Mechanistic insights into UHRF1-mediated DNA methylation by structure-based functional clarification of UHRF1 domains (Review)

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Abstract. Epigenetic modification is crucial for transmitting genetic information, while abnormalities in DNA methylation modification are primarily associated with cancer and neurological diseases. As a multifunctional epigenetic modifier, ubiquitin like with PHD and ring finger domains 1 (UHRF1) mainly affects cell energy metabolism and cell cycle control. It also inhibits the transcription of tumor suppressor genes through DNA and/or histone methylation modifications, promoting the occurrence and development of cancer. Therefore, comprehensively understanding the molecular mechanism of the epigenetic modification of UHRF1 in tumors will help identify targets for inhibiting the expression and function of UHRF1. Notably, each domain of UHRF1 functions as a whole and differently. Thus, the abnormality of any domain can lead to a change in phenotype or disease. However, the specific regulatory mechanism and proteins of each domain have not been fully elucidated. The present review aimed to contribute to the study of the regulatory mechanism of UHRF1 to a greater extent in different cancers and provide ideas for drug research by clarifying the function of UHRF1 domains.

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Abbreviations: 5mC, 5-methylcytosine; UHRF1, ubiquitin like with PHD and ring finger domains 1; TSGs, tumor suppressor genes; UBL,N-terminal ubiquitin-like domain; TTD, tandem Tudor domain; PHD, plant homeodomain; SRA, set and ring-associated domain; RING, really interesting new gene domain; HAUSP, herpes virus-associated ubiquitin-specific protease; HDAC1, histone deacetylase 1; ERα, estrogen receptors α; PCNA, proliferating cell nuclear antigen; pRb, retinoblastoma gene product; ECReM, epigenetic code replication machinery; CpG, cytosine-phosphate-guanine; hmDNA, hemi-methylated DNA; PI5P, phosphatidyl-5-phosphate; RFT, the replication foci targeting; EGCG, epigallocatechin-3-gallate; E2, ubiquitin-binding enzyme; TQ, thymoquinone; DSG, diosgenin; HIV-1, human immunodeficiency virus type 1; OS, overall survival; PFS, progression-free survival

Key words: ubiquitin like with PHD and ring finger domains 1, epigenetic modification, DNA methylation

Contents

1. Background

During tumorigenesis, abnormalities in key genes and/or epigenetic events always occur in cell metabolism, survival and proliferation. Epigenetic modification refers to genetic changes in gene expression without altering the structure or sequence of DNA. This includes DNA methylation, histone modification, genomic imprinting, X chromosome inactivation and microRNA regulation (1). Among these, DNA methylation and histone modification are the most significant (2). DNA methylation is the process of transferring the methyl group to the C5 position of cytosine to form 5-methylcytosine (5mC). This process typically inhibits gene expression (3). DNA methylation includes two forms: *de novo* methylation and maintenance methylation or hemimethylation. Complete DNA methylation involves three aspects: Recognition, establishment and removal, and requires the cooperation of three molecules (writer, eraser and reader). A number of studies have revealed that ubiquitin like with PHD and ring finger domains

1 (UHRF1) is involved in both *de novo* methylation and maintenance methylation, which is mainly used as a reader to identify the DNA to be methylated and then recruits writers to complete DNA methylation (4), thus inhibiting transcription.

The methylation effect of UHRF1 varies in different types of cancer. DNA methylation of cancer cells (such as non-small cell lung cancer, malignant pleural mesothelioma, endometrial cancer and liver cancer) can be induced by UHRF1 (5-9). By contrast, DNA methylation can also be inhibited by UHRF1 in esophageal squamous cell carcinoma and glioma (10,11). Additionally, UHRF1 has little effect on DNA methylation in retinoblastoma (12). Moreover, a number of studies have reported that UHRF1 is involved in the proliferation of Treg cells (13) and adult vascular smooth muscle cells by methylating promoters of cyclin-dependent kinase suppressor genes (including P21 and P27) (14). It has been revealed that the overexpression of UHRF1 is related to the hypermethylation of tumor suppressor genes (TSGs) in numerous cancers (15-21). In addition to affecting TSGs, UHRF1 can also affect cancer progression in immune, proliferative, apoptosis (including ferroptosis) (22), and other aspects through epigenetic modifications to proteins. A recent study indicated that UHRF1 can affect the immune ability of interferon against tumors by affecting the methylation of cyclic GMP AMP synapse (23). Currently, testing all-natural anticancer compounds involves the downregulation of UHRF1 and the upregulation of TSG expression (24-28). However, numerous regulatory functions of UHRF1 involved in regulation have not been thoroughly studied. Therefore, understanding the molecular mechanism of the epigenetic modification of UHRF1 in tumors will help identify targets for the inhibition of the expression and function of UHRF1, which could thus play an anticancer role.

Generally, the clinical significance of UHRF1 has two aspects. First, it can improve the prognosis and survival rate as a therapeutic target for radiotherapy and chemotherapy (29). Second, it can serve as an effective biomarker for diagnosis, prognosis and survival rate. The present review aimed to comprehensively summarize the role of UHRF1 in DNA methylation by clarifying the functions of its domains to provide convenience for further exploration and clinical treatment of cancers in the future.

2. Structure of UHRF1

UHRF1 is a 90 kDa reverse CCAAT box-binding protein (ICBP90). The *UHRF1* gene consists of 59,075 bases on chromosome 19 (19p13.3). UHRF1 has five main functional domains (Fig. 1): i) N-terminal ubiquitin-like domain (UBL), ii) tandem Tudor domain (TTD), iii) plant homeodomain (PHD), iv) set and ring-associated domain (SRA) and v) really interesting new gene domain (RING) (30). In the methylation process of UHRF1, each domain plays a crucial role. Abnormality in any domain may cause abnormal function of UHRF1, resulting in disease occurrence or phenotypic changes. It has been reported that the PHD and SRA domains are necessary for the maintenance of UHRF1-dependent DNA methylation through mutation of different domains of UHRF1 (31). In addition to methylation, UHRF1 interacts with various proteins, including DNA methyltransferases 1 (DNMT1), herpes virus-associated ubiquitin-specific protease (HAUSP), histone deacetylase 1 (HDAC1), Tip60, heat shock protein 90α family (HSP90), SUV39H1 histone lysine methyltransferase (SUV39H1), proliferating cell nuclear antigen (PCNA) and retinoblastoma gene product (pRb). A macromolecular protein complex called 'epigenetic code replication machinery (ECReM)' is formed through these domains. This complex interacts with each other and participates in the transmission of the epigenetic codes (32).

3. Role and characteristics of UHRF1 domains in DNA methylation

DNA methylation mainly occurs on the 5'-carbon in the cytosine of cytosine-phosphate-guanine (CpG) dinucleotide (33), which varies greatly in different human tissues (34). The maintenance of methylation can be divided into two stages. The first stage is the rapid replication-coupling stage, which occurs within a few min after DNA double-strand bifurcation. This stage is responsible for maintaining more than 80% of hemimethylation. The other is the relatively slow replication-uncoupling stage that occurs later (35), with UHRF1 and DNMT1 involved. This stage mainly consists of five steps and two conformations (Fig. 2).

Step 1. At first, UHRF1 is in a closed conformation: SRA combines with PHD. The diversity region (PBR) between SRA and RING binds to TTD competitively with the linker (but mainly PBR), thus preventing TTD from binding to H3k9me3. However, this state does not hinder the interaction along UBL, RING, and ubiquitin-binding enzyme (E2)-ubiquitin molecules (36).

Step 2. UHRF1 undergoes a conformational change from a closed state to an open conformation in the following three scenarios: i) HAUSP binds to PBR of UHRF1 and hemi-methylated DNA (hmDNA; where only one of the two complementary strands is methylated); ii) SRA binds to hmDNA and iii) phosphorylation of S651 by phosphatidyl-5-phosphate (PI5P) leads to the release of the PBR's binding to TTD, allowing TTD to bind histone with the PHD domain and linker (37). Since the concentration of PI5P is different in the G1 and S phases, the localization of UHRF1 in chromatin in the cell cycle can be determined by analyzing the concentration of PI5P (38).

Step 3. In the open state, TTD-PHD binds to H3K9me2/3, UBL and histone H3 ubiquitinated by RING, and then UHRF1 recruits DNMT1 (39) in a cell cycle-dependent manner (40-42) and relieves the autoinhibitory activity of DNMT1 (37). In addition, UBL and SRA also recruit DNMT1, releasing its catalytic domain. Moreover, H3K27me3 can affect DNA methylation by inhibiting UHRF1-mediated H3 ubiquitination in this process (43).

Step 4. The binding of the replication foci targeting (RFT) domain of DNMT1 with two monoubiquitinated histones H3 disrupts the interaction between RFT and its C-terminal catalytic domain, resulting in the conformational change of DNMT1, allowing hmDNA to enter the catalytic center and undergo DNA methylation. It is also considered that DNMT1 is unlikely to dissociate and bind repeatedly from UHRF1 or the UHRF1 complex during methylation modification of multiple methylation sites of hmDNA. Otherwise, the time for UHRF1 to recruit DNMT1 will be too long. Therefore,

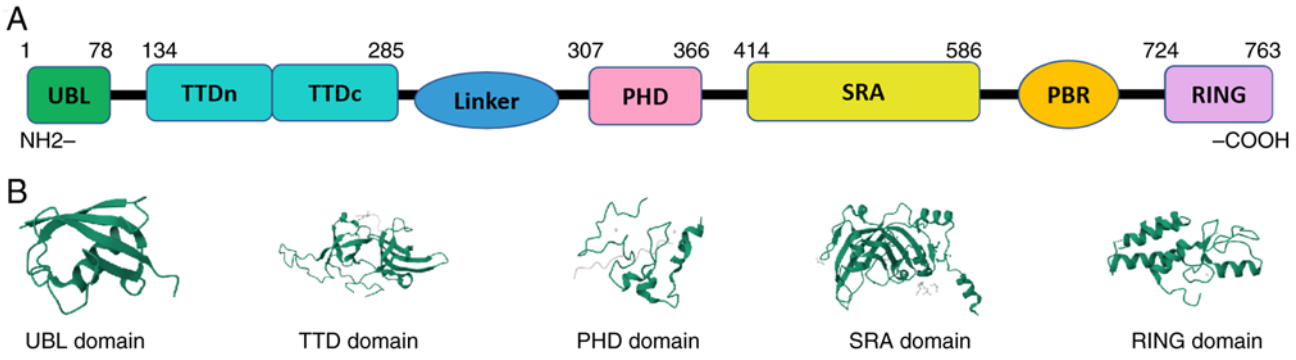

Figure 1. Primary structure of UHRF1. The spatial structure diagram of UHRF1 domain was obtained from the EMBL-EBI (https://www.ebi.ac.uk/) database. (A) UBL participates in ubiquitination; PHD and TTD are involved in the reading of histone methylation; SRA recognizes hemi-methylated DNA and interacts 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; https://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; 5xpi); 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.

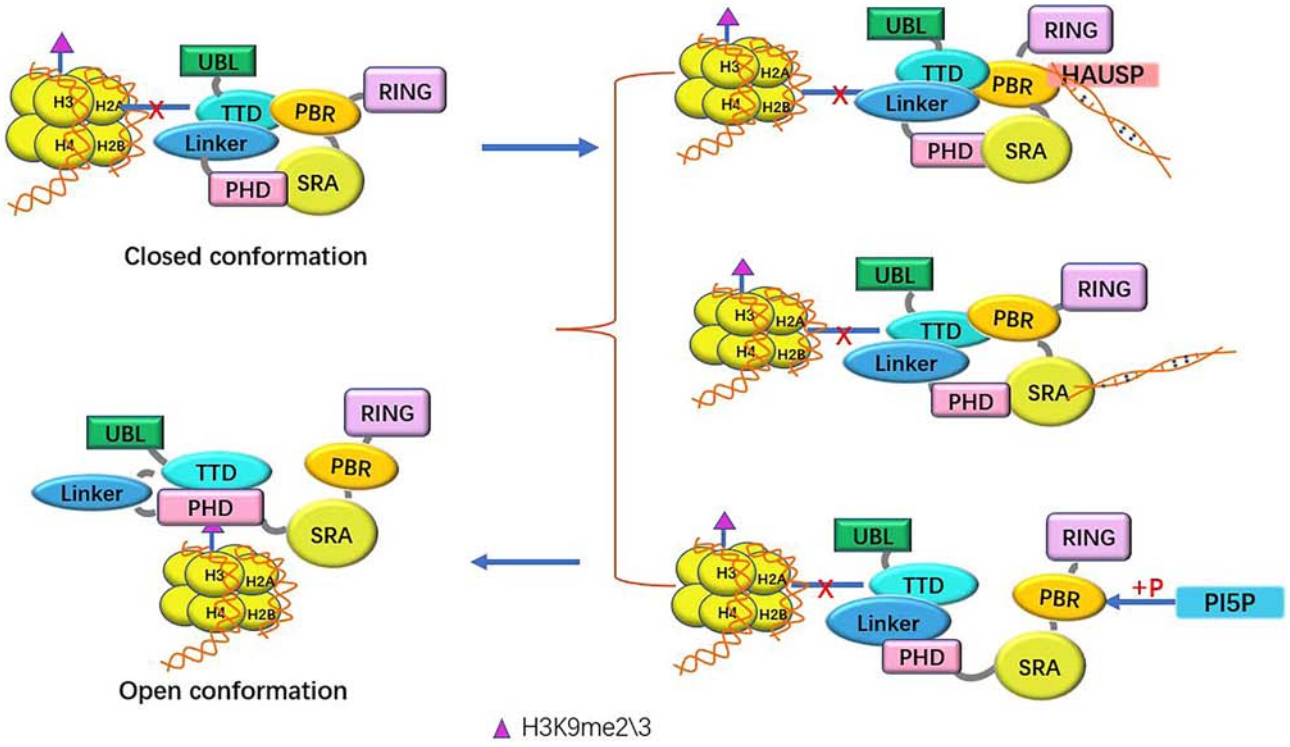

Figure 2. Methylation of UHRF1. UHRF1 changes from closed conformation to open conformation, then RING domain ubiquitinates H3 with UBL, SRA binds 5-methylcytosine, TTD and PHD bind methylated H3K9 to recruit DNMT1. After methylation modification, HAUSP deubiquitinates and DNMT1 dissociates. UHRF1, ubiquitin like with PHD and ring finger domains 1; RING, really interesting new gene domain; UBL, N-terminal ubiquitin-like domain; SRA, set and ring-associated domain; TTD, tandem Tudor domain; PHD, plant homeodomain; HAUSP, herpes virus-associated ubiquitin-specific protease; DNMT1, DNA methyltransferases 1; PBR, diversity regions; PI5P, phosphatidyl-5-phosphate; P, phosphorus.

Bronner *et al* (33) proposed a new possibility that a macromolecular complex with DNMT1 formed after recruitment. The complex slides along the newly synthesized DNA for DNA replication and modification, controlled by the semi-methylation state of DNA. If hmDNA is not encountered, the SRA domain may not interact with the RFT sequencing (RFTS) domain of DNMT1, as DNMT1 has no enzymatic activity and abnormal DNA methylation will not occur. At the same time, the two combination methods can be used as a double check or double lock to ensure the fidelity of methylation map transmission. However, there is no clear and recognized binding mode, which needs to be confirmed through the interaction between the two protein structures and *in vitro* experiments (33).

Step 5. HAUSP removes the ubiquitin labeling from histone H3 in the synthesized intact methylated DNA region after DNA methylation modification. DNMT1 dissociates from ubiquitinated histone H3 and repeats the process when it encounters new hmDNA sites (44).

In the replication coupling stage of DNA methylation, the arginine binding cavity of the TTD domain of UHRF1 can recognize the guanidine group in the Arg121 side chain of DNA ligase 1 (LIG1), which helps the TTD domain to be recruited to the replication site through the Lys126 di/trimethylation (45-47) on LIG1. Subsequently, UHRF1 monoubiquitinates Lys15 and Lys24 of the PCNA-associated factor 15 (PAF15) (48,49). PAF15 with double monoubiquitin recruits DNMT1 into the new replication chain (50). Afterwards, PAF15ub2 may be deubiquitinated by HAUSP in two cases: i) One case is the dissociation of UHRF1 from chromatin after the semi methylated DNA is converted to fully methylated DNA. The second case is the binding of DNMT1 to semi methylated DNA, which induces conformational changes in USP7 or PAF15ub2, although the mechanism is not yet fully clear (51). The two modes of methylation complement each other and work together to maintain the stable inheritance of epigenetic information.

TTD domain. TTD Domain includes two subdomains: i) TTDn and ii) TTDc. The aromatic structures constructed by F152, Y188 and Y191 in TTDn residues recognize dimethylated and trimethylated lysine residues (H3K9me2/me3). During DNA methylation, TTD and PHD domains read histone code information and transmit it to the SRA domain, allowing the SRA domain to flip methylated cytosine out of the DNA double-strand to locate the CpG site that needs to be methylated. The combination of H3K9me2/me3 and LIG1 lysine 126 dimethylation (LIG1K126me2) with UHRF1 may not play a vital role in maintaining DNA methylation (52). However, a previous study demonstrated that the arginine binding cavity in the TTD domain is crucial for the interaction of LIG1. A specific inhibitor, 5-amino-2,4-dimethylpyridine, was developed to target the Arg binding cavity. This inhibitor binds with the Arg binding cavity and effectively inhibits the binding of LIG1 and UHRF1 (53).

In addition, there is a number of studies targeting the tight binding between TTD and H3K9me2 or H3K9me3, screening and optimizing the small molecule antagonist, NV01, that disrupts this binding. This has significant reference value for studying drugs that target the structural domain (54). In addition, a recent study indicated that TTD prefers binding to histone H3 tails containing K4me1 in the context of H3K9me2/3. Moreover, the H3K4me1-K9me2/3 specific binding of UHRF1-TTD to enhancers and promoters of transcription factor binding sites downregulates these genes (55).

PHD domain. As one of the most common families of chromatin reader domains, the PHD finger domain has a shallow acidic groove used to identify the N-terminal of the ligand. Recognition of the K4 methylation state of the H3N terminal tail is a relatively stable and common recognition pattern in the PHD family (56-58). TTD/PHD tandem module can stimulate H3K9 methyltransferase (H3K9MT) and methylate adjacent H3K9 of adjacent nucleosomes. During this process, UHRF1-related inhibitory complexes (including DNMT1, H3K9MT, PCNA and HDAC1) may play a synergistic role (59,60), while the phosphorylation of H3 threonine 3, symmetric or asymmetric demethylation of H3R2, and acetylation of H3A1N terminal may disrupt this binding (61).

In addition, the combination of H3K9me3 with TTD-PHD also leads to a conformational change of TTD-PHD. However, this conformational change does not affect its ubiquitination activity or binding affinity with semi-methylated DNA. The potential function of this conformational change requires further studies (62). Moreover, the combination of PHD and H3 could affect the combination of TTD and H3. When the PHD domain mutates (mainly D334) or the N-terminal of H3 is modified, the PHD separates from the H3 tail, thereby disrupting or weakening the binding of TTD and methylated H3K9. Conversely, TTD mutation or histone modification (such as H3K4me3) does not affect the interaction between PHD and the unmodified H3 N-terminal (62-65). This indicates that PHD is the critical domain to identify H3, which is also consistent with the aforementioned situation of TTD (66).

Previous studies have shown that the C-terminal region of Stella (also known as Dppa3/PGC7) competitively inhibits the binding of UHRF1 to H3K9me3 by binding to the PHD domain of UHRF1, thereby damaging the DNA methylation function of UHRF1. In addition, Stella can also inhibit DNA methylation by antagonizing UHRF1 activity and isolating UHRF1 from the nucleus. Disrupting Stella's interaction with UHRF1 may be a new potential direction for developing UHRF1-targeted drugs (56,67).

SRA domain

Role of SRA domain in epigenetic modification. In the process of DNA methylation modification involved in UHRF1, SRA binds to PHD, which inhibits PHD from recognizing H3R2 and keeps UHRF1 in a closed state. SRA has a high affinity and specificity for hmDNA and could be released from PHD when hmDNA exists. SRA binds to unmethylated cytosine in hmDNA through N489 in the NKR finger (483-496 residues, named after the abbreviation of asparagine, lysine and arginine) (41,68,69) and converts UHRF1 into the open state. Previously, some experiments pointed out that NKR combines with cytosine to stimulate DNA deformation and turn out cytosine instead of SRA directly (68).

P300/CBP-related factor, which is located in the NKR of the SRA domain, and HDAC1 can acetylate and deacetylate UHRF1 at K490, respectively. Acetylated UHRF1 hinders the binding of UHRF1 to hmDNA and the methylation modification of DNA, while the effect of deacetylated UHRF1 is the opposite. This indicated that abnormal DNA methylation can be eliminated by inducing the acetylation of UHRF1 in some types of cancer, thus becoming a treatment option in cancer therapy (70).

SRA can interact with HDAC1 in the methylation promoter region of some TSGs (15,71,72), including p16INK4a and p14ARF (also known as mouse p19ARF). In addition, studies have shown that SRA can also impact the expression of TSGs by altering their acetylation. For example, the SRA domain interacts with the histone acetyltransferase domain of KAT7, partially inhibiting the acetylation of H3K14 on the TUSC3 gene promoter mediated by KAT7, thereby inhibiting the expression of TUSC3 and affecting the proliferation of colon cancer cells (73). A recent study demonstrated that the SRA domain may also affect ubiquitination modification. The SRA domain of UHRF1 binds with the AF2 domain of estrogen receptors α (ERα), thereby suppressing K48 ubiquitination in ERα and enhancing its stability. This provides a new idea for

the treatment of breast cancer (74). SRA has varying effects on different genes in different cancers, therefore further research on SRA is needed for targeted cancer treatment.

Role of SRA as a cancer-targeting drug. SRA domain is the unique domain of UHRF1 and UHRF2 (32). Therefore, a compound targeting the SRA domain will be a specific inhibitor for UHFR1, such as chicoric acid (75), uracil derivative NSC232003 (71) and epigallocatechin-3-gallate (EGCG). EGCG can downregulate UHRF1 and DNMT1, reverse the methylation of tumor suppressor p16INK4a and induce cell cycle arrest and apoptosis in Jurkat cells (24). The anthraquinone compound UM63 (an inhibitor of this process) performs the role of 5mC in DNA methylation. UM63 can merge with a 5mC binding pocket to inhibit the base reversal process and reduce the overall DNA methylation by damaging the UHRF1/DNMT1 interaction (76).

Based on the UM63 structure, some studies have identified new inhibitors of UHRF1-SRA, such as AMSA2 and MPB7, using multidisciplinary methods. Similar to UM63, they can inhibit SRA-mediated base flipping at low concentrations but do not intercalate into DNA. These inhibitors prevent the involvement of UHRF1 and DNMT1 in DNA methylation. In addition, because they prioritize affecting cells with high levels of UHRF1, they will reduce damage to normal cells (77). Another inhibitor targeting the SRA domain, UF146, has been shown to effectively eradicate leukemia-initiating cells, confirming the potential of UHRF1 inhibitors in cancer treatment (78). However, due to UF146 being a pan-assay interference compound (79), its specificity is not high, and it may have unpredictable reactions with numerous biological targets, resulting in false positive results (80). Through molecular docking, molecular dynamics simulation and toxicity analysis, other inhibitors targeting the SRA domain can also be screened, such as chicoric acid. However, the specific therapeutic effects and indications require extensive experiments for further verification and screening (75).

UBL domain. UBL domain is also known as the N-terminal of a novel Np95/icbp90-like ring finger protein, which is the target of single- and multi-ubiquitination (81). Some studies have proved that UHRF1 cannot play its role in DNA methylation modification without the UBL domain (47,82,83). This highlights the two crucial functions of UBL in DNA methylation inheritance (47): i) Cooperating with the RING domain to ubiquitinate histone H3, recruiting the ubiquitin-binding enzyme E2 to form a stable E2/ubiquitin ligase E3 /chromatin complex. Subsequently, ubiquitin is transferred from E2 to histone H3 (this binding is universal, meaning that other proteins containing the UBL domain can also occur); ii) UBL recruits DNMT1 into chromatin through a hydrophobic patch and enhances DNMT activity by binding to DNMT1-621 (amino acids: 621-1,616) (47,82,83).

RING domain. RING Domain has ubiquitin ligase activity, including ubiquitination of UHRF1 itself. UHRF1 protects itself from ubiquitination by interacting with HAUSP (69). The natural compound thymoquinone (TQ) eliminates the protective effect on UHRF1 by reducing the expression of HAUSP, leading to the ubiquitination of UHRF1 under the action of ubiquitin ligase, reactivating TSG, inhibiting cell proliferation, promoting cell cycle arrest and inducing apoptosis (84). TQ can selectively induce the degradation of UHRF1 in cancer cells without affecting its expression level in normal cells (85). In addition to TQ, a recent study has observed that diosgenin (DSG) induces the dissociation of UHRF1 and HAUSP protein complexes by directly binding to UHRF1, inhibiting the protective effect of HAUSP to UHRF1, thereby reducing the expression of UHRF1 and increasing the expression of TSGs. However, the specific binding sites between DSG and UHRF1 are not clear, and the effect of DSG needs to be achieved at high drug concentrations (86). Therefore, further research is needed.

As a ubiquitin ligase, RING ubiquitinates the target genes of DNMT1, which are histone H3Lys23 and Lys18 (87,88). The ubiquitin ligase activity of the RING domain is crucial for the growth of tumor cells, and inhibitors targeting this activity may be a method to produce anticancer drugs (16). In addition to tumor cells, a previous study indicated that the RING domain can interact with the human immunodeficiency virus type 1 (HIV-1) protein Tat, which is involved in virus replication, thus promoting the ubiquitination degradation of Tat, inhibiting HIV-1 transcription and maintaining HIV-1 latency (89).

Linker domain. In the methylation modification involving UHRF1, the linker replaces the H3 tail in the TTD peptide binding tank so that the H3 tail connects PHD at the N-terminal and the TTD domain at K9me3. The two arginine and one lysine of the linker residue (R295-R296-K297) are essential to stabilize this TTD-PHD conformation (64,65). Additionally, phosphorylation of S298 in linker can change the interaction between UHRF1 and H3, potentially serving as a functional switch for UHRF1 and participating in a variety of regulatory pathways, including DNA methylation maintenance, transcriptional inhibition and cell cycle progression (17). *In vitro* studies have confirmed that PIM1, an essential regulatory factor of aging, can regulate the function of UHRF1 through Ser311 phosphorylation. This regulation inhibits the binding of TTD-PHD to H3K9me3, thereby affecting the activation of DNMT1 and triggering DNA hypomethylation (90).

PBR domain. PBR Domain has five kinds of functions: i) It binds to TTD in the closed state of UHRF1, inhibiting its interaction with H3K9me3; ii) it promotes the recognition and binding of SRA and hmDNA; iii) it enhances the interaction between RFTS of DNMT1 and SRA (36); iv) it interacts with the UBL1 and UBL2 domains of HAUSP, keeping UHRF1 in the open state and facilitating the binding of UHRF1 to H3K9me3 (65,91,92); and v) it binds to PI5P, opening the closed conformation of UHRF1 and increasing the affinity of H3K9me3 for TTD (38). All domains of UHRF2 and UHRF1 have a very high sequence similarity, except for pRb (93). This may be why UHRF2 cannot replace UHRF1 to maintain DNA methylation (94).

4. Expectation

Targeting the highly expressed oncoproteins or genes is a novel approach to anticancer drugs research (66). As a multifunctional epigenetic modifier, UHRF1 has significant differential expression between tumor and normal tissues and is a potential

cancer treatment target. Overexpression of UHRF1 can silence TSGs, inhibit DNA repair and apoptosis and promote tumor growth and migration. Conversely, the deletion of UHRF1 leads to DNA demethylation and histone acetylation, which promotes tumor cell apoptosis and inhibits tumor proliferation and invasion through TSGs reactivation and DNA repair (44).

Moreover, the expression of UHRF1 was an independent factor affecting overall survival (OS) and progression-free survival (PFS) (OS, P=0.038; PFS, P=0.014) (95). A previous study reported that patients with elevated UHRF1 levels had lower OS and PFS (96). The high expression of UHRF1 may also be related to tumor size, stage and metastasis (97). It has been reported that UHRF1 can be used as a cancer diagnostic tool, stem cell marker and therapeutic tool (98). With the progress of research on the function and mechanism of UHRF1 in cancer, the clinical research on UHRF1 will be more extensive and profound.

There are three directions of targeted drugs for UHRF1. One direction aims for the complex composed of UHRF1, such as DNMT1, HDAC1 and HAUSP in ECReM. For example, combining UHRF1 and low-dose DNMT inhibitors can effectively reduce DNA methylation and reactivate TSGs (99). Due to the expression level of UHRF1 in all normal tissues being 5-70-fold lower than that of HDAC1 and DNMT1, the side effects of UHRF1 inhibitors are moderate compared with current HDAC and DNMT inhibitors. This can help reduce the tolerance of the patients to DNMT inhibitors. In addition, a previous study revealed that loss of UHRF1, combined with HDAC inhibition, can reactivate TSGs and inhibit the proliferation of colorectal cancer cells (100). The second direction is targeted at UHRF1 domains. Since UHRF1 has multiple functional domains, it is necessary to clarify the function of each domain to determine which of the several domains can achieve sufficient tumor inhibition effect (66). At present, the regulation mechanism of UHRF1 has been detected in a variety of cancers (40), which plays an enlightening role in clinical treatment, especially in personalized therapies. The last method is to indirectly inhibit the expression of UHRF1 by affecting the upstream molecules. For example, in prostate cancer, especially in cases that are resistant to abiraterone, UHRF1 and p-AKT are abnormally overexpressed. AKT phosphorylation inhibitor MK2206 can induce the degradation of UHRF1 protein, thereby increasing the expression of epigenetic silenced TSGs (such as p21), and reducing the typical biomarkers of neuroendocrine prostate cancer in prostate neuroendocrine carcinoma, SYP and NCAM1, thereby improving the therapeutic effect of abiraterone on tumors (101). The present review aimed to provide ideas for drug research and direction for the functional identification of other proteins with similar structures by clarifying the function and regulatory pathway of UHRF1 domains.

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Authors' contributions

YZ conceptualized the study and approved the final version of the manuscript. YS made substantial contributions in writing the original draft. HL responded to the questions raised by the reviewers, made systematic revisions to the article, and gave the final approval of the version to be published. QX, CG and MX were mainly involved in the interpretation of the data through the figures. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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