interfering RNAs), miRNAs (micro RNAs) and lncRNAs (long non coding RNAs) have the potential to effectuate sequence-specific gene silencing[14], consequently, their usage as advancing biomarkers and anti-cancer agents is not too far from exceeding current research fields.[15,16]

Epigenetics has far-reaching consequences from causing two genetically identical twins to acquire different heights and interests, regulating cellular pathways, designing one's nature, induce varying susceptibility to apparently the same environment to driving diseases without the exception of cancer. Their ever-changing mechanisms allow them to transform and evolve distinctly in different individuals along with different tissues of the same individual.[17] Although, this may complicate investigating them, at the same time, it makes them extremely essential to put under the lens on account of their reversion abilities in various contexts that may enable us to alter aberrant, convenient mistakes made in cancerous cells.

DNA METHYLATION IN CANCER

DNA methylation extensively occurs on the fifth carbon of cytosine that is found 5' to the guanine, both generally referred together as CpG dinucleotide; 'p' depicting phosphodiesterase bond between them.[18] Higher frequency regions of CpG dinucleotides, called CpG islands, are found at the promotor region of 60% of the human genes subsequently exhibiting control attributed to their privileged upstream location of transcriptional machinery attachment, they are inarguably considered being associated with controlling gene activity.[19,20] Mammalian genomic DNA methylation is carried out by three core DNA methyltransferases (DNMTs) which are DNMT1, DNMT3B, and DNMT3A.[21] Though all three of them lay DNA methylation marks on CpG dinucleotides their functionality remains distinguishable.[22] While both DNMT3A and DNMT3B are de novo methyltransferases that lay novel methylation marks during embryogenesis and primordial germ cell development, DNMT1 concentratedly maintains methylation marks through generations.[23] Correspondingly, the serviceability of DNMT1 is most accounted for mitotic heritability of DNA methylation that is unvaryingly transferred from parent to daughter cells.

As far as genome-wide distribution is considered, CpG islands mostly occur in an unmethylated state ensuring normal gene expression and functioning.[24] Hypermethylation of CpG islands equates with repression of concerned gene activity brought about either by inhibition from the binding of transcription factors to DNA or recruitment of gene repressing proteins.[25] Global hypermethylation of these CpG islands is a hallmark of almost all cancer types.[26]

Hypermethylation and successive repression of tumour suppressor genes and hypomethylation followed by expression of oncogenes is a well-known trait of the spectrum of cancers.[27,28] O6 methylguanine DNA methyltransferase (MGMT) demonstrates aberrant promoter methylation in an array of cancer types including colorectal cancer[29], breast cancer[30], non-small cell lung cancer[31], gastric cancer[32,33] and glioblastoma[34] In a study conducted on 244 colorectal tumour samples, 71% of the samples that showed guanine to

adenine mutations had aberrant promoter methylation on MGMT gene which encodes a DNA repair protein responsible to prevent G to A transition in ras genes.[35] Other studies that highlighted tumour suppressor gene promoter hypermethylation in cancer concluded that promotor of tumour repressing RASSF1A gene was frequently methylated in small cell lung cancer (SMLC), non-small cell lung cancer (NSCLC), and breast cancer.[36,37] Distinct hematological malignancies portrayed varying promotor region hypermethylation profiles in vital cell growth restrictors p15INK4B and p16INK4A.[38] The frequency of hypermethylated von Hippel-Lindau (VHL) gene in 26 samples of renal carcinoma was found to be low yet significant (19%).[39] Similarly, the BRCA1 (Breast Cancer gene 1) was found to be hypermethylated in considerable number of samples of both ovarian tumours and primary breast cancers. This was observed more frequently in the state of loss of heterozygosity (LOH), necessary for facilitating the progression of cancer even further.[40]

Although the unmethylated state of promotor regions is crucial for uninterrupted expression of tumour suppressor genes, methylation of CpG dinucleotides in peculiar locations is indispensable for stability of genome as well. For instance, methylation of CpGs in repetitive DNA sequences and intragenic transcriptional elements is essential to repress translocation of transposable elements and silencing of cryptic promotor induced activity respectively.[41-43] Hypomethylation at these sites can withdraw a variety of consequences that may act as fodder for tumours. DNA hypomethylation almost always accompanies DNA hypermethylation in all cancer types but not all cancer samples, and always in a context that benefits cancer, rarely otherwise.[44] Narayan et al. studied 25 breast adenocarcinoma samples, half of which demonstrated hypomethylation of satellite 2 which is a long heterochromatic region near the centromere of chromosome 1 which in healthy tissues is highly methylated.[45] Ubiquity of hypomethylation does not stop here, it has far-reaching consequences in a variety of cancer types. For instance, satellite 2 has also been found to be frequently hypomethylated in the cases of ovarian carcinoma[46,47], Wilms tumour[48], and hepatocellular carcinoma[49]. Additionally, satellite 1, satellite 3, α-satellite, LINE-1, LTR containing repeats and ALU

sequences consistently undergo hypomethylation in a variety of tumours.[50] Having said that, hypomethylation of single-copy genes is as recurrent as repeated sequences. Extensively studied MAGE-A gene which exhibits expression exclusively in the placenta and testicular germ cells while being highly methylated in somatic cells has been found to depict partial hypomethylation in an array of cancers including renal carcinoma, gastric cancers[51], lung cancer[52] and cancer cell lines from rhabdomyosarcoma.[53] Simultaneously, the list of hypomethylated genes in tumorigenesis only seems to extend over both time and research. To name some, MAGE-B[54], MAGE-C[54], Maspin[55-62], XIST[63,64], HOX 11[65], CAGE[66] have shown substantial hypomethylation in different cancers and more importantly so, to varying extents.

Another prevalent and commonly observed corollary of hyper and hypo-methylation is loss of imprinting (LOI) wherein both gene copies remain sequentially unchanged yet behave functionally aberrant owing to loss of parent-of-origin-specific gene expression to either instigate its overexpression owing to the eccentric activation of silent parental allele or downregulation of certain genes due to silencing of its usually active state on its parent locus.[67] In cancers it's common for imprinting aberration to yield upregulation of oncogenes and downregulation of tumour suppressor genes to disrupt the normal functioning of cell metabolism[68]. A widely studied example of imprinting would be IGF2/H19 locus. H19, a maternally expressed extensively studied long non-coding RNA, is known to possess growth regulatory properties highly dependent on the unmethylated state of the imprinting control region (ICR). Unmethylated ICR on maternal allele binds CTCF, an insulator protein sensitive to ICR methylation, that ensures H19 expression but insulates IGF2 from upstream enhancers resultantly blocking its expression.[69] On the contrary IGF2 is paternally active by means of a hypermethylated state of ICR that blocks CTCF from binding resultantly enabling IGF2 expression.[70]

In cancer types such as colorectal[71], bladder[72], lung[73], ovarian[74], and Wilm's tumour[75,76] where the loss of imprinting via hypermethylation of ICR on maternal allele has been found

to cause abnormal biallelic expression of IGF2, thereby facilitating tumour growth. Another imprinting aberration is observed in a maternally imprinted cyclin dependant kinase inhibitor 1C (CDKN1C) which is described as a tumour suppressing gene owing to its ability to restrict cell growth at the G1/S phase.[77] CDKN1C encounters imprinting disruption by loss of DNA methylation in Beckwith-Wiedemann syndrome[78], bladder cancer[79], rhabdoid tumour[80] and oesophageal tumour[81]. Additional genes like MEST and DIRAS3 repeatedly encounter loss of imprinting in several cancer types.[82,83] As much as we would like to limit the list of genes there, it only seems to lengthen as we take the liberty to look closely along with the cancer types and through the variations of the same cancer. The superficial overview over disrupted imprinted genes is simpler to state yet difficult to draw any conclusions from. Its complexity only seems to intensify when observed in an immense number of tumour samples in different cell lines on the backdrop of healthy tissues.

HISTONE MODIFICATIONS IN CANCER CELLS

Discovery and analogy between post-translational histone modifications and RNA synthesis were established in 1964 by Allfrey et.al[85] but it wasn't until 1988 when the underlying interconnection between histone modifications and gene expression via transcriptional control was recognized.[86] The N and C tails of histone octamers composed of pairs of H2A, H2B, H3 and H4 that protrude out from nucleosome tend to act as a platform for various covalent modifications such as methylation of arginine and lysine, phosphorylation of serine and threonine, ubiquitylation or sumoylation of lysines and so on.[87,88] Irrespective of how portrayed superficially, histone tail modifications have far from benign percussions in maintaining genomic stability and therefore undergoing disruption in the carcinogenic environment. When chemical covalent marks say, methylation, acetylation or ubiquitylation are laid on a specific amino acid in defined quantity and on the desired histone, they produce a characteristic sequence of the marks hovering over the DNA called histone code which signify predetermined implication in the context of expression or repression.[89,90] However,

histone modifications are not entirely devoted to controlling gene expression and providing reliable package material as their role in recombination, replication and DNA repair is increasingly recognized[90]. Exclusive histone codes unique for every expected follow-up mechanism determine the DNA accessibility for transcription by their ability to be read and interpreted by either inhibition or recruitment of transcriptional machinery.[91] Histone code is assembled, decoded and re-established by means of absolute co-ordination between writer proteins that accurately navigate and lay down histone marks, reader proteins that comprehend these marks, and utilize machinery to bring about the anticipated action and erasers that function to remove laid histone marks eventually exposing them for de-novo histone modifications.[92] An aberrant co-ordination of writers, readers or erasers or no functioning of at least one of them at all has a key role to play in major cancer types, evaluation of which has a promising future in delivering value with regards to cancer prognosis, diagnosis and therapeutics.[93,94,95]

Some post-translational histone modifications have fore-destined implications in a healthy state which if subjected to disruption may lead to subsequent reverberations. For example, histone acetylation is generally attributed to gene activation.[96] The competency of histone acetylation to stimulate gene activation serves an invaluable purpose in the constitution of tumours as an aberrant acetylation profile can activate proto-oncogene and bring about the repression of tumour suppressor gene by incurring hypoacetylation.[97] On the other side, both histone methylation and phosphorylation are followed by rather complex outcomes in terms of expression or regulation depending upon several factors.[98-100]

Loss of monoacetylation on H4Lys16 and trimethylation on H4Lys20 is extensively co-related with several cancer types and is assumed to indicate poor prognostics in breast carcinomas.[101,102] Circulating blood of colorectal cancer patients have been found to contain nucleosomes with low levels of H3Lys9 trimethylation and H4Lys20 trimethylation when compared with healthy individuals, thereby, flagging their emergence as a novel biomarker

for colorectal cancer.[103,104] Multitude of cancers has depicted mutations and or or an aberrant functioning in writer, reader and eraser proteins. For instance, genes responsible for the production of histone methyltransferases such as EZH2[105,106], G9a[107], and PRMT1/5[108] are repeatedly subject to erratic functionality that seems to facilitate tumour progression in a wide range of carcinomas. Similarly, histone demethyltransferases[109], histone acetyl transferases[108] and histone deacetyltransferases[108, 110] are found to be dysfunctioning in numerous cancer types.

Another groundbreaking discovery pertaining to the contribution of histone variants in maintaining genomic stability is hastily establishing its own identity in cancer research. Although at a relatively naïve stage of research today, histone variants may be playing a bigger role in genomics than originally thought of. Take, for example, H2A.X, one of the six minor variants of H2A, which responds to DNA double-strand breaks and is presumed to be involved in DNA repair mechanisms, is mapped to a genomic locus which is recurrently altered in numerous tumour types depicting disruption of DNA repair mechanisms during the progression of cancer.[111-113] H2A.Z, another variant of H2A is overexpressed in colorectal cancer[114], breast cancer[115-118], melanoma[119], and prostate cancer.[120-122] Equivalently, more histone variants including mH2A.1, mH2A.2, CENP-A, H3.3 and others have shown aberrant expression patterns in diverse human cancers.[123]

Histone modifications have found escalating usage in oncology as biomarkers for effective prognosis and categorization of tumours in subtypes.[124]To illustrate further, lowered levels of both H3Lys4 dimethylation and H3Lys18 acetylation indicate a higher probability of recurrence in prostate cancer.[125] Lower levels of H3Lys4 dimethylation and H3Lys18 acetylation act as a prognosticator of minimum survival possibility in lung and kidney cancer patients.[124] Another histone modification called H3Lys9 dimethylation shows lower levels in prostate or kidney patients with poorer clinical outcomes.[114] Loss of H3Lys9 dimethylation mark also accompanies thoroughly noted in imprinting disruption of CDKN1C

Although histone modifications impart many prominent consequences solely by their influence, often their interaction with chromatin re-modellers and DNA methyltransferases is overlooked. As far as tumorigenesis is concerned, understanding inter-connection between DNA methylation and histone modifications is imperative as their global interdependence remains at the center of many silencing mechanisms and shall not be studied exclusively for the sake of a comprehensive understanding, deciphering functional linkage and application-based approach. Inevitably, addressing the role of histone modifications in inducing, facilitating or restricting DNA methylation is important. The interplay between histone modifications and DNA methylation can be appreciated from an example of SETDB1, a histone methyltransferase and DNMT3A, a de-novo DNA methyltransferase which has been perceived to co-function together to induce silencing at the promoters of commonly repressed genes in cancer cell lines.[126] In addition to what has been demonstrated, LOI in CDKN1C is not driven solely by aberrant DNA methylation but is enthusiastically accompanied by loss of H3K9 dimethylation[78]. Though many other observations remain discrete and incomprehensible due to their poorly understood mechanisms, the visible outcomes are significant and unignorable. This obvious and contemplated cross-talk between DNA methylation and histone modifications is becoming ever so prominent and more importantly complex over time.[127]

CHROMATIN REMODELING AND CANCER

Chromatin remodelers alter genomic condensation via ATP dependant mechanisms for better access of binding sites to transcriptional machinery[128]. They do so by three core mechanisms including sliding of nucleosome along the DNA to gain more exposure for transcriptional machinery binding[128,129], eviction of octamers to generate histone-free DNA[130,131], or replacement of canonical core histones with histone variants to allow specialized genomic remodelling.[132]

As discerned from DNA methylation, Histone tail modifications and non-coding RNAs, a recurring theme of dependency and small-scale impact seem persistent contrary to the chromatin remodellers who occupy a rather bigger role in the nuclear architecture manifesting developments that are often irreversible.

Widely studied subunits of ATP-dependant SWI/SNF (SWitch/Sucrose Non Fermentable) chromatin remodelling complex have been found to be dysfunctional in a variety of tumours, many times as a consequence of prior genetic aberration and sometimes as the causal factor of tumorigenesis[133]. SNF5, one of the core subunits of SWI/SNF complex and an important tumour suppressing component is found mutated in almost all malignant rhabdoid tumours[134-136], some familial schwannomatosis[137], hepatoblastoma[138], round cell soft tissue sarcoma[139], epithelioid sarcoma[140], familial meningioma[141] and chordomas.[142] In an extensive study conducted on mice, 100% of subjects developed lymphoma or rhabdoid tumour by the employment of reversibly inactivating conditional SNF5 allele within a median short span of 11 weeks is enough to emphasize the tumour suppressing potential of SNF5.[143] PBRM1 which encodes BAF180, another important component of SWI/SNF complex, has been found to undergo mutation in renal cell carcinomas[144]and breast cancers[145]. Tumour suppressing activity of ARID1A is systematically appreciated from a detailed study addressing the vitality of ARID1A for regular cell cycle arrest.[146] ARID1A is also found mutated in 50% of OCCCs (ovarian clear cell carcinomas)[147], 30% of endometrioid carcinoma[148], medulloblastomas[149], primary breast cancers[150] and lung adenocarcinoma[150]. Other constituents of SWI/SNF such as BRM[151-153], BRG1[152-158] and BRD7[159] have been identified to undergo aberrant downregulation or undetermined derangement in an array of cancers. It is important to note that simply downregulation of components by monoallelic disruption of chromatin remodellers is not enough. Their complete depletion in a way that they utterly fail to contribute in effective genomic remodelling is a highlight of many tumours as suggested by Knudson's two-hit hypothesis.[160] Many cancers that harbour heterozygous expression of tumour suppressing genes often undergo homozygous disruption to completely seal tumour

suppressing activity as seen in the case of SNF5.[161] Aberrancy of other chromatin remodelling components such as p400, CHD4/5, ARID2, etc. can be addressed and comprehended from a variety of studies.[97]

As mentioned before, chromatin remodelling complexes share an intertwined co-relation with histone tail modifiers to accomplish complete gene repression or activation. BAF180 has the ability to recognize acetylated histones by utilization of their constitutional six tandem bromodomains[162]. Similarly, BRM targets acetylated histones via carboxy-terminally located bromodomains.[163] Recruitment and utilization of HDAC1 by SNF5 has implications in the deactivation of cyclin D1 supported by successive removal of acetyl marks[164].

Although a naïve overview over insights of chromatin remodelling complexes and their abnormal behaviour in cancer is not enough to understand detailed intercommunication over and above genome that strives to maintain integrity, functionality, stability and metabolism in each cell of the three trillion of them in the human body but is sufficient to appreciate its complexity and work on our ignorance towards better understanding and even superior non-invasive, painless and effective cancer treatments.

NON-CODING RNAS IN CANCER

It was implied from Crick's central dogma that the expression of RNAs was a purely intermediatory step in protein synthesis from DNA until the early 1970s when the non-coding RNAs (ncRNAs) along with their possible functionalities came into light. It was assumed for the genome that does not code for proteins to be referred to as junk DNA, but it was soon realized with the emergence of ever extensive technology that they were anything but that. When it was understood that merely 2% of DNA is coding for proteins but 90% of DNA is being transcribed[165], it was evident that genome-wide transcriptional activity, yet lesser translational output has a greater objective to serve in cell biology. Noncoding RNAs have managed to support promising findings in almost all fields of human physiology including cancer within not more than their truly short ten years of history, development and research.

Their role in controlling gene expression has cross-disciplinary implications in carcinogenesis and if understood and interpreted well, they are likely to stay and grow as effective biomarkers, prognosticators, and even decisive therapeutic agents.

ncRNAs are divided into two main classes, small ncRNAs which are usually 20kb to 200kbs in length and long noncoding RNAs which extend longer than 200kbs[166]. Small ncRNAs are further subcategorized into piRNAs, miRNAs and siRNAs amongst which both miRNAs and siRNAs act post-transcriptionally on mRNAs rather than directly on DNA.[167] This contradicts the definition of epigenetics as it literally refers to mechanisms that act on genes and not their transcriptome. Although they accomplish the ultimate goal of controlling gene expression since our study aims to review epigenetic influence solely, we will be excluding both miRNAs and siRNAs only for their divergent mode of action. With that being said, their crucial role in tumour progression and its management is thoroughly appreciated. piRNAs too depict post-transcriptional control of gene expression but their partial role as transcriptional gene silencer is undisputable.[168] 24-31 kb long piRNAs or piwi complex interacting RNAs bring about gene silencing by assisting in laying H3K9me3 repressive mark, removing activating H3K4me2 mark with the aid of Lsd1 (Lysine-specific demethylase 1), recruiting HP1 (heterochromatin protein1) and DNMT to methylate CpG sites.[169,170] Evidently, one can expect aberrant expression of piRNAs in a spectrum of cancers as their key role in silencing tumour suppressor genes and upregulating oncogenes by their own downregulation can serve a valuable purpose in advancing tumorigenesis in many cancer types. Upregulation of different piRNAs is observed in breast[171], lung[172-174], gastric[175,176], colorectal[177-180], hepatocellular carcinoma[181,182], kidney cancer[183,184], hematological malignancies[185-188], and ovarian cancer[189] while their downregulation was reported in breast[190], lung[172], gastric[191-193], kidney[183], gliobastoma[194-197], fibrosarcoma[198], and pancreatic cancer[199]. It's important to note that, different piRNAs depict varying up or down expressions in distinct cancers. This is becoming increasingly important as their consideration as a biomarker, monitor and prognostic contributor is being investigated.[168]

Long noncoding RNAs facilitate epigenetic regulation by directly acting in a cis or trans manner to target genes by recruitment of epigenetic machinery.[200] One of the most widely studied lncRNA called HOTAIR has been found to depict aberrant expression in almost 26 cancer types.[201] HOTAIR, a trans-acting lncRNA, is expressed as an antisense strand of the HoxC gene and acts on genes other genes such as HoxD4[202]. It is capable of recruiting PRC2 (polycomb repressive complex 2) which lays repressive H3Lys27 trimethylation marks on target genes to induce its silencing.[203] Additionally, HOTAIR can also recruit Lsd1 to regulate gene expression by removing the methylation mark on H3Lys4. [204,205] By illustrated mechanisms you can begin to appreciate and predict the intertwined significance of overexpressed HOTAIR in oncogenesis. It has a deliberate contribution to make in the progression of carcinogenesis[206], fostering malignancy[207], encouraging metastasis[208], proliferation[209,210], invasion[211], aggression[212] and inhibiting apoptosis[209].

Along with HOTAIR other lncRNAs like HULC, ANRIL, GAS5, NKILA, H19. Etc. bear aberrancy over a range of cancers and to varying degrees. A comprehensive overlook demonstrates various applications of apparent abnormalities in lncRNAs such as their utilization to approach monitoring [213], prognosis[214], and therapeutic responsiveness.[215,216]

Targeting both transcriptionally and post-transcriptionally acting ncRNAs is a novel field that is hypothesized as a future of cancer treatment. Not only the practicality of targeting ncRNAs is more promising than other genetic and other epigenetic modifications but is much more accurate, economical, and opportunistic. Their all-inclusive involvement in cancer management to meet several intentions including inhibition of metastasis, controlling proliferation, effective monitoring, prognostic contribution and delivering therapeutic value is by far the most highlighting feature than any other epigenetic modification.

CONCLUSION:

Epigenetic aberrations are global and their spread in cancers is highly variable. Though virtually rendered more accessible than genetic aberrations, they harbour complexity that can

hardly be assessed juxtaposing genetic mutations. The interplay between chromatin remodelers, histone modifiers and histone methyltransferases impart one of the most complex cross-talk that remains yet to be clearly deciphered in both healthy tissues and cancer cells. It also stands as a wall between epigenetic drugs and carcinogenesis since we can't administer drugs without a transparent understanding of the mechanisms we are presumed to deal with. DNA methylation aberrations are what we have managed to close the most distance with to fully understand and effectively manage with the aid of marketed drugs and yet the specificity of DNA demethylating drugs remains extremely poor. In addition to that, while aiming to demethylate hypermethylated DNA remains alive and kicking, fear of accidentally demethylating oncogenes or intragenic regions which may even worsen tumour progression continues to hang over the cancer treatments. As for the erratic expression of non-coding RNAs is concerned, they have been rather more used for both diagnostic and prognostic purposes with an eye for developing efficacious anti-cancer agents in the near future.

Abnormal behaviour is the nature of cancer, the unchangeable one. What current chemotherapy and radiation therapies attempt to do is kill as many cancer cells as they can. The fact that cancer cells can be treated with something other than lethal agents was out of the equation until epigenetic aberrations that amputated several core mechanisms but kept room for the possibility for reversion emerged. Epigenetic mechanisms and their ability to be modified can be looked at as the opportunity that presents us with an option to alter, to give cells a chance to right what they wronged. If these aberrations are comprehended thoroughly and well, the day when targeted epigenetic therapies coupled with conventional cancer therapies that would fasten diagnosis, make accurate predictions and prolong the life expectancy of cancer patients isn't far.

List of abbreviations:

1. piRNAs (piwi complex interacting RNAs)
2. siRNAs (small interfering RNAs)

3. miRNAs (micro RNAs)
4. lncRNAs (long non-coding RNAs)
5. DNA methyltransferases (DNMTs)
6. O6 methylguanine DNA methyltransferase (MGMT)
7. small cell lung cancer (SMLC)
8. non-small cell lung cancer (NSCLC)
9. von Hippel-Lindau (VHL)
10. BRCA1 (Breast Cancer gene 1)
11. loss of heterozygosity (LOH)
12. loss of imprinting (LOI)
13. imprinting control region (ICR)
14. cyclin dependant kinase inhibitor 1C (CDKN1C)
15. SWI/SNF (SWitch/Sucrose Non Fermentable)
16. OCCCs (ovarian clear cell carcinomas)
17. non-coding RNAs (ncRNAs)
18. Lsd1 (Lysine-specific demethylase 1)
19. PRC2 (polycomb repressive complex 2)

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