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Review

The promises and pitfalls of epigenetic therapies in solid tumours

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ABSTRACT

Epigenetic inactivation of tumour suppressor genes, in contrast to gene mutations, can be modulated or reversed by small molecules. This has lead to several recent studies of drugs targeting epigenetic mechanisms as novel cancer therapies. So far, epigenetic therapies, including HDAC inhibitors and demethylating agents, show considerable activity in haematological malignancies, but their value in the treatment of solid tumours remains much more uncertain. This review will discuss some of the challenges that are expected in the treatment of solid tumours with epigenetic therapies and discuss approaches to overcome these obstacles. There is an increasing need for trials driven by pharmacodynamic biomarkers for these agents, which are aimed at finding the optimum biological dose rather than the maximal-tolerated dose, and also investigating their use in combination with cytotoxics – for example as chemosensitisers. Such trials already suggest that improved tumour delivery and specificity, with decreased normal tissue toxicity, will be required to take full advantage of this class of agents in solid tumours.

1. Background

Epigenetics describe a hereditable change in gene expression without a change in the DNA sequence. Abnormal gene deregulation as a result of genetic and/or epigenetic mechanisms is central to the initiation and maintenance of cancer. Since more key genes are epigenetically silenced in tumours than are genetically silenced, it has been argued that epigenetic mechanisms are the most prevalent driver of tumourigenesis.[1] Furthermore, epigenetic silencing, in contrast to gene mutations, can be modulated or reversed by small molecules.[2] This has led to an ever-increasing number of preclinical and clinical studies of epigenetic therapies. Such therapies have shown a considerable activity in haematological malignancies, but their value in the treatment of solid tumours remains much more uncertain.

One of the most widely studied epigenetic changes is DNA methylation, which occurs in mammalian DNA at CpG dinucleotides, where the hydrogen bond at the fifth position of cytosine becomes methylated.[3] DNA methylation is catalysed by a group of enzymes called the DNA methyl transferases (DNMT's) (Fig. 1). CpG dinucleotides are under represented in the genome; however, there are CpG rich regions (CpG islands) that generally remain unmethylated, and are located in the promoter or first exon regions of approximately 60% of genes. Aberrant methylation of CpG islands occurs in all tumour types and is strongly correlated to transcriptional gene silencing and epigenetic maintenance of the silenced

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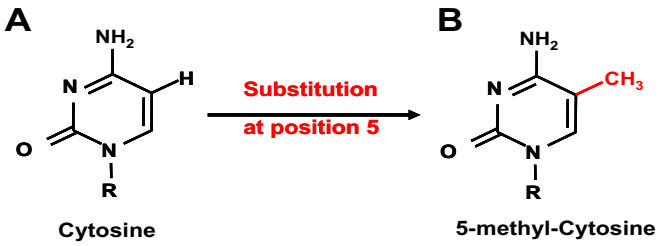

Fig. 1 – Chemical modification of cytosine methylation: (A) the chemical structure of the base cytosine and (B) the chemical structure of 5-methylcytosine following enzymatic transfer of a methyl (CH_3) group.

state.[4] Two examples of physiological roles for methylation are the silencing of the second X chromosome in females (so they do not have twice as much expression of genes), and the silencing of potentially harmful viral sequences.[5] CpG islands at gene transcription start site are usually unmethylated, while other CpG sites in coding sequence are relatively more methylated. In aging and cancer, these contrasting states of methylation tend to reverse,[6–10] with coding CpG sites becoming hypomethylated, while certain CpG islands become hypermethylated (Fig. 2).

DNA methylation at CpG islands is associated with chromatin being in a repressive state for gene transcription. Nucleosomes form the basic repeating unit of chromatin and consist of DNA wrapped around a histone octomer that is formed by four histone partners. In general, condensed chromatin (heterochromatin) mediates transcriptional repression, whereas transcriptionally active genes are in areas of open chromatin (euchromatin). Extending out of the nucleosome are charged amino-terminal histone tails, which are subjected to post-translational modification such as acetylation, phosphorylation and methylation. As an example, the histone position H3-K9 is a site of both acetylation and methylation. Deacetylation of H3-K9 is required for methylation to occur, which is then a repressive epigenetic mark. Trimethylation of H3-K9 results in the recruitment and binding of the transcriptional repressor, heterochromatin protein HP1. HP1 binding to the methylated H3 forms a positive feedback loop, mediating the propagation of heterochromatin over wide chromosomal ranges. Thus, covalent modification of the histone tails directly affects higher-order chromatin structure, and thereby offers a mechanism of epigenetic gene activation or silencing (Fig. 3).

A crucial aspect of both DNA methylation and histone acetylation is that they are reversible. Epigenetic change in gene expression is maintained during cell division and requires active maintenance of the epigenetic signature. Enzymes are required to maintain this epigenetic signature at each cell division and this can, therefore, be manipulated using small molecules that have the potential to be developed into epigenetic drugs. Those most investigated epigenetic therapies to date are the DNMT inhibitors and HDAC inhibitors.

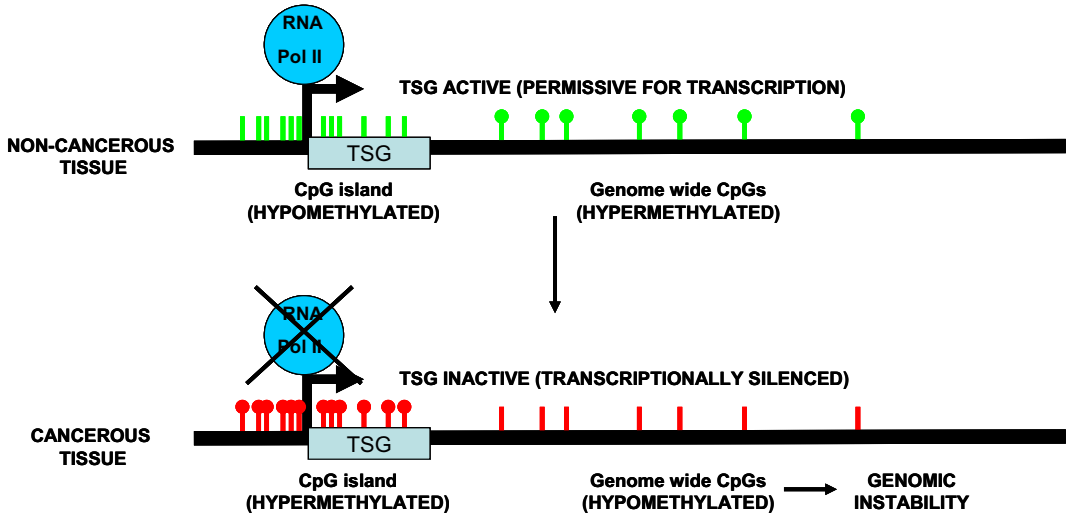

Fig. 2 – DNA methylation and cancer. A representation of a region of DNA in non-cancerous (top; green) and cancerous (bottom; red) tissues showing the differences in DNA methylation in the two phenotypes. In non-cancerous tissue, genome wide hypermethylation of CpGs (closed green circles) and an actively transcribed tumour suppressor gene (TSG) is associated with a hypomethylated CGI (green lines). In cancerous tissue, the opposite is seen with genome wide hypomethylation (red lines) leading to genomic instability, and CGI hypermethylation (closed red circles) contributing to transcriptional silencing of a TSG. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)