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Review Article

UHRF1-DNMT1 Cooperation in DNA Methylation Maintenance: Mechanistic and Oncogenic Insights

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Abstract

In mammalian cells, faithful propagation of DNA methylation patterns during S phase is crucial for epigenetic inheritance. The functional collaboration between DNA methyltransferase 1 (DNMT1) and ubiquitin-like with PHD and RING finger domains 1 (UHRF1) is central to this process. According to structural research, the SRA domain of UHRF1 licenses maintenance methylation by identifying hemi-methylated CpG sites and extruding the methylated cytosine from the duplex via a base-flipping mechanism. Further research revealed that UHRF1 is a multidomain chromatin integrator rather than just a DNA sensor. Its tandem Tudor domain (TTD), plant homeodomain (PHD), ubiquitin-like domain (UBL), and RING finger work together to couple DNA replication, DNMT1 recruitment, and histone state. This pathway is further refined by ubiquitin sensing by the DNMT1 RFTS region and histone H3 ubiquitylation by UHRF1, which help explain how methylation patterns are replicated with high fidelity following replication. Aberrant UHRF1 expression in cancer is frequently linked to poor clinical outcomes, repression of tumor-suppressor networks, and epigenetic instability, particularly in proliferative epithelial malignancies. The idea that UHRF1 and DNMT1 accumulate in replication foci is supported by earlier reports, including findings in HeLa cells. This is consistent with a replication-coupled maintenance machinery functioning in living cancer cells. The structural logic of UHRF1 function, the mechanistic underpinnings of UHRF1-dependent DNMT1 activation, and the mounting evidence that the UHRF1–DNMT1 axis is both an actionable therapeutic vulnerability and a driver of malignant epigenetic maintenance are all covered in this review.

Keywords: UHRF1, DNMT1, DNA methylation, SRA domain, cervical cancer, epigenetic treatment

1. Introduction

Epigenetic modifications are essential for maintaining genome integrity and cellular identity. A key element of epigenetic memory is DNA methylation. The newly synthesized strand is initially unmethylated during DNA replication, while the parental strand retains methyl marks. This results in hemimethylated DNA, which needs to be restored to its fully methylated state. This replication-linked copying process is essential for maintaining cell identity throughout divisions and forms the basis of mitotic epigenetic inheritance. Epigenetic inheritance during the cell cycle requires precise restoration of chromatin modifications following DNA replication, ensuring stable transmission of gene expression patterns through successive cell divisions [1]. Genome-wide epigenomic mapping studies revealed that DNA methylation patterns are highly cell-type specific and must be precisely maintained to preserve cellular identity [2]. The primary maintenance methyltransferase in this context is DNMT1, but its effectiveness and specificity in chromatin are largely dependent on accessory factors rather than just DNA sequence recognition [3].

For maintenance methylation of DNA to be accurate and efficient, additional regulatory factors have evolved that facilitate the recruitment of DNMT1 to newly replicated DNA. Recent studies confirmed that DNA methylation

marks are faithfully transmitted during mitosis through coordinated action of DNMT1 and its regulatory factors at replication sites [4]. Among these factors, the role of ubiquitin-like with PHD and RING finger domains 1 (UHRF1) has gained significant importance in the regulation of DNA methylation in the context of histone modifications and chromatin structures [5], [6]. UHRF1 possesses multiple functional domains through which it simultaneously interacts with hemi-methylated DNA, histones, and chromatin structures associated with DNA replication [7], [8].

UHRF1 was first identified as ICBP90 and found to be a nuclear protein overexpressed in proliferating and cancer cells [9]. Further studies have shown that UHRF1 plays a crucial role in the regulation of epigenetic inheritance and tumorigenesis through the maintenance of aberrant DNA methylation patterns [10]. High levels of UHRF1 in cancer cells, including HeLa cells derived from cervical carcinoma, play a critical role in the silencing of tumor suppressor genes and stabilization of cancer epigenomes [11], [12].

Another important discovery that revealed the mechanism of maintenance methylation by DNMT1 is the base flipping mechanism mediated by the SRA domain of UHRF1 that enables the selective recognition of hemi-methylated DNA [13], [14], [15]. This mechanism, along with chromatin-dependent regulation and ubiquitin signaling, reveals the precise targeting of DNMT1 to replicated DNA.

2. UHRF1 Structure and Cytosine Base Flipping Mechanism

The protein structure of UHRF1 consists of an N-terminal ubiquitin-like domain (UBL), a tandem Tudor domain (TTD), a plant homeodomain (PHD), a SET- and RING-associated domain (SRA), a polybasic region, and a C-terminal RING finger domain. Fig 1. The protein structure of UHRF1 is crucial for the function of the protein because it enables the protein to act as a chromatin sensor that recognizes the signals of DNA methylation, histone modification, and replication [6], [7].

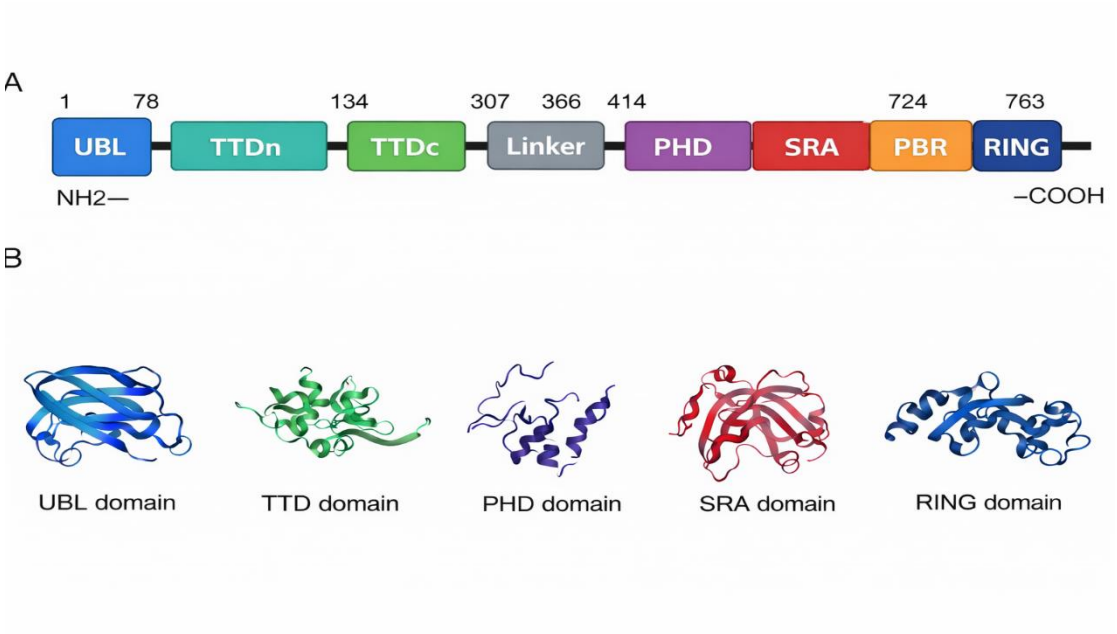

Figure 1. Primary structure of UHRF1 [16].

The spatial structure diagram of UHRF1 domain was obtained from the EMBL-EBI (https://www.ebi.ac.uk/) database (Figure 1). (A) UBL participates in ubiquitination; PHD and TTD are involved in the reading of histone methylation; SRA recognizes hemi-methylated DNA and interacts with DNMT1 and histone deacetylase 1 (HDAC1) and RING has E3 ligase activity. (B) Three-level structure of UHRF1 was illustrated through data obtained from the Protein Data Bank (PDB; http://www.rcsb.org/): UBL has classic α/β folding (PDB; 2FAZ); both TTDn and TTDc of TTD have five strands typical of Tudor family β- folding (PDB; 5×pi); PHD is zinc finger

structure (PDB; 2LGL); on both sides of the SRA are α spiral, the middle is made of β barrel structure formed by folding (PDB: 3BI7); RING has 5 α screw structures (PDB: 3FL2). UHRF1, ubiquitin like with PHD and ring finger domains 1; UBL, N-terminal ubiquitin-like domain; PHD, plant homeodomain; TTD, tandem Tudor domain; SRA, set and ring-associated domain; DNMT1, DNA methyltransferase 1; RING, really interesting new gene domain; PBR, diversity regions.

The interaction between the SRA domain of UHRF1 and DNMT1 contributes not only to maintenance methylation but also to transcriptional regulation of specific genes such as VEGF, highlighting the multifunctional role of UHRF1 in epigenetic control [17]. The SRA domain of UHRF1 plays a crucial role in the maintenance methylation process by recognizing the hemi-methylated CpG sites. The SRA domain recognizes the hemi-methylated CpG sites by flipping the methylated cytosine base out of the helix and into a specific binding pocket [13], [14], [15].

This was confirmed by biophysical experiments that showed the interaction between the SRA domain and DNA was dynamic and sequence-dependent. This supports the view that base flipping is an active rather than passive binding event [18]. Targeting this mechanism has become an attractive strategy for drug discovery. Small molecules that inhibit the base flipping function of UHRF1 have been identified [19], [20].

In addition to the recognition of DNA, the Tudor and PHD domains recognize histone H3 modifications, particularly H3K9 methylation. H3K9 methylation is associated with repressive chromatin [21]. The RING domain of UHRF1 has the capacity to act as an E3 ubiquitin ligase. This allows it to modify histones and establish the appropriate chromatin environment for the recruitment of DNMT1 [22].

Thus, the combination of DNA recognition, histone recognition, and ubiquitination provides the essential role of UHRF1 as the master regulator of epigenetic inheritance.

3. Cooperation Between UHRF1 and DNMT1 in Maintenance Methylation

Maintenance methylation depends on the functional interaction between UHRF1 and DNMT1. Once it binds to hemi-methylated DNA, it recruits DNMT1 to the replication site. This allows the methylation of the newly synthesized DNA strand [23], [8].

One of the crucial mechanisms of the functional interaction between UHRF1 and DNMT1 is the ubiquitination of histone H3 by the RING domain of UHRF1. The monoubiquitination of histone H3 on lysines 18 and 23 provides a binding platform that recruits DNMT1 [22], [24]. Replication factors that also play important roles in the maintenance methylation of DNA include PAF15 and DNA ligase 1 [25], [26].

The activity of UHRF1 is also regulated by conformational changes. Structural studies demonstrated that UHRF1 activity is regulated by intramolecular interactions that control histone binding through allosteric mechanisms, allowing coordinated recognition of chromatin signals [27]. The binding of hemi-methylated DNA or histone ligands induces conformational changes that activate the RING domain of UHRF1 and facilitate the recruitment of DNMT1 [28]. These various modes of regulation ensure that DNMT1 activity is restricted to appropriate genomic locations.

Intramolecular regulation of UHRF1 ensures that its chromatin-binding modules remain inactive until appropriate DNA or histone signals are detected, preventing aberrant methylation activity [29]. Experiments conducted on cancer cells have shown that disruption in the interaction between UHRF1 and DNMT1 results in loss of DNA methylation and thus activation of silenced genes [30], [31]. Association of UHRF1 with methylated H3K9 is essential for proper targeting of DNMT1 to chromatin and ensures accurate maintenance of DNA methylation after replication [32]. These experiments have thus confirmed that UHRF1 is necessary for the maintenance of epigenetic states in proliferating cells.

4. Role of UHRF1-DNMT1 Axis in Cancer and HeLa Cells

Overexpression of UHRF1 has been observed in cancer cells, and it has been associated with hypermethylation of tumor suppressor genes, global methylation, and poor prognosis in cancer patients [33], [34], [35]. UHRF1 thus

maintains methylation patterns in cancer cells, leading to stable silencing of tumor suppressor genes that regulate cell cycle and apoptosis.

In cervical cancer cells, including HeLa cells, UHRF1 is necessary for tumor cell survival. UHRF1 down-regulation in cancer cells results in reactivation of tumor suppressor genes and apoptosis [11], [36], [37]. These experiments have thus shown that cancer cells require methylation maintenance mechanisms to sustain cancer.

The HeLa cell culture model can be used to study the cooperation between UHRF1 and DNMT1. This is because these two proteins are localized in replication foci in S phase, thus showing that there is active methylation machinery in these cells. These findings suggest that the base flipping mechanism and ubiquitin signaling pathway are active in cancer cells, not only in in vitro experiments.

As HeLa cells are derived from cervical carcinoma, they are also a paradigm for understanding how sustained activation of the UHRF1-DNMT1 axis contributes to the maintenance of oncogenic epigenetic states.

5. Therapeutic Perspectives and Conclusion

The key position of UHRF1 as a regulator of maintenance methylation makes it a promising drug target. Several studies have demonstrated that inhibiting UHRF1 expression or activity results in re-expression of tumor suppressor genes and reduced proliferation of tumor cells [36], [38]. Structural studies have identified UHRF1 inhibitors targeting the SRA domain or histone-binding modules, which show that it is possible to pharmacologically target the maintenance methylation machinery [19], [39].

However, it is difficult to discover specific inhibitors of UHRF1 activity as epigenetic enzymes are often pleiotropic. The validation of potential inhibitors is essential to circumvent nonspecific compounds that are common in epigenetic drug screens [40].

In summary, UHRF1 is a multidomain epigenetic integrator that coordinates DNA methylation, histone modifications, and replication-related signals. UHRF1's unique mechanism of action involving a base flipping activity and an ubiquitin-mediated regulation of chromatin is essential for the precise recruitment of DNMT1 to DNA. Because of its central role in maintenance methylation and cancer epigenetics, UHRF1 has been proposed as a promising target for epigenetic therapy. In cancer cells, notably cervical carcinoma cells like HeLa cells, the UHRF1-DNMT1 axis is disrupted to maintain oncogenic epigenetic states. The understanding of UHRF1-DNMT1 cooperativity at a molecular level could provide new opportunities for epigenetic therapy.

Author Contributions

The author contributed to the conceptualization and methodology of the study, prepared, reviewed, and edited the manuscript.

Conflict of Interest

The author declares no competing financial or personal interests.

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Abbreviations

Cytosine–Phosphate–Guanine Dinucleotide (CpG), Deoxyribonucleic Acid (DNA), DNA Methyltransferase 1 (DNMT1), Ubiquitin Ligase Enzyme (E3), Histone H3 Lysine 9 (H3K9), Histone Deacetylase 1 (HDAC1), Human Cervical Carcinoma Cell Line (HeLa), DNA Ligase 1 (LIG1), PCNA-Associated Factor 15 (PAF15), Polybasic Region (PBR), Protein Data Bank (PDB), Plant Homeodomain (PHD), Really Interesting New Gene Domain (RING), Ribonucleic Acid (RNA), SET and RING-Associated Domain (SRA), Tandem Tudor Domain (TTD), Ubiquitin-like Domain (UBL), Ubiquitin-like with PHD and RING Finger Domains 1 (UHRF1), Ubiquitin-specific Protease (USP7).

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