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Review

Chromatin-remodelling mechanisms in cancer

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This paper has been dedicated to the memory of our friend and colleague María Mühlmann.

Abstract

Chromatin-remodelling mechanisms include DNA methylation, histone-tail acetylation, poly-ADP-ribosylation, and ATP-dependent chromatin-remodelling processes. Some epigenetic modifications among others have been observed in cancer cells, namely (1) local DNA hypermethylation and global hypomethylation, (2) alteration in histone acetylation/deacetylation balance, (3) increased or decreased poly-ADP-ribosylation, and (4) failures in ATP-dependent chromatin-remodelling mechanisms. Moreover, these alterations can influence the response to classical anti-tumour treatments. Drugs targeting epigenetic alterations are under development. Currently, DNA methylation and histone deacetylase inhibitors are in use in cancer therapy, and poly-ADP-ribosylation inhibitors are undergoing clinical trials. Epigenetic therapy is gaining in importance in pharmacology as a new tool to improve anti-cancer therapies.

Keywords: Epigenetics; DNA methylation; Histone acetylation; Poly-ADP-ribosylation; ATP-dependent chromatin remodelling; Cancer therapy

Contents

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1. Epigenetics and cancer

Epigenetics refers to modifications in genome function that occur without changes in DNA. Eu- or heterochromatic organizations, once established can be somatically maintained as heritable epigenetic states [1,2]. Chromatin conformation depends on several epigenetic processes acting in concert, such as DNA methylation, histone-tail acetylation, poly-ADP-ribosylation and ATP-dependent chromatin-remodelling mechanisms (i.e. SWI/SNF, ISWI). Distinct histone covalent modifications on a specific histone tail can occur sequentially or in combination, determining a "histone code" that can be read by chromatin-associated non-histone proteins. Specific sets of multiple covalent modifications on different histone tails can be inter-dependent, allowing the establishment of different epigenetic states, which results in distinct readouts of the genetic information [3–6]. There is also a crosstalk among different chromatin-remodelling mechanisms. A correspondence between the chromatin acetylation pattern and the DNA methylation status related to gene expression has been described [7]. Poly-ADP-ribosylation is essential for the maintenance of the imprinted state of specific genes, whose loss of imprinting is associated with many malignancies [8]. Moreover, it has been reported that members of the Snf2 family of ATPases (the largest family enzymes from the ATP-dependent chromatin-remodelling mechanisms) interact with histone deacetylases [9] and methyl DNA-binding proteins [10]. Epigenetic modulation of chromatin conformation can affect the access of transcription factors to DNA, having a role on regulating transcriptional activation in eukaryotic genes. Moreover, it has been demonstrated that DNA damage induction and DNA repair mechanisms can be modulated by chromatin-remodelling processes. Since epigenetic changes are mitotically heritable, they can contribute (together with the genetic changes) in cancer development [1,11].

Cancer is a multi-step process derived from the combination of changes in the genetic background, the presence of epigenetic alterations and the influence of environmental factors. Moreover, it has been suggested that environmental exposures to nutritional, chemical and physical factors could alter gene expression and modify adult disease susceptibility through changes in the epigenome. Therefore, it has been proposed that epigenetic modifications could act as a link between the environment and alterations in gene expression. Moreover, it has been demonstrated that reversible transgenerational alterations in phenotype can be environmentally induced by heritable epigenetic modifications [12,13]. DNA methylation is the best-studied epigenetic mechanism. As the methylation rate is thought to be faster than the genetic mutation rate, epigenetic mutations might be more likely to initiate neoplasms than genetic mutation. Moreover, increasing evidence points out that the epigenetic alterations can appear before cancer development; and even more, they can be considered possible events for tumour initiation [14]. Several chromatin-remodelling mechanisms are reviewed in relation to their association with cancer, namely, DNA methylation, histone acetylation, poly-ADP-ribosylation and ATP-dependent chromatin remodelling. Sensitization to chemotherapy or suppression of tumour growth could be achieved using drugs that induce inactivation of over-expressed oncogenes, re-expression of tumour suppressor genes or inactivated DNA repair genes by means of epigenetics modification.

2. DNA methylation

DNA methylation is a chemical heritable modification characterized by the covalent addition of a methyl group to cytosines. In human somatic cells, DNA methylation typically occurs at CpG dinucleotides, which accounts for ∼1% of the total genome [15]. Moreover, 60–90% of all disperse CpG sequences are methylated. On the other hand, CpG islands (GC-rich regions located at the 5′ ends in ∼60% of human genes) possess high relative densities of unmethylated CpG dinucleotides at all stages of development and in all tissue types. A small proportion of all 5′ CpG islands become methylated during development for stably transcriptional silencing [16,17]. This pattern of developmental programme for CpG-island methylation is specie and tissue specific, and is involved in the control of tissue-specific gene expression, genomic imprinting as well as X chromosome inactivation. DNA methylation provides a defence mechanism against the expression of exogenous DNA in bacteria, plants and animals that constricts the expression of transgenes, transposons and repetitive DNA elements, increasing the latency of cellular viruses, and conferring genome stability. Besides, the methylation of non-transcribing regions such as centromeric heterochromatin is essential for the maintenance of chromosome integrity [18]. Nevertheless, CpG methylation increases the risk of spontaneous mutations. 5-methyl-cytocine has an increased mutability with respect to cytocine because its differential repair efficiency and rate of spontaneous deamination. Deamination of cytocine forms uracil, which is efficiently repaired by uracil DNA glycosylase.