Epigenetic Error and Large-scale Genomic Instability in Cancer

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Introduction

Epigenetics and DNA Methylation

From an evolutionary point of view, it is likely that epigenetic markers arose as a means of protecting genetic information [1]. The primary epigenetic marker is DNA methylation and DNA methylation would furnish a way to distinguish between ‘self’ and ‘foreign’ genetic material as, for example, for the selective action of the restriction endonuclease system in bacteria [2]. Such an epigenetic marker might plausibly have become subsequently recruited to enable the stabilization of alternative phenotypic states in differentiated tissues of multicellular organisms, as envisaged by Waddington [3,4]. For terminally differentiated tissues in which no further cell division takes place, such as CNS neurons, there is no mechanistic difficulty in retaining the status quo, but in order to maintain the stable differentiated phenotype of cells with identical genomes undergoing replication it is necessary for the epigenetic information to be duplicated. The significance of DNA methylation in conferring phenotypic stability to differentiated proliferating cells was proposed by Holliday and Pugh [5] and Riggs [6].

The DNA methylation copying process involves a DNA methyl transferase 1 complex which recognizes and binds to segments of DNA containing hemi-methylated CpG dinucleotides in the duplicated strands formed by semiconservative DNA replication and converts them to fully methylated copies of the original [7,8]. The primary importance of DNA methylation patterns rests on their ability to selectively recruit the binding of various protein complexes including histones and sets of enzymes able to modify histones such as histone acetylation and deacetylation complexes and histone methyl transferase complexes which affect the structure of nucleosomes.

Nucleosome Structure

In eukaryotic genomes the nucleosome core particles consist of an octamer of two copies each of the core histones (H2A, H2B, H3, and H4) round which 146 bp DNA is wound in two turns of a left-handed superhelix [9,10]. Although core histone structures are strongly conserved there are variants of H2A and H3 (such as H2AZ macroH2A, and H33 and CENP-A). In addition there are post-translational modifications of the core histones including acetylation, methylation, ubiquination and phosphorylation. The effect of these substitutions and histone modifications is to create differing epitopes that determine the binding of various macromolecular complexes. The packaging of chromatin is dependent on the structure of nucleosomes mediated through modification of histones. This in turn is directed by the local pattern of DNA methylation, which is thus the primary determinant of chromatin architecture.

Chromatin Architecture

Chromatin is the ultimate carrier of heritable epigenetic information. Four general categories of chromatin are recognised: euchromatin, in which the nucleosomes are readily accessible to transcription factors; heterochromatin, in which the nucleosome structure is not normally accessible for transcription; centromeric chromatin, a densely compacted region of chromatin that provides attachment sites for kinetochore proteins and spindle microtubules; and pericentromeric chromatin, which acts as a centromere boundary. Chromatin organisation is usefully defined in terms of the histone variants with which they are associated. The structural category of chromatin and some of the associated histone modifications are summarised in Table 1.
Table 1: Chromosomal architecture and histone modifications.

<table>
<thead>
<tr>
<th>Histone variant or modification</th>
<th>Euchromatin</th>
<th>Heterochromatin</th>
<th>Centromere</th>
<th>Pericentromere</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3K4me2</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3K4me3</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3K9ac</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3K9me2</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3K9me3</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3K27me3</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3R2me</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H4K20me2</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H4K20me3</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>CENP-A</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H2A.Z</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3S10P</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3S37P</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H3T3P</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>H4S1P</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

The characteristic distribution of variant or modified histones shown in the left hand column is indicated by a filled circle (●) in the chromatin categories listed. The phosphorylated variants shown in the Table are mainly generated during mitosis by kinases such as the aurora kinases which are directed to the appropriate binding sites by structural cues.

Chromosomal Instability In Cancer

The fundamental biological abnormality of cancer is the breakdown in multicellular organisms of the normal controls that restrict competition between cells exhibiting different functional characteristics and permit intercellular cooperation. The nature of the crucial abnormalities exhibited by malignant cells is not clear, although abnormal migratory capability and dysregulated proliferation appear to be essential components, and the evidence indicates that these properties arise from large-scale disturbances of the genome. The cytological diagnosis of cancer rests on a number of criteria. The recognised cellular features of malignancy include cellular enlargement, increased nuclear/cytoplasmic ratio, nuclear hyperchromasia, prominent and large nucleoli, abnormal distribution of nuclear chromatin, the presence of abnormal mitoses, as well as nuclear membrane abnormalities and cellular and nuclear pleomorphism.

These criteria essentially reflect various aspects of chromosomal instability (CIN) which include chromosome doublings, chromosomal fragmentation and other abnormalities occurring during mitosis. This results in large-scale chaotic changes to the genome of cancer cells and the expression of abnormal characteristics, some of which endow the cells with malignant potential such as the ability to transgress normal tissue boundaries and migrate to distant sites. Chromosomal instability is associated with alterations in chromatin structure, particularly those involving centromere defects.

Centromere Chromatin Structure

The location of regions of euchromatin and heterochromatin are regulated by the pattern of DNA methylation and there is much evidence that the location of the centromere is similarly determined epigenetically [11-15]. Epigenetic determination of the centromere locus provides a mechanism for karyotypic evolution [16], a phenomenon that appears to underlie much of the chromosomal instability in cancer cells. Centromeric and pericentromeric DNA is normally heavily methylated and loss of DNA methylation of this region is associated with segregation defects [17-19]. The pattern of DNA methylation within the centromere consists of specific non-methylated zones within extensively methylated regions. The non-methylated sites are recognised by the kinetochore protein CENP-B which, with CENP-A and CENP-C, binds to a region of α-satellite DNA which is important for establishing kinetochore location and preventing duplication [20].

The histone modifications of centromeric chromatin are distinct from constitutive heterochromatin. The highly conserved histone CENP-A substitutes for H3 in some centromeric nucleosomes [16] and centromeric chromatin is composed of alternating zones of H3 and CENP-A-containing nucleosomes [17]. CENP-A is a central factor in recruiting proteins that are essential for kinetochore assembly and progression during mitosis [15,18]. H2AZ is a variant of H2A present in non-CENP-A nucleosomes and appears to promote sister chromatid adhesion prior to chromosomal segregation [19].

Pericentromere Chromatin

H3K9 and H4K20 methylases accumulate in the pericentromeric region at mitosis [21] and pericentromeric chromatin includes nucleosomes containing the histone H3K9me3, but these are located distal to the centromere and may establish a boundary signal to avoid expansion and duplication of the centrosome [22]. Although many of the details of the processes involved remain to be elucidated, it is clear that DNA methylation affects chromosomal stability through chromatin remodeling and the recruitment of...
specific factors that are central to the controlled distribution of the cellular genome at mitosis and that this epigenetic signal is critical to genomic stability [23]. The importance of DNA methylation in cancer is well established [24-26]. DNA methylation patterns are intimately linked to chromatin structure [27] and exert their influence through interaction with histone-modifying enzymes [28,29] and by affecting the association with, and activity of, methylation-binding proteins involved in nucleosome remodelling complexes [30].

Evidence of genome-wide histone modifications in cancer [31] implies genome-wide DNA methylation defects. Direct evidence that DNA methylation plays a central role in chromosomal stability is that loss of DNA methylation of centromeric and pericentromeric loci is associated with large-scale chromosomal changes [32]. It seems highly probable that alterations in DNA methylation represent the fundamental defect that underlies the genomic instability which is characteristic of cancer cells [33-35]. The widespread nature of the abnormalities in DNA methylation inferred from the above argument suggests that the methylation disturbance arises from a generalised defect, and it has been suggested that this crucial epigenetic error arises through lack of fidelity of epigenetic copying during stem cell mitosis [36,37]. The lack of fidelity in the vertical transmission of the epigenetic signal is ascribed, in adult malignancies, to mutations affecting the mechanism responsible for replication of the pattern of DNA methylation [38,39]. Mutations affecting the DNA methyltransferase 1 complex or the associated proof-reading and authentication mechanisms occurring in tissue stem cells as the initiating cause of carcinogenesis would be consistent with the age-dependent incidence of adult human cancers described by models [40,41] essentially similar to those of Armitage and Doll [42]. Such a process affecting tissue stem cells would be consistent with a strong relationship between stem cell population size of individual tissues and their relative cancer incidence. Moreover, the likelihood of expression of the initiating mutation will be a function of the proliferation rate of specific tissue stem cells. Both these relationships have been demonstrated for human cancers by Tomasetti and Vogelstein [43].

Conclusion

The fundamental diagnostic abnormality of cancer cells is widespread disturbances of the genome with many abnormal derangements of genetic expression and rapid clonal evolution. This is the consequence of chromosomal instability (CIN) which is a cardinal feature of cancer cells. It is proposed that the basic metabolic process underlying this process is failure of fidelity of epigenetic copying during replication by a clone of tissue stem cells. The faulty epigenetic copying is attributed to one or more initiating mutations affecting the replication mechanism in the progenitor cell. During DNA replication the chromosomal structure is opened up and the nucleosomes separated. Under normal circumstances the histone framework is restored, partly from the conservative transfer of pre-existing H3/H4 histone tetramers, and partly by recruitment of newly synthesised histones. The histone variants and their post-translational modification are determined by the methylation pattern of the replicated DNA, such that the histone chaperone complex in the replisome brings about an identical nucleosome assembly and the reformed chromatin structure is preserved in the division products [44].

However, failure to accurately copy the DNA methylation pattern will result in altered histone assembly giving rise to modified nucleosome structure, and hence chromosomal variation in the division products. It will be readily seen that with succeeding generations this process will lead to rapid divergent chromosomal structure and hence wide-ranging and variable sets of cellular characteristics and rapid clonal evolution of cells exhibiting abnormal properties, including cellular autonomy with loss of cooperative function within the organism, disorganized behavior, loss of territorial limitations, failure of appropriate responses to intercellular and inter-tissue signals, deranged metabolism and unregulated proliferative activity - the essential biological features of malignant cells.

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References


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