CHAPTER 9

PARP and Epigenetic Regulation

Paola Caiafa

Abstract

In the post-genome era attention is being focused on those epigenetic modifications which modulate chromatin structure to guarantee that information present on DNA is read correctly and at the most appropriate time in order to meet cellular requirements. In this chapter data are reviewed which show that along the chain of events that induce DNA methylation-dependent chromatin condensation, a post-synthetic modification other than histone acetylation, phosphorylation and methylation, namely poly(ADP-ribosyl)ation, participates in the establishment and maintenance of methylation-free regions of chromatin. In fact, several lines of in vitro and in vivo evidence have shown that poly(ADP-ribosyl)ation is involved in the control of DNA methylation pattern, protecting genomic DNA from full methylation. Molecular mechanism(s) that might underpin the correlation between inhibition of poly(ADP-ribose) polymerases and DNA hypermethylation will be discussed. Finally the hypothesis is posited that inhibition of the poly(ADP-ribosyl)ation process in the cell may be responsible for the anomalous hypermethylation of tumor suppressor gene promoters during tumorigenesis.

Several Epigenetic Modifications Work Together in the Regulation of Gene Expression

The term “epigenetics” covers all those phenomena which control the functional state of DNA without changing the DNA sequence (i.e., without inducing genetic mutation). Among these, post-synthetic modifications of DNA and of chromatin proteins are of extreme importance as by interfering with chromatin structure they determine its remodeling, which is necessary to modulate the accessibility to information that is present on DNA. In fact, two meters of human DNA is packed into chromatin so that it can be contained in cell nuclei of a few micrometers diameter.1,2 Through specific interactions with chromatin proteins, DNA becomes part of an ordered structure which is more or less prone to allow gene expression as a function of its architecture. The fact that the DNA molecule is not only great in size but also in the number of functions it carries out, makes it even more difficult to understand how, being in so complex a structure, it is able to satisfy all needs at any required time according to cell’s necessity. To explain the “omnipotence” of DNA, attention is being focused on the study of those epigenetic processes which, without modifying the genetic code, allow DNA to guarantee the normal flux of events during cellular life (Fig. 1).

Methylation is the only physiological postsynthetic modification of DNA able to modify DNA function and consists in the introduction of methyl groups on cytosines mainly at the CpG dinucleotides of the mammalian genome.3 This epigenetic modification introduces as fifth base in DNA, the 5mC. It is well-known that 5mCs are distributed in a non-random fashion in genomic DNA so that the methylation pattern is characterized by the presence of methylated cytosines on the bulk of DNA while the unmethylated ones are mainly located

Figure 1. Figure summarizes some of the most important epigenetic modifications that occur on DNA, on aminoterminal tails of core histones and on H1, highlighting their relevance for determining that architectural structure of chromatin that makes it competent or not to allow gene expression. Little red asterisks indicate the presence of 5mC in DNA. M, methyl groups on histones. Ac, acetyl groups on histones. Molecules depicted on top right represent automodifying PARP-1. DB, DNA-binding domain; AM, automodification domain; C, catalytic domain.

within particular regions termed CpG islands. Summarizing some characteristics of CpG islands, one should note that there are about 30,000 in the human genome. They are generally located in the 5' promoter region of housekeeping genes sometimes overlapping with coding sequences to variable extents. They are 0.5-2 Kbp size and their sequence is enriched about six-fold in CpG dinucleotides. This is particularly interesting as, although CpG dinucleotides are the best substrate for DNA methyltransferase, they are unmethylated when located in CpG islands and there is evidence that the transcription of genes associated with CpG islands is active when these regions are in the unmethylated state while gene expression is inhibited when these regions undergo methylation. It is to note that CpG islands have recently been found within coding sequences of genes, yet their methylation did not block transcription in several tissue-specific and imprinted genes. In vitro experiments have shown that the CpG islands are not unmethylatable per se and this increases interest in these DNA regions. The mechanisms involved in protecting the unmethylated state of CpG islands in genomic DNA remain far from being understood.