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Methylation in Tumorigenesis

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1. Introduction

The development, maturation, and maintenance of tissues and organisms are anchored in distinct programs for protein expression which define the identities and roles of individual cell lines [1, 2]. These programs are maintained in a heritable state by epigenetic mechanisms that convey cellular memory [3, 4]. In this way, the global synchronization of patterns in gene expression broadly dictates developmental consequences [5, 6]. At the foundation of such gene regulation are coordinated cascades that affect the packaging of DNA into chromatin, thereby establishing the degree of DNA accessibility to transcriptional complexes [7-10]. These pathways include histone methylation, methylation of transcriptional regulators, DNA methylation, histone replacement, chromatin remodeling, and other alterations to histone tails [11-16]. Abnormalities in these epigenetic events are commonly associated with tumorigenesis and subsequent clinical outcomes [17-23].

From tightly regulated transcription to mitosis, chromatin is an elastic repository of the genome [24]. In this state, a chromosome is sequentially condensed through a succession of organized compaction while limited regions of DNA are selectively made available to transcriptional complexes [25, 26]. Hence, chromatin exists in a dynamic state into which approximately 2 m of DNA is packaged in the nucleus while maintaining an extraordinary level of utility [25, 26]. At its core, chromatin is established in a series of nucleosomes, their basic structural unit [25, 27], comprised of 146 base pairs of DNA, wrapped 1.7 times around an octamer of histones and interspersed by regions of roughly 50 base pairs [28]. The key histones participating in the assembly of a nucleosome include histones H2A, H2B, H3 and H4. These histones form hetero-dimers resulting in each being twice represented in the nucleosomal unit [29-31]. Structurally, histones are highly conserved, including a folded core followed by an unstructured tail [30, 31]. A globular domain forms the histone core as a

helix-turn-helix motif, which allows dimerization [31]. In contrast, the tails of histones do not exist in defined conformations except when attached to their cognate proteins [31]. Within the sequence of histone tail domains is a large representation of conserved amino acid residues including lysine, arginine, and serine [31, 32]. Under normal conditions, histone tails have a net basic charge facilitating their interaction with the poly-anionic backbone of DNA, thereby contributing to the stability of nucleosomes [31]. Consequently, chromatin structure and transcriptional regulation are commonly mediated through post-translational modifications that impact specific residues within the sequence of these tails [33, 34]. Modifications to tail residues can regulate the accessibility of nuclear factors to regions of DNA or induce the recruitment of such factors involved in chromatin structural and transcriptional regulatory pathways [33, 34].

The Histone-DNA interface is formed principally by inelastic hydrogen bonds between the phosphate oxygen of DNA and the main chain amide of the histone. Electrostatic interactions between basic side chains and negatively charged phosphate groups and other nonpolar interactions further strengthen the association between histones and DNA [35]. While this, in theory, should facilitate the establishment of nucleosomes upon any DNA sequence, there are likely specific sequence parameters for nucleosomal placement [36]. The composition of the DNA sequences, by which the histone core is enveloped, is likely a major factor contributing to the positioning of core histones and the dynamic comportment of the nucleosome under the influence of the SWI/SNF ATPase and sequence-specific transcription factors [37]. The most broadly characterized nucleosomal assembly is the 30 nm fiber [38], which is anchored by linker histones [39-41] and the relative juxtaposition of each nucleosome [42], establishing close physical proximity while generating only marginal internucleosomal attraction energy [38, 43-45]. Hence, this architecture allows a great degree of variation in condensation without producing serious topological changes. Chromatin exists in a series of more densely compacted structures [46], which are commonly driven by interaction with non-histone, structural proteins [47].

In recent decades, a number of process which impact the structure and/or function of chromatin including post-translational modifications of histones, DNA methylation, incorporation of histone variants, and ATP-dependent chromatin remodelling have been the subjects of intense study. The findings of these studies clearly show that chromatin modifications and the complexes involved with their facilitation are linked to the control of many biological processes which depend upon the level of chromatin accessibility [48-51]. Such processes include chromosome segregation during mitosis, X chromosome inactivation, gene expression, DNA repair, and chromatin condensation during apoptosis [23, 52-56].

Chromatin modifications convey epigenetic regulation of protein expression without alterations in DNA sequence. Disturbing the equilibrium of epigenetic networks has been shown to be associated with numerous pathological events, including syndromes involving chromosomal instability, neurological disorders, and tumorigenesis [57-59]. Advances in knowledge related to epigenetic inheritance and chromatin structure/regulation have paved the way for promising novel therapeutics directed against the specific factors that are responsi-

ble [60]. Of particular importance in the role of chromatin modifications in human disease are methylation of DNA, histone targets, and other regulatory targets.

2. DNA methylation in tumorigenesis

Methylation of DNA is a covalent modification that occurs at cytosines within CpG-rich regions of DNA and is catalyzed by DNA methyltransferases [61, 62]. The methylation of DNA affects the binding of proteins to their cognate DNA sequences [61, 63]. Such addition of methyl groups can prevent the binding of basal transcriptional machinery and ubiquitous transcription factors [61]. Thus, DNA methylation contributes to epigenetic inheritance, allele-specific expression, inactivation of the X chromosome, genomic stability and embryonic development. It is through these pathways that progressive DNA methylation is thought to be an agent for both normal aging as well as neoplasias [64, 65]. The majority of methylated CpG islands are located within repetitive elements including centromeric repeats, satellite sequences and gene repeats. These CpG regions are often found at the 5' end of genes where DNA methylation affects transcription by recruiting methyl-CpG binding domain (MBD) proteins that function as adaptors between methylated DNA and chromatin-modifying enzymes [66]. There is a clear relationship between DNA methylation and other silencing mechanisms including histone modifications and chromatin remodeling [65, 66]. In fact, several studies suggest that DNA methylation affects genes that are already suppressed by other mechanisms [65].

Changes in the pattern of DNA methylation have been correlated with altered histone post-translational modifications and genetic lesions [67]. Either hypermethylation or hypomethylation have been identified in almost all types of cancer cells examined, to date [18, 21, 68]. Hypomethylation at centromeric repeat sequences has been linked to genomic instability [18] whereas local hypermethylation of individual genes has been associated with aberrant gene silencing [21]. In oncogenic cells, hypermethylation is often correlated with the repression of tumor suppressor genes while hypomethylation is associated with the activation of genes required for invasion and metastasis [68, 69]. In neoplastic tissues, the incidence of hypermethylation in genes with promoter associated CpG islands is markedly increased which, in turn, is associated with repression of tumor suppressors [70]. Although the complete mechanistic pathway for DNA methylation in cancers is still being determined, aberrant methylation in tumors is already being examined as an instrument for diagnosis [21, 70]. For example, techniques, such as the polymerase chain reaction amplification of bisulfite-modified DNA, have enabled the study of patterns of DNA methylation [71-73]. These methods are currently being improved and adapted for cancer cell identification, profiling of tumor-suppressor-gene expression, and prognostic factors that are linked to CpG island hypermethylation [74]. Likewise, reversal of hypermethylation by several indiscriminant demethylating compounds has been approved for therapeutic intervention associated with blood-borne cancers [21].

Detection of DNA methylation has recently been added to the armory of preventative/diagnostic medicine for the prevention and treatment of colorectal cancer [75]. This represents

the most common form of gastrointestinal cancer and is a leading killer among all malignancies. The colonoscopy is broadly employed for detection of lesions which often give rise to colorectal tumors. The invasiveness of this procedure and consequent lack of patient cooperation with recommended colonoscopies is a limiting factor in the efficacy of this procedure as a preventative. Fortunately, epigenetic screening has arisen as a new tier in preventative medicine targeting colorectal cancer. Specifically, DNA methylation is associated with gene-silencing related to onset of colorectal cancer. Given that these changes are detectable prior to tumorigenesis, target-specific screening of DNA methylation represents a promising front in the war against colorectal cancer [75].

Similar to colorectal cancer, the role of DNA methylation in prostate cancers has been the subject of numerous studies [76-78]. Indeed, aberrant hyper/hypo methylation has been linked in numerous prostate-specific malignant processes ranging from early tumorigenesis to late stage, androgen independent tumors [79]. The identification of specific targets which are down-regulated as a result of hypermethylation at their promoters has led to the development of methylation biomarkers for early detection [80]. These targets of inactivation by promoter hypermethylation include Ras-association domain family 1A (RASSF1A), GSTP1, and retinoic acid receptor beta2 (RARbeta2). Though the role of hypomethylation in prostate cancer is less understood, there are several recent studies which link it to alterations in the expression of genes associated with early and late stage prostate tumors [81-83].

Additional studies indicate that hyper/hypomethylation of specific promoter regions is associated with tumorigenesis in a broad range of tissues including lung, breast, thyroid, head and neck squamous cell carcinomas, and hepatocellular carcinomas [84-86]. There are ongoing studies in dozens of other tissue types indicating a role for hyper/hypomethylation in a broadening range of cancers. Thus, aberrant alterations in methylation promise to provide a broad-spectrum mechanism for early detection and prognostication of tumors.

3. Histone methylation in tumorigenesis

Modifications to histone tails comprise the broadest range of variation in epigenetic controls, encompassing more than four dozen known sites of alteration [87]. Histone proteins are the targets of many forms of post-translational modification such as citrullination, acetylation, phosphorylation, SUMOylation, ADP-ribosylation and methylation (Figure 1) [87, 88]. These alterations are translated into biological consequences by impacting the structure of the nucleosome as well as facilitating the recruitment of specific regulatory complexes. The combination of different histone modifications in concert communicates a "histone code" that is interpreted in the form of distinct nuclear events [89].

Histone methylation has been observed to be a mark that imparts long-term epigenetic memory [90]. Histone lysine methylation is a central factor in such processes as X chromosome inactivation, DNA methylation, transcriptional regulation, and the formation of heterochromatin [91, 92]. This modification, catalyzed by histone methyltransferases, often facilitates the regulation of protein expression in a residue-dependent manner [90]. The de-

degree of achievable specificity is increased by the breadth of biological outcomes which are dependent upon whether a residue is mono-, di-, or tri-methylated [93-95]. Likewise, it has also been widely observed that histone lysine methylation works concomitantly with many transient histone modifications, thereby further enhancing the degree of information which can be communicated by this epigenetic modification [15].

Figure 1. Common sites of Histone Methylation

Almost all histone lysine methyltransferases are dependent upon a SET domain for catalyzing the transfer of methyl groups. The SET domain is present in many proteins that control a range of biological processes, including several involved in development and proper cell cycle progression [7, 96]. Promoter associated, residue-specific histone methylation often correlates with distinct patterns of protein expression [96]. The bulk of known modifications occur on histone H3 which thereby serves as a central conduit of epigenetic regulation. Lysine methylation at histone H3, lysine 9 (H3K9), H3K27, and H4K20 is most often associated with gene silencing, whereas methylation of H3K4, H3K36, or H3K79 is commonly linked to the activation of transcription [7, 96]. Accumulating evidence points to histone methylation in the recruitment of chromatin remodeling complexes, such as CHD1, an ATP-dependent chromatin remodeling factor that binds specifically to methylated the forms of H3K4 [97]. While histone lysine methylation was previously believed to be a permanent mark, a num-

ber of enzymes have now been identified that are capable of reversing histone methylation in a site-specific manner [98-100].

The presence of histone variants creates yet another tier to the potential of epigenetic mechanisms to communicate cellular information [53]. Variants affect the nucleosomal architecture as well as the proclivity of local chromatin to be remodeled. Thus, the inclusion of histone variants may modify nucleosome mobility, stability, and/or potential patterns of histone modifications. These, in turn, impact higher order structure and downstream events [101-104]. For example, a specialized H3-like variant CENP-A, replaces H3 in centromeric nucleosomes to establish a distinct architecture that is essential for proper segregation of the chromosomes [105]. In recent years, there have been an increasing number of experimental outcomes emphasizing the biological relevance of histone variants and their central role in epigenetic control [53].

Regulating the architecture of chromatin involves complex and dynamic mechanisms. The structure of chromatin is controlled on multiple levels by distinct processes such as nucleosome remodeling, DNA methylation, histone post-translational modifications, incorporation of histone variants, and non-coding RNA. Aberrant activity within such epigenetic processes is likely to broadly affect protein expression as well as other biological events such as apoptosis and condensation and segregation of chromosomes.

Tumorigenesis is a graded process through which a succession of genetic aberrations leads to the progressive transformation of healthy cells. While modifications in genetic sequence certainly account for many of these aberrations, an increasing number of modifications in gene expression observed in tumorigenesis have been found to be the result by epigenetic aberrations. These observations point to the relevance of epigenetic mechanisms in the maintenance of proper cell function. Aberrant events related to such mechanisms often act in concert with genetic mutations thereby contributing to the development and progression of cancer.

Over the last two decades, an increasing number of investigations have highlighted the aberrant gain or loss of histone methyltransferase activity in carcinogenesis. At one end of the spectrum, it has been shown that mice which fail to express the H3K9-specific histone methyltransferase, SUV39H1, are subject to increased incidence of chromosomal instability and subsequent tumorigenic potential [106]. At the opposite end of the spectrum, it is over-expression of Smyd3, another histone methyltransferase that is specific for H3K4, that has been shown to be responsible for unrestrained proliferation of many cancer cells [107]. A transcription factor binding element polymorphism in the upstream regulatory sequence for Smyd3 has been associated with an increased risk for cancer [108, 109].

In addition to histone targets, some SET domain-containing methyltransferases have been shown to methylate other proteins including tumor suppressors. Smyd2, which methylates H3K36 [6, 110], has also been directly linked to the regulation of p53 [111, 112]. Methylating lysine 370 of p53, Smyd2 has been shown to inhibit the transcriptional regulatory activity of p53. Smyd2 regulation of the retinoblastoma tumor suppressor (RB) has also been observed by its capacity to methylate of RB at K860 [113]. In a second example, Set9, which methylates

H3K4 [114, 115], has also been linked to the regulation of p53 by its capacity to methylate that protein at lysine 372 [116, 117]. Methylation of that site stabilizes p53 and limits its localization to the nucleus [116].

The broad roles of aberrant lysine methylation in the induction of carcinogenesis have paved the way for a novel line of cancer therapeutics. [118]. Those therapeutics bank on the potential to manipulate of the demethylating activity of a host of demethylases. The fact that many demethylases target highly specific substrates heightens their potential utility as highly effective therapeutics with lower likelihood of instigating adverse effects.

4. Conclusion

While it is true that chromatin architecture has the capacity to be epigenetically maintained and inherited via modified states of methylation, recent studies have highlighted the fact that methylation-induced control of gene expression may be altered by environmental stressors and toxicants. Such modifications may, in consequence, induce aberrations toward genome integrity and stability. Distinct from genetic mutations, these epigenetic aberrations have been termed epimutations. In contrast to genetic mutations, which may be passively inherited, epimutations require active maintenance [119]. That epimutations rare appearance in normal tissues highlights the potential for epigenetic therapies based on high tumor specificity. Likewise, while therapeutics based on genetic deletions commonly induce an irreversible loss of gene function, epigenetic alterations are reversible, further enhancing their potential utility for therapeutic intervention [120]. Reversal of epimutations to restore normal expression of tumor suppressors has become the holy grail in epigenetic cancer therapeutics. Already, numerous studies have proven that aberrant gene silencing mediated by DNA methylation can be easily reversed by the incorporation of DNA methyltransferase inhibitors [121]. Positive results have been observed after treating tumor cells with such pharmacological agents [122, 123].

In the last two decades, our knowledge of chromatin methylation patterns and their role in the regulation of nuclear processes have been broadly elucidated. Understanding those patterns of histone changes, decoding the association between those alterations and DNA methylation, and characterizing their relevance in tumorigenesis comprise the next hurdles in the etiology of the role of methylation in cancer.

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