DNMT1 and Genomic Instability in Cancer

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Abstract

DNA (cytosine 5-) MethylTransferase 1 (DNMT1) maintains the pre-existing methyl marks onto daughter strands by faithfully copying the methylation pattern from hemimethylated DNA during replication phase. The fundamental role of DNA methylation in cell physiology makes a controlled regulation of DNMT1 necessary. DNMT1 loss and global DNA hypomethylation are correlated with genomic instability in cancer. This mini review aims to provide a scenario of the mechanisms whereby DNMT1 dysfunction could induce genomic instability so as to clarify its functions and understand the dynamics of DNA methylation at cellular level with a focus on cancer.

Keywords: DNMT1; DNA methylation; Genomic instability

Introduction

DNA methylation is a fundamental epigenetic signal, cited as the "epigenetic writer" [1], that guarantees efficient temporal and spatial gene expression during cell life and development, and that insures the higher order of chromatin architecture. Imbalances of this process compromise genome integrity and its message throughout generations.

DNA methyltransferases (DNMTs) catalyse the transfer of a methyl-group from S-adenosyl-L-methionine (SAM) to the 5-position of cytosine residues placed almost exclusively at the so called "CpG islands", DNA regions that contain a high frequency of CpG sites. Four members of the DNMT family are known in humans (DNMT1, DNMT3a, DNMT3b and DNMT3L). All DNMTs have an N- and a C-terminal part separated by a KG repeat; the N-terminus is the DNA-binding, the C-terminus harbours usually the catalytic domain of cytosine residues placed almost exclusively at the so called "CpG islands", DNA regions that contain a high frequency of CpG sites. All DNMTs have an N- and a C-terminal part separated by a KG repeat; the N-terminus is the DNA-binding, the C-terminus harbours usually the catalytic domain except for DNMT3L that, in fact, has not an associated enzymatic activity. DNMT3a and DNMT3b are "de novo" methyltransferases that establish DNA methylation pattern; only DNMT1 is responsible for the DNA methylation marks maintenance across successive cell divisions [2,3]. During DNA replication DNA is hemimethylated: the mother strand is methylated and the newly synthesised one is not. The protein UHRF1 (ubiquitin-like, containing PHD and RING finger domains 1) recognizes and binds the hemimethylated sites, then recruits DNMT1 that thereby methylates the newly synthesized DNA strand. The existence of a complex containing DNMT1, UHRF1 and PCNA (Proliferating Cell Nuclear Antigen), an auxiliary protein of DNA polymerase, shows the occurrence of DNA methylation during replication [4]. DNMT1 shows a 30- to 40-fold preference for hemimethylated sites [5], but the distinction between de novo and maintenance methylation is not so clear because DNMT1 de novo methylates non-CpG cytosines and to an extent even CpG islands [6]. Moreover, human cancer cells showed cooperation between DNMT1 and DNMT3b in maintaining DNA methylation suggesting a more complex situation [7].

The importance of correct DNA methylation arises from the observation that DNMTs are essential for mouse viability [3,8] and is emphasized by the high number of human diseases that are correlated to this epigenetic alteration. The paradox regarding DNA methylation pattern that shows both gene specific hypermethylation and genome wide hypomethylation is a characteristic of cancer cells, suggesting a role in human tumorigenesis [9].

Genomic instability is a distinguishing feature of the majority of human cancers and is considered a driving force for tumorigenesis. Various forms of genomic instability exist.

Chromosomal instability (CIN) implies structural and/or numerical changes of chromosomes; microsatellite instability (MSI or MIN) consists in alteration of the number of oligonucleotide repeats present in microsatellite sequences [10].

Global hypomethylation at repetitive sequences in cancer and DNMT1 reduction have been correlated to chromosomal instability, translocations, gene disruption and microsatellite instability [11]. In this short review we examine and outline the links between DNMT1 and genomic instability, and discuss the possible mechanisms of how they are orchestrated with a focus on cancer.

DNMT1 and Chromosomal Instability

Downregulation of DNMT1 is frequently observed in human tumors and is associated with DNA hypomethylation and genomic instability (i. e. chromosomal instability) [11-13]. Reduction of DNMT1 even of only 10% [14,15], or disruption of DNMT1/PCNA/ UHRF1 interactions, essential for DNMT1 recruitment onto DNA causes chromosome structural and numerical alterations [4]. The exact mechanism involving DNMT1 in CIN is not well understood yet, but the predominant hypothesis is that the DNMT1 reduction induces, through global DNA hypomethylation, loss of methylated marks at the repetitive sequences such as chromosome's pericentromeric region. The so created disorder would impair cellular processes such as DNA repair mechanisms and sister chromatids segregation triggering chromosomal instability. The essentiality of the interaction with PCNA/UHRF1 at the replication fork suggests that DNMT1 controls (and is highly controlled) in some way DNA replication. We
methylation aberrations [16]. DNA hypomethylation would be chromosomal instability [14]. Accordingly, DNMT1 is regulated by or of its regulation could cause genomic instability acquisition/road to cancer. Future perspective should be to understand if DNMT1 (CIN and MIN). Genomic instability is a characteristic of almost all events. Thus, DNMT1 activity during DNA replication and DNA repair is essential in order to control that everything is going well in the cell, reflecting the importance of DNA methylation for cell fitness. Conversely, DNMT1 dysfunctions will result in genome instability (CIN and MIN). Genomic instability is a characteristic of almost all human tumors and it has been suggested that it could not be a simple cancer capability but a feature that triggers all of the others (unlimited replication, deregulated growth signals, metastasis.) [10]. If DNMT1 controls genome stability in different contexts, it could be an important target of cancer cells. Loss of DNMT1 functional integrity or of its regulation could cause genomic instability acquisition/propagation towards malignant transformation. In such a way understanding the fine mechanism(s) by which DNMT1 controls genome stability and is controlled itself would be interesting in order to develop a therapeutic strategy against genome instability on the road to cancer. Future perspective should be to understand if DNMT1 role in replication and repair is a structural or an active one, and/or the cell mechanisms that recognize DNMT1 alteration.

DNMT1 and Microsatellite Instability (MIN)

DNMT1 loss in mouse ES has been correlated with increased microsatellite instability [17,18]. MIN phenotype is the result of impaired DNA Mismatch Repair (MMR) that corrects errors that spontaneously occur during DNA replication. Lot of evidences demonstrated the involvement of DNMT1 in MMR [17-19] through PCNA, probably due to the necessity of methylyating repaired DNA [20]. Recently Ha et al showed that DNMT1 is implicated also in double strand breaks (DSB) repair system by interacting with RAD9 (member of 9-1-1 complex) and being recruited at damaged site [21]. Taken together these results suggest a role for DNMT1 in the direct control of DNA health.

Prospect

DNA needs to be methylated in two moments, during its replication and after repair. In both DNMT1 is a key player not only for its DNA methyltransferase activity, but also for the control of these crucial events. Thus, DNMT1 activity during DNA replication and DNA repair is essential in order to control that everything is going well in the cell, reflecting the importance of DNA methylation for cell fitness. Conversely, DNMT1 dysfunctions will result in genome instability (CIN and MIN). Genomic instability is a characteristic of almost all human tumors and it has been suggested that it could not be a simple cancer capability but a feature that triggers all of the others (unlimited replication, deregulated growth signals, metastasis.) [10]. If DNMT1 controls genome stability in different contexts, it could be an important target of cancer cells. Loss of DNMT1 functional integrity or of its regulation could cause genomic instability acquisition/propagation towards malignant transformation. In such a way understanding the fine mechanism(s) by which DNMT1 controls genome stability and is controlled itself would be interesting in order to develop a therapeutic strategy against genome instability on the road to cancer. Future perspective should be to understand if DNMT1 role in replication and repair is a structural or an active one, and/or the cell mechanisms that recognize DNMT1 alteration.

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