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Epigenetics and Carcinogenesis: DNA Methylation Abnormalities Associated with Cancer and their Possible Source

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Introduction

It is now well-established that the majority of the aberrant gene expression profiles described in human cancers are due to epigenetic changes. These patterns reflect DNA methylation changes, including both hypo- and hypermethylation. There is evidence to suggest that, in general, hypomethylation is associated with the expression of previously silenced genes whereas DNA hypermethylation is involved in the silencing of previously transcribed genes and there has been much interest in the inhibition of tumour-suppressor genes as a possible carcinogenic mechanism. This brief overview discusses the possible origins of the observed anomalies of DNA methylation and proposes that the initiating carcinogenic mechanism lies in the failure of accurate copying of the epigenetic pattern during stem cell proliferation.

DNA Hypomethylation

The first epigenetic abnormality detected in human cancer cells was DNA hypomethylation [1-3] and many subsequent studies have confirmed this phenomenon as a constant feature of the cancer genome in a wide range of neoplasms that include ovarian, prostatic, hepatocellular, cervical, colon cancer and also leukemias and developmental tumours such as Wilms' tumors [4]. It can be concluded that DNA hypomethylation is an ubiquitous feature of human cancers [5]. DNA hypomethylation is most frequently found in the highly repeated DNA sequences which comprise about half of the human genome, but specific cancer-associated hypomethylation has been demonstrated in transcription control sequences [6]. It can be argued that DNA hypomethylation is the primary abnormality in carcinogenesis. Hypomethylation occurs early in tumorigenesis and has been observed in pre-neoplastic lesions such as hyperplasia [7-9]. The specificity of the hypomethylated regions appears to be related to the tissue of origin [9-11] and there is evidence that the pattern is influenced during tumour progression [12,13].

Possible Mechanisms of Demethylation

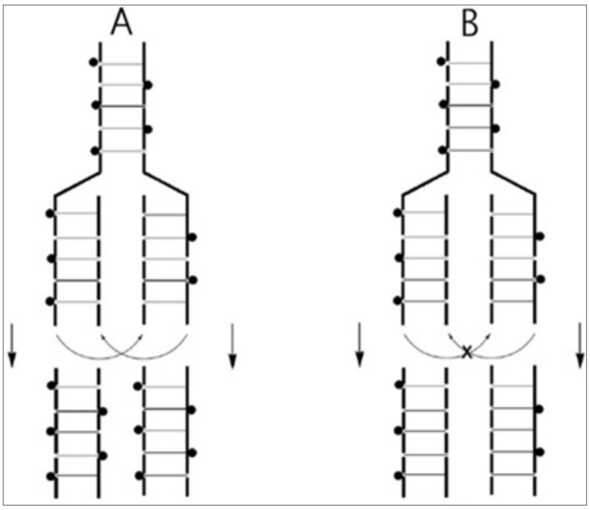

Figure 1: Schematic outline of the process of copying the epigenetic methylation pattern during DNA replication.

There would appear to be two basic mechanisms that could be responsible for the hypomethylation of the DNA. One is by enzymatic demethylation, a process that is known to occur as a result of the oxidation of 5-methylcytosine to its hydroxylated

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derivative. This involves 'ten-eleven translocase' (TET) enzymes [14] and ultimately leads to base excision repair with replacement by unmethylated cytosine. Such a process is likely to constitute a random outcome of metabolic oxidation.

An alternative source of DNA demethylation would be the failure of preservation of the DNA methylation pattern during the process of stem cell proliferation (Figure 1). The 5-methylcytosine residues are represented by black circles which are copied onto the duplicated strands as indicated in the sequence A. This involves the 'maintenance' methylase DNA methyl transferase 1 (DNMT1) which has an affinity for hemimethylated regions [15]. Failure of this methylation process would result in dissimilar post-division products, as shown in the sequence B.

Such a failure in the fidelity of copying of the epigenetic pattern established in differentiated tissues would result in regions of hypomethylated DNA with the associated re-expression of previously silenced genes [16]. Moreover, such a hypomethylation mechanism occurring at each stem cell division would generate an expanding set of epigenetically anomalous genomes and thus account for the increasing diversity of characteristics observed in the progression phase of carcinogenesis [17]. The preferred model to explain the hypomethylation of DNA associated with cancer cells as outlined above requires the initiation of carcinogenesis to be dependent on an event (e.g. a mutation)causing a derangement of the epigenetic copying mechanism and/or an authentication process that ensures the perpetuation of the differentiated state during stem cell proliferation, such as p53 [18]. This approach is consistent with observation of the relationship with stem cell proliferation shown by Tomasetti & Vogelstein [19] and age-related cancer incidence data [20].

DNA Hypermethylation

Hypermethylation of homeobox genes and other sequences, and particularly affecting promoters of tumour-suppressor genes is a prominent feature of the cancer genome [21,22]. In most instances there is a close association between hypomethylation and hypermethylation, although affecting different regions of the genome [5,23]. It can be argued that the observed DNA hypermethylation is a secondary compensatory hypermethylation and may be the consequence of a process such as the demethylation of silenced genes such as those coding for DNA methyl transferase enzymes. Given that DNA methylation is dysregulated in all tumour types, the recent advances in methylation screening techniques offer optimistic prospects for the development of screening and monitoring methods and the possibility of constructive interference with the fundamental processes underlying cancer biology.

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