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Epigenetics in cancer therapy

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Epigenetics plays an important role in oncogenesis and the first marked and most extensively studied epigenetic modification in mammals is DNA methylation. DNA methylation is a process that causes covalent modification by adding a methyl group to the 5th carbon of the ring in which the methyl donor is from S-adenosyl methionine that occurs in the cytosine ring at the 5th position of CpG dinucleotide in the presence of an enzyme called DNA methyltransferase (DNMT). Three fundamental DNMTs are found in mammals that are involved in the generation and maintenance of DNA methylation patterns and they are DNMT1, DNMT3a, and DNMT3b. DNMT1, the maintenance enzyme restores paternal DNA methylation profile, and DNMT3a and DNMT3b initiate methylation by targeting the unmethylated or de novo DNA methylation of CpGs. 70% of CpG sites are methylated in normal cells in the human genome. The CpG rich DNA stretches are called CpG islands. They contain 500-1000 base pairs. DNA methylation functions by either preventing or promoting the requirement of regulatory protein to DNA. Various patterns of DNA methylation observed in cancer are hypermethylation, hypomethylation, and loss of imprinting (LOI). Cancer epigenome exhibits global hypomethylation and promoter hypermethylation. DNA hypomethylation causes tumorigenesis and malignant cell transformation. It acts on various genomic sequences in repetitive elements, retrotransposons, CpG poor promoters, introns, and gene deserts, which leads to genomic instability by a germline mutation in the DNMT3B enzyme. Site-specific hypermethylation silences the tumour suppressor genes, which are involved in DNA repair, cell cycle, cell adhesion, apoptosis and angiogenesis causing tumorigenesis. The promoter methylation of the tumour suppressor genes is shown in saliva as early biomarkers, which can become a non-invasive biomarker tool in early diagnosis. Similarly, drugs that inhibit DNA methylation caused by DNMTs could become potential molecules in targeting cancer therapy. In the future, the development of more specific epigenetic drugs by understanding cancer stem cells might help in successfully resetting the abnormal cancer epigenome.

Keywords: Epigenetics, Cancer, DNA methylation, Tumorigenesis, Enzymes, CpG dinucleotide, DNA methyltransferase

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