Signalling pathways in UHRF1-dependent regulation of tumor suppressor genes in cancer

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Abstract

Epigenetic silencing of tumor suppressor genes (TSGs) through DNA methylation and histone changes is a main hallmark of cancer. Ubiquitin-like with PHD and RING Finger domains 1 (UHRF1) is a potent oncogene overexpressed in various solid and haematological tumors and its high expression levels are associated with decreased expression of several TSGs including p16^INK4A, BRCA1, PPARG and KiSS1. Using its several functional domains, UHRF1 creates a strong coordinated dialogue between DNA methylation and histone post-translation modification changes causing the epigenetic silencing of TSGs which allows cancer cells to escape apoptosis. To ensure the silencing of TSGs during cell division, UHRF1 recruits several enzymes including histone deacetylase 1 (HDAC1), DNA methyltransferase 1 (DNMT1) and histone lysine methyltransferases G9a and Suv39H1 to the right place at the right moment. Several in vitro and in vivo works have reported the direct implication of the epigenetic player UHRF1 in tumorigenesis through the repression of TSGs expression and suggested UHRF1 as a promising target for cancer treatment. This review describes the molecular mechanisms underlying UHRF1 regulation in cancer and discusses its importance as a therapeutic target to induce the reactivation of TSGs and subsequent apoptosis.

Keywords: Epigenetic, DNA methylation, p16^INK4A, p53, p73, Tumor suppressor genes, UHRF1,

Background

Beside genetic alterations in cancer cells, epigenetic changes (DNA methylation and histone modifications) can also induce silencing of tumor suppressor genes allowing cancer cells to escape apoptosis and promote tumor progression [1–4]. The epigenetic reader UHRF1 (Ubiquitin-like, containing PHD and RING Finger domains 1), an oncogene overexpressed in various human cancer cells is one of the major players involved in apoptosis inhibition by inducing epigenetic silencing of TSGs [5–8]. UHRF1 has several functional domains (Fig. 1): UBL (ubiquitin-like) domain, TTD (Tandem Tudor Domain), PHD (Plant Homeo Domain) domain, SRA (Set and Ring Associated) domain and RING (Really Interesting New Gene) domain. Through these domains, UHRF1 interacts with various proteins, forming a large macro-molecular protein complex called ECREM « Epigenetic Code Replication Machinery », which is engaged in the transmission of the epigenetic code including the silencing of TSGs, from a mother cancer cell to daughter cells during cell proliferation [5, 6]. By its original structure, UHRF1 might be the driver of this complex to ensure the replication of the epigenetic code (DNA methylation and histone code) after DNA replication, allowing cancer cells to conserve the silencing of TSGs during cell division. The SRA domain of UHRF1 behaves as a “hand” with two fingers that serve to flip out the methylated cytosine with subsequent recruitment of DNMT1 to methylate the cytosine of the newly synthetized DNA strand [9–11]. This recruitment was proposed to be under the control of SRA binding to hemi-methylated DNA, challenging enhanced activity of the UHRF1 RING finger that exhibits E3 ligase activity towards histone H3 [12, 13]. The TTD
exhibits affinity for methylated histones and allows to confer a fabulous property to UHRF1 of connecting DNA methylation to histone modifications [14, 15]. Recently, new insights have been gained into the mechanism of this connection. Indeed, Fang et al., showed how UHRF1 can coordinate histone modifications and hemi-methylated DNA [16]. UHRF1 adopts a closed conformation, in which a spacer located in the C-terminal region of UHRF1 binds to the TTD and thus hinders this latter from H3K9me3 binding [16]. The SRA domain binds to the PHD and inhibits this latter from H3R2 recognition. In the presence of hemi-methylated DNA, the intramolecular interactions were impaired thanks to a preferred affinity for hemi-methylated DNA vs PHD domain. Subsequently, H3K9me3 recognition by TTD–PHD is facilitated and thus is supporting a crucial role for UHRF1 in connecting DNA methylation with histone post-translational modifications. The close conformation has been recently proposed as being regulated by phosphatidyl-5-phosphate [17], a small molecule involved in cell signaling and cell traffic [18]. The authors suggested that phosphatidyl-5-phosphate, since its concentration is varying from G1 to S phase, might determine the localization of UHRF1 in chromatin during the cell cycle [17]. Consistently with these studies, the contribution of UHRF1 to the interconnection between DNA methylation and histone methylation has been further deciphered by a new study, which supports a model in which H3K9 methylation recognition, through the TTD domain, while not essential, promotes DNA methylation maintenance [19].

Recently, new highly interesting functions were uncovered for UHRF1. One of the most interesting is a sensor role for interstrand crosslinks, showing that UHRF1 is also involved in DNA repair processes [20–22]. Of note, it was also shown that the decrease of UHRF1 protein levels is a major cause of DNA demethylation in embryonic stem cells [23]. Therefore, UHRF1 appears to have a triple role during cell proliferation, i.e., in DNA methylation pattern inheritance, sensor of DNA crosslinks and a facilitator of DNA demethylation during development. It is thus easily conceivable that a dysregulation of one or more of these functions may lead to genomic alteration and thus to cancer.

Considering the fact that UHRF1 is overexpressed in various solid [5, 24] and haematological tumors [25, 26] and that UHRF1 via its domains (Fig. 1) guarantees a strong relationship between DNA methylation and histone post-translational changes [5, 6, 27, 28], targeting this epigenetic actor could be a new promising anticancer strategy. In this review, we highlight the role of UHRF1 in the epigenetic silencing of TSGs and the molecular mechanisms underlying UHRF1 regulation in cancer cells as well as the increasing importance of UHRF1 as a promising target for anticancer therapy.

**Role of UHRF1 in the epigenetic silencing of TSGs in cancer**

Several TSGs, among which p16INK4A seems to be the most interesting, were shown as being silenced through UHRF1-mediated epigenetic modifications, mainly DNA methylation [6, 29]. The tumor suppressor gene p16INK4A is involved in the G1/S cell cycle checkpoint and its lost expression leads to apoptosis inhibition, enhanced cell proliferation and loss of cell contact inhibition. UHRF1 uses its functional domains to exert epigenetic inhibitory effects on TSGs including p16INK4A [30–32]. Indeed, one of the most important features of UHRF1’s structure, is the presence of an intriguing “Set and Ring Associated” domain (SRA), which is found only in the UHRF family [5]. Using its SRA domain, UHRF1 interacts with histone deacetylase 1 (HDAC1) and DNMT1 [7, 31, 33]. This interaction takes place at methylated promoter regions of several TSGs including p16INK4A, p14ARF (known as p15ARF in mouse), both...
encoded by the CDKN2A gene [34], and RARalpha [7]. However, to our knowledge no data are so far available in the literature about the consequence on p14ARF and RAR protein levels [7]. Interestingly, UHRF1 depletion resulted in DNMT1 downregulation and an upregulation of p16INK4A [31]. In the same context, we have shown that the natural anti-cancer drug, epigallocatechin-3-gallate (EGCG) induces a significant decrease in UHRF1 and DNMT1 expression in Jurkat cells in association with p16INK4A upregulation, cell cycle G1/S arrest and apoptosis [32]. The EGCG-induced p16INK4A upregulation was related to a significant decrease in UHRF1 protein binding to p16INK4A promoter [32]. Interestingly, wild type UHRF1 overexpression, but not SRA UHRF1 mutants, was able to decrease p16INK4A expression indicating that UHRF1 negatively controls the expression of p16INK4A in leukemia cells [32]. It appears that p16INK4A upregulation through a UHRF1 downregulation is a key mechanism of many natural drugs exhibiting anti-cancer properties [9, 29, 32].

UHRF1 was also shown to be overexpressed in colorectal cancer (CRC) and its overexpression is associated with CRC progression [35]. In this type of cancer, UHRF1 knockdown induced an upregulation of p16INK4A, inhibition of cell proliferation and metastasis as well as apoptosis [35]. UHRF1 was also shown to be overexpressed in primary non-small cell lung cancer (NSCLC) and its high expression level was associated with an increase in the expression of DNMT1, DNMT3A, and DNMT3B and correlated with hypermethylation of p16INK4A promoter [36]. In accordance with this, enhanced UHRF1 expression was also reported in gastric cancer (GC), and correlated with tumor progression [37]. Again, UHRF1 depletion induced the reactivation of several TSGs, including p16INK4A, and led to cell proliferation inhibition [37]. Recently, we showed that activation of CD47 in two human astrocytoma cell lines, upregulated the expression of UHRF1 with subsequent downregulation of p16INK4A [38]. All these studies support the existence of a common mechanism in cancer that UHRF1 regulates the expression of p16INK4A with subsequent inhibition of the apoptotic pathways. It is also noteworthy that UHRF1 regulates a plethora of other TSGs among which RB1 especially in Jurkat and osteosarcoma cells [31, 39, 40], CDX2, CDKN2A, RINX3, FOXO4, PPARG, BRCA1 and PLM, in gastric cancer [37], SOCS3 and 3OST2 in endometrial carcinoma [41] as well as BRCA1 in cancer breast cell lines [42].

The overall well admitted mechanism of tumor suppressor gene silencing is thought to be DNA methylation as almost all promoters of TGS regulated by UHRF1 are hypermethylated. Note that UHRF1 is also able to silence, in DNA methylation dependent process, KiSS1, a gene known to have anti-metastasis functions [43]. However, it has not to be neglected that other mechanisms might be involved such as histone post-translational modifications. Indeed, considering that UHRF1 has several histone modifiers as partners, all these may putatively exert a contribution in the definitive interlocking of TSGs. For instance, UHRF1 has been shown to recruit histone lysine methyltransferase G9a to the BRCA1 promoter and with subsequent histone 3 lysine 9 methylation [42]. In another study, it has been reported that UHRF1 associates with PRMT5 (Protein arginine N-methyltransferase 5) in endometrial carcinoma [44]. In the same study, it has been shown that the promoters of TSGs CH13 and SHP1 were hypermethylated but whether there is a link between the activity of PRMT5 and TSGs silencing still remains elusive. But if it is the case, it would mean that UHRF1, by recruiting PRMT5 to the TSGs promoters, favors the participation of the dimethylation of arginine 8 of histone H3 (H3R8me2) and arginine 3 of histone H4 (H4R3me2) to gene silencing of TSGs ST7 and RBL2 [45]. Whilst these possibilities cannot and should not be discounted, it is worth pointing out that the complexity of UHRF1-dependent TSGs regulation might be as directly proportional to the size of the macromolecular UHRF1 complex.

One important member of this macromolecular complex is USP7 (Ubiquitin Specific Peptidase 7) or HAUSP (Herpes virus-Associated Ubiquitin-Specific Protease). HAUSP has been reported to regulate several TSGs, including p53 [46]. The deubiquitinase HAUSP was shown to interact with UHRF1 to maintain its deubiquitination status protecting it from autoubiquitination and degradation by the proteasome [47–49]. Overexpression of HAUSP increased UHRF1 level while HAUSP down-regulation induced UHRF1 ubiquitination causing its degradation via a proteasome-dependent process [48]. These findings indicate that HAUSP acts as a UHRF1 protector from autoubiquitination-mediated degradation using RING domain [48]. Recently, it has been shown that HAUSP controls the stability of UHRF1 not only by maintaining its deubiquitination, but also by promoting its chromatin association [50]. Indeed, HAUSP was shown to reduce the E3 ligase activity (autoubiquitination) of wild-type UHRF1 but not in the UHRF1 K659E mutant, disturbing the UHRF1 domain involved in its interaction with HAUSP [50]. Interestingly, HAUSP interaction with UHRF1 facilitated its binding to the H3K9me3 and induced a significant increase in its association with chromatin in the cervical cancer cell line Hela-60 [50]. Taken together, these data show that HAUSP has a dual regulatory role of UHRF1, by protecting it from autoubiquitination (Fig. 1) and by facilitating its association to the chromatin through the readout of the histone code. Therefore, HAUSP tandem may control TSGs expression via UHRF1 mediated by a ubiquitination/deubiquitination balance and might be further considered...
as a key mechanism involved in controlling cell proliferation and apoptosis [51].

A regulatory influence on TSGs by UHRF1 might also be mediated independently of DNA methylation, for instance through an enzymatic partner. Indeed, it has been demonstrated that UHRF1 inhibits the interplay between Tip60 and p53 [52]. Tip60, an essential partner of UHRF1 [53], acetylates p53 at K120 to induce apoptosis [54]. It was suggested that increased expression of UHRF1 found in cancer might be responsible for decreased activity of p53 and apoptosis failure in tumors [52].

All these findings indicate that UHRF1 is a main key in the epigenetic silencing of various TSGs in cancer. So, understanding the molecular mechanisms underlying UHRF1 overexpression in cancer will help to find new targets to inhibit UHRF1 expression which will allow cancer cells to undergo apoptosis through the reactivation of silenced TSGs. In other words, the goal would be to re-express TSGs in cancer cells to allow them to commit “suicide” via a re-activation of the apoptotic pathways.

**Signalling pathways involved in UHRF1 regulation in cancer cells**

**Role of TSGs in UHRF1 regulation**

The tumor suppressor gene p53 is involved in controlling cell cycle at G1/S transition ensuring a successful cell division [55, 56]. p53 is silenced in 50 % of human cancers causing loss of cell cycle G1/S checkpoints which allows cancer cells to escape apoptosis [57–59]. In contrast to p53, p73, a p53 functional and structural homolog [60], is rarely mutated in cancer [61]. UHRF1 has been shown to be targeted by TSGs such p53 and p73 [62–64] suggesting that UHRF1 overexpression observed in many human cancer could result from abnormal TSGs expression or from non-functional TSGs. We have shown that thymoquinone (TQ) triggers apoptosis in the p53-deficient Jurkat cell line through the activation of p73 [63]. Interestingly the depletion of p73 in TQ-treated cells prevented UHRF1 from TQ-induced degradation, indicating that p73 negatively controls the expression of UHRF1 [63]. In the same context, UHRF1 expression was shown to be decreased by p53 upregulation as a response to anticancer drugs-induced DNA damage [62]. Taken together, these findings suggest that UHRF1 expression levels observed in cancer could result from defects in the expression of some TSGs such as p53 and p73. Thus, UHRF1 is regulated by TSGs expression but by a feed-back mechanism can also control the activity of TSGs.

**Regulation of UHRF1 by miRNA**

microRNAs (miRNAs: 18–25 nucleotides) are considered as negative regulators for several genes at the post-transcriptional level [65, 66]. These small noncoding RNAs exert their action by binding to the 3′-untranslated region (3′-UTR) of their target mRNA resulting in degradation of mRNA from more than 60 % of human genes [67–69]. Depending on the cellular function of miRNAs targets, these molecules could be either an oncogene or a tumor suppressor gene [70]. Moreover, several studies revealed a strong relationship between many cancers and either mutations or abnormalities in miRNAs expression [70, 71]. In this context, it has been shown that miR-206 acts as a tumor suppressor able to inhibit the expression of both oncogenes c-Met and Bcl2, that are overexpressed in various cancers including lung cancer [72]. miR-720 expression was shown to be significantly reduced in acute myeloid leukemia (AML) patients compared to normal controls, while its overexpression induced an upregulation of tumor suppressor p53 leading to cell proliferation inhibition and apoptosis [73].

Considering the fact that UHRF1 overexpression, observed in cancer, is associated with decreased expression levels of several miRNAs which act as tumor suppressor genes, it can be thus speculated that the large quantities of the UHRF1 produced in tumors might result from abnormalities in the expression of miRNA. In agreement with this, it has been shown that UHRF1 overexpression in GC results from a reduction in the expression of miR-146a and miR-146b, which are known to act as tumor suppressors in GC [74]. Interestingly, miR-146a/b overexpression significantly decreased UHRF1 expression by directly targeting its binding sites (3′-UTR) triggering DNA demethylation-dependent reactivation of some TSGs such as RUNX3 [74]. Reduction in GC migration and in metastasis were the consequences [74]. In contrast, the downregulation of miR-146a/b induced an increase in UHRF1 expression, further and definitively confirming that miR-146a/b negatively regulates the expression of UHRF1 in GC [74].

miR-9 acts as tumor suppressor in CRC and its expression has been observed to be decreased in CRC compared to corresponding normal tissues [75, 76]. UHRF1 expression was shown to be more pronounced in human CRC tissue than matched normal tissues and its overexpression was linked to decreased expression levels of miR-9 and reduced survival rates of CRC patients [77]. Interestingly, transfection of CRC cells by pre-miR-9 induced a significantly decrease in UHRF1 expression indicating that pre-miR-9 negatively controls UHRF1 expression and that UHRF1 overexpression in CRC may result from a decrease in the expression of miR-9 [77].

The tumor suppressor, miR-193a-3p, has been reported to inhibit NSCLC progression but the molecular pathways through which this miRNA induces its inhibitory effects are largely unknown [78]. Nevertheless, it has been recently observed that miR-193a-3p repressed
the metastasis of lung cancer cells by targeting several proteins highly expressed in NSCLC including UHRF1 [79] indicating that miR-193a-3p negatively modulates the expression of UHRF1 in NSCLC. In the same way, the tumor suppressor gene, miR-145-5p and 145-3p as well, were shown to down-regulate UHRF1 in bladder cancer, with subsequent apoptosis by targeting genes such as BIRC5 and CENPF [80]. The regulatory mechanism involves a direct targeting of miRNA to the 3′-UTR of UHRF1 mRNA. Interestingly, in this study UHRF1 was reported to be upregulated in bladder cancer clinical specimens and to promote anti-apoptotic effects through regulation of several oncogenic genes [80]. Finally, it was suggested that UHRF1 might be a useful prognostic marker for survival of bladder cancer patients [80]. More recently UHRF1 has been shown to be regulated by miR-101 in renal cell carcinoma [81].

miR-34a acts as a tumor suppressor in various cancers and its decreased expression levels were suggested to play a causal role in the initiation and progression of the tumor [82, 83]. Recently, it has been shown that TQ-encapsulated nanoparticles induce apoptosis in cancer cells by increasing the expression of miR-34a through p53-dependent pathway [84]. TQ, the most abundant biologically active component of black cumin oil, has potent anticancer activities on many human cancer cell lines by targeting numerous signalling pathways involved in the regulation of cell cycle and apoptosis including p53 and p73 pathways [29, 63, 85]. Considering that TQ targets UHRF1 in p53-mutated Jurkat cells through p73-dependent pathway [63] and that UHRF1 is also regulated by p53 [62], we might imagine that TQ decreases the expression of UHRF1 in cancer cells through the upregulation of miR-34a. Taken together, all these findings show that miRNAs exert a fine tuning of tumor-suppressor expression via regulation of UHRF1 expression (Fig. 2).

Regulation of UHRF1 by CD47/ NF-κB pathway
Cancer cells use several strategies to escape immune system control. CD47, also called integrin-associated protein, is an immunoglobulin protein found on the surface of many human cells [86, 87]. Through its extracellular domain, CD47 exerts phagocytosis inhibitory activities via its ligation to the inhibitory receptor SIRPα (signal regulatory protein alpha) expressed on macrophages [88, 89]. Both solid and haematological tumors cells produce high amount of CD47 protein on their surface, compared with normal cells [90, 91]. CD47 overexpression is used by cancer cells to escape from the macrophages-mediated “don’t eat me” signal allowing tumor to progress [92–94]. Blocking the CD47/SIRPα axe-mediated “don’t eat me” signal allow macrophages to recognize CD47-positive cancer cells with subsequently destroy and elimination through a phagocytosis process [93, 95]. Several strategies have been used to target CD47 in cancer therapy. For instance, blocking CD47 function, using monoclonal antibodies against the CD47/SIRPα, showed in vitro and in vivo an important impact in many tumors overproducing CD47, such as leukemia and glioblastoma [94, 96]. It has been shown that CD47 is overexpressed in human melanoma and its depletion using CD47 siRNA significantly inhibited melanoma growth and metastasis [97]. In the same way, CD47 knockdown using specific siRNA inhibited the migration of intestinal epithelial cell by reducing the expression of cyclooxygenase-2 (COX-2) [98]. Recently, we showed that CD47 activation using 4 N1 (CD47 agonist) peptide induced a significant increase in the expression of both UHRF1 gene and protein in human astrocytoma cell lines U87 and CCF-STTG1 (Grade IV) without affecting their expression in normal human astrocytes NHA [38]. The enhancement of UHRF1 expression induced by CD47 activation was associated with the phosphorylation of IκBα, a NF-κB inhibitor, downregulation of p16INK4A and enhancement of cell proliferation [38]. In contrast, antagonizing CD47 function using monoclonal antibody (B6H12) induced downregulation of UHRF1 accompanied by dephosphorylation of IκBα, an upregulation of p16INK4A and decreased cell proliferation [38]. Interestingly, CD47 knockdown using siRNA in U87 cell line induced a significant downregulation of UHRF1 indicating that CD47 positively controls the expression of UHRF1 in glioblastoma cells [38].

The transcription factor NF-κB is activated in many human cancer including brain tumors [99, 100]. Consid-ering that CD47-induced IκBα phosphorylation was associated with UHRF1 upregulation and increased cell proliferation [38] and that CD47 activation induced the phosphorylation of Akt [101], we suggest that CD47 activation increases UHRF1 expression and promotes cell proliferation through the activation of the Akt-dependent NF-κB pathway (Fig. 3). Furthermore, we hypothesise that CD47 activation leads to IκBα phosphorylation, thus releasing the active NF-κB complex (p50 and p65) which translocates into nucleus (Fig. 3a). p50 or p65 then binds to UHRF1 promoter inducing its activation and subsequently inhibits p16INK4A expression via UHRF1 binding to the promoter of this latter, promoting thus cell proliferation and metastasis (Fig. 3a). In contrast, CD47 function blocking will inhibit NF-κB transactivation leading to decrease in NF-κB binding to UHRF1 promoter thereby inhibiting cell proliferation through p16INK4A reactivation (Fig. 3b). These findings indicate a key role of CD47 receptor in the regulation of UHRF1 expression most likely through the activation of the NF-κB pathway and also suggest that the overexpression of UHRF1 observed in many human cancers might result from high levels of cell plasma membrane CD47.
Regulation of UHRF1 by TRα1/Sp1 pathway

The thyroid hormone T3 (3,5,3′-triiodo-L-thyronine) is an important regulator of development, metabolism and cell proliferation [102]. The thyroid hormone receptors (TRs) act as tumor suppressors and their abnormal expression can lead to cancer progression [103]. T3 binds to TR regulating the expression of various genes including those involved in cell proliferation [103]. In this context, it has been shown that T3 negatively regulates the expression of UHRF1 in hepatoma cell line, which highly overexpresses TRα1 [104]. UHRF1 was shown to be overexpressed in liver cancer patients and its overexpression was accompanied with the size of tumor [104]. Exposure of TR-expressing HepG2 cells to T3 decreased the levels of UHRF1 mRNA and protein compared to TR-mutated HepG2 [104]. T3-induced UHRF1 downregulation was associated with a decreased level of the transcription factor Sp1, upregulation of p21, G0/G1 cell

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Fig. 2 Schematic model of the role of miRNA in UHRF1 regulation in cancer cells. Several miRNAs act as tumor-suppressor by binding to the 3′-untranslated region (3′-UTR) of mRNA UHRF1 leading to its degradation. TQ increases the expression of miR-34a which leads to upregulation of p53 in wild type p53 cancer cells or p73 in p53-mutated cancer cells with subsequent UHRF1 inhibition. UHRF1 downregulation results in the reactivation of others TSGs including p16INK4A, BRCA1, PPARG and KiSS1 conducting to cell proliferation inhibition and apoptosis.

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Fig. 3 Role of CD47/NF-κB pathway in UHRF1 regulation. a. CD47 activation induces IκBα phosphorylation allowing the translocation of the active NF-κB complex (p50 or p65) into nucleus to activate the UHRF1 gene with subsequent p16INK4A repression and enhanced cell proliferation. b. Blocking CD47 function inhibits NF-κB transactivation leading to decrease in binding of NF-κB components (p50 or p65) to UHRF1 promoter inducing cell proliferation inhibition via p16INK4A reactivation.
cycle arrest and cell proliferation inhibition [104]. Interestingly, DNA ChIP assay showed that Sp1 binds to a specific site on UHRF1 promoter indicating that T3 regulates the expression of UHRF1 through the transcription factor Sp1 [104]. UHRF1 and Sp1 mRNA levels were also increased in hepatocellular carcinoma HCCs patient tissues compared to adjacent normal tissues in parallel with a decrease in the expression of TRa1 and p21 [104]. UHRF1 overexpression in HepG2 counteracted the T3-induced p21 overexpression, G0/G1 cell cycle arrest and cell proliferation inhibition allowing cell passage to G2/M phase [104]. Taken together, these findings show that T3/TRa1 pathway is involved in the regulation of UHRF1 expression in liver cancer through the transcription factor Sp1 (Fig. 4). This suggests that defects in T3/TR pathway in cancer cells result in UHRF1 overexpression through increasing of Sp1 binding to its promoter with subsequent cell proliferation and metastasis (Fig. 4a). Exposure of cancer cells to T3 induces a decrease in Sp1 binding to UHRF1 promoter causing its inactivation and subsequent p21 reactivation and cell proliferation inhibition (Fig. 4b).

**Inhibitors of UHRF1 and its signalling pathways**

In vitro and in vivo studies have shown that a drug-induced inhibition of UHRF1 activity or expression leads to the reactivation of several tumor suppressor genes enabling cancer cells to undergo apoptosis [8, 29]. So far, only one direct inhibitor of UHRF1 has recently been reported [24]. Indeed, through a tandem virtual screening, a uracil derivative (NSC232003, Fig. 5), was described as a putative compound able to fit within the 5-methylcytosine binding pocket of the UHRF1 SRA domain. Interestingly, NSC232003 induces a global DNA hypomethylation probably through prevention of hemi-methylated DNA recognition by the SRA domain concomitantly to a disruption of UHRF1/DNMT1 interactions [24]. However, further investigations on this compound must be performed to check its capacity to reactivate silenced tumor suppressor genes through a UHRF1-dependent mechanism.

While, as stated above, the uracil derivative is the sole direct inhibitor, several inhibitors of the signaling pathways regulating UHRF1 expression are documented. UHRF1 expression was shown to be targeted by the natural product naphthazarin (Fig. 5) [105]. Naphthazarin induced cell proliferation inhibition and apoptosis of MCF-7 cells exposed to radiation through decreased binding of UHRF1, DNMT1 and HDAC1 to p21<sup>CIP/WAF1</sup> promoter [105]. In the same context, shikonin (Fig. 5), a natural naphthoquinone isolated from the Chinese traditional medicine Zi Cao (purple gromwell), has been shown to induce apoptosis in MCF-7 and HeLa cells, this effect was associated with a decrease in UHRF1 binding to p16<sup>INK4A</sup> promoter [106]. We have shown that TQ (Fig. 5) inhibits cell proliferation and induces apoptosis of Jurkat cells through p73 and caspase 3 upregulation and UHRF1 downregulation [63]. In accordance with these studies, we have also shown that treating B16F10 murine melanoma cells with curcumin induced a downregulation of UHRF1 and p73 upregulation, G1/S

![Fig. 4](https://example.com/image.png)

**Fig. 4** Schematic model of the role of TRa1/Sp1 pathway in the regulation of UHRF1. **a** Abnormalities in T3/TRa1 pathway result in increasing of Sp1 binding to UHRF1 promoter causing its activation. UHRF1 overexpression suppresses the expression of p21 gene with subsequent cell proliferation and metastasis. **b** Exposure of TR-expressing cells to T3 induces a decrease in Sp1 binding to UHRF1 promoter causing its inactivation. UHRF1 repression results in p21 reactivation with subsequent inhibition of cell proliferation and metastasis.
cell cycle arrest and apoptosis [107]. EGCG (Fig. 5) appears to take the same pathway to achieve the induction of apoptosis in Jurkat cells, i.e. UHRF1 downregulation and p16\textsuperscript{INK4A} upregulation [32]. Although, several studies [37, 44, 108, 109] tend to show that reactivation of tumor suppressor gene involves a UHRF1 downregulation-dependent promoter demethylation, the contribution of other mechanisms are not excluded. Indeed, UHRF1 has been suggested to be a main player in the reactivation of the tumor suppressor gene Pax1 (Paired box gene1) in several cancer cell lines in response to curcumin and resveratrol through a mechanism involving histone methylation and deacetylation rather than a DNA methylation-dependent process [110].

Other natural compounds, such as anisomycin and luteolin (Fig. 5), have been also reported to efficiently affect UHRF1 expression [111, 112]. Nevertheless, the mechanism of UHRF1 downregulation induced by natural compounds that target the signaling pathways of UHRF1 expression remains to be deciphered, but might involve the proteasome pathway. Indeed, for instance, the small molecule 17-AAG, a HSP90 inhibitor has been shown to induce UHRF1 ubiquitination leading to its degradation through proteasome-dependent pathway [113].

Conclusion
The overexpression of the anti-apoptotic UHRF1 has been shown to coordinate the epigenetic silencing of several TSGs in many human haematological and solid cancers causing apoptosis inhibition. Via its structural domains, UHRF1 interacts with several proteins involved in the silencing of TSGs including DNMT1, HDAC1, G9a and Suv39H1 which make it a strong candidate to be the driver of this macro-protein complex to ensure the transmission of epigenetic code from a mother cancer cell to daughter cells during cell proliferation. The large quantities of UHRF1 produced in cancers could be result from abnormalities in the upstream regulatory mechanisms of UHRF1. This review highlighted the signalling pathways underlying UHRF1 regulation in cancer cells. Thus, understanding the molecular mechanisms involved in UHRF1 regulation will allow us to find new targets in order to inhibit the expression of UHRF1 allowing cancer cells to undergo apoptosis through a re-expression of tumor suppressor genes. As an interesting perspective in the field of cancer therapy, we have recently identified an inhibitor of UHRF1 (a uracil derivative) that targets the SRA domain with subsequent impact on DNMT1/UHRF1 interactions and decrease in global DNA methylation [24].

Abbreviations
3′-UTR: 3′-untranslated region; CRC: Colorectal cancer; DNMT1: DNA methyltransferase 1; ECREM: Epigenetic Code Replication Machinery; EGCG: Epigallocatechin-3-gallate; GC: Gastric cancer; HAUSP: Herpes virus-Associated Ubiquitin-Specific Protease; HDAC1: Histone deacetylase 1; NSCLC: Non-small cell lung cancer; PDEs: Phosphodiesterases; PHD: Plant Homeo Domain; RING: Really Interesting New Gene domain; SRA: Set and Ring Associated domain; T3: Thyroid hormone 3; TQ: Thymoquinone; TRs: Thyroid hormone receptors; TSGs: Tumor suppressor genes; TTD: Tandem Tudor Domain; UBL: Ubiquitin-like domain; UHRF1: Ubiquitin-like with PHD and RING Finger domains 1

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MA and CB designed the review and drafted part of it. ZO, MAZ, ALA, HC and MM equally contributed to the writing the other part of the review. All authors read and approved the final manuscript.

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References

1. Venza M, Visalli M, Biondo C, Oleri R, Agliano F, Mosabito S, Tetti D, Venza I. Epigenetic marks responsible for cadmium-induced melanoma cell overgrowth. Toxicol In Vitro. 2015;29(1):242–50.

2. Li LL, Shu XS, Wang ZH, Cao Y, Tao Q. Epigenetic disruption of cell signaling in nasopharyngeal carcinoma. Chin J Cancer. 2011;30(4):231–9.

3. Hayashi Y, Montero A. Tumor suppressor gene methylation in follicular lymphoma: a comprehensive review. Mol Cancer. 2006;5:44.

4. Gronbaek K, Hother C, Jones PA. Epigenetic changes in cancer. APMIS. 2007;115(10):1039–59.

5. Bronner C, Achour M, Arima Y, Chataigneau T, Saya H, Schini-Kerth VB. The UHRF1 family: oncocenes that are druggable targets for cancer therapy in the near future? Pharmacol Ther. 2007;115(3):419–34.

6. Bronner C, Kirla M, Moussi M. Increasing role of UHRF1 in the reading and inheritance of the epigenetic code as well as in tumorigenesis. Biochem Pharmacol. 2013;86(2):1643–9.

7. Unoki M, Nishidate T, Nakamura Y. ICBP90, an E2F-1 target, recruits HDAC1 and binds to methyl-CpG through its SRA domain. Oncogene. 2004;23(46):7601–10.

8. Unoki M, Constant and potential anticancer drug targets involving the UHRF1 complex including epigenetic modifiers. Recent Pat Anticancer Drug Discov. 2011;6(1):116–30.

9. Hashimoto H, Horton JR, Zhang X, Bostick M, Jacobsen SE, Cheng X. The inheritance of DNA methylation. Genes Dev. 2013;27(11):1288–98.

10. Liang CC, Zhan B, Yoshikawa Y, Haas W, Gygi SP, Cohn MA. UHRF1 is a sensor for DNA interstrand crosslinks and recruits FANC D2 to initiate the Fanconi anemia pathway. Cell Rep. 2015;10(12):1947–56.

11. Arita K, Ariyoshi M, Tochio H, Nakamura Y, Shirakawa M. Recognition of tandem Tudor and PHD domains of UHRF1 is required for the epigenetic mechanism. Nature. 2008;455(7214):818–22.

12. Harrison JS, Cornett EM, Goldfarb D, DaRos A, Li ZM, Yan F, Dickson BM, Guo AH, Cantu DV, Kaustov L, et al. Hemi-methylated DNA regulates DNA methylation inheritance through allosteric activation of H3 ubiquitylation by UHRF1. Elife. 2016;5:e17101.

13. Nishiyama A, Yamaguchi L, Sharif J, Johmura Y, Kawamura T, Nakanishi K, Nueder P, Bronner C, Benitez M, Mikros E. Tandem virtual screening targeting the SRA domain of UHRF1 identifies a novel chemical tool modulating DNA methylation. Eur J Med Chem. 2016;114:390–6.

14. Hopfer N, Moussi M, Gammier JA, Redon R, van Manoors S, Chatton B, Ghyselinck N, Oudet P, Bronner C. Genomic structure and chromosomal mapping of the gene coding for ICBP90, a protein involved in the regulation of the topoisomerase I/palp gene expression. Gene. 2001;266:215–23.

15. Xu Q, Davison J, Li D, Storer B, Stirewalt D, Heimfeld S, Estey E, Appelbaum FR, Fang M. Identification of differentially methylated markers among cytogenetic risk groups of acute myeloid leukemia. Epigenetics. 2015;10(6):526–35.

16. Unoki M, Brunet J, Moussi M. Drug discovery targeting epigenetic codes: the great potential of UHRF1, which links DNA methylation and histone modifications, as a drug target in cancers and toxoplasmosis. Biochem Pharmacol. 2009;78(10):1279–88.

17. Cheng X, Blumenthal RM. Introduction–Epiphanies in epigenetics. Prog Mol Biol Transl Sci. 2011;101:1–21.

18. Alhosin M, Sharif T, Moussi M, Etienne-Selloum N, Fuhrmann G, Schini-Kerth VB, Bronner C. Down-regulation of UHRF1, associated with re-expression of tumor suppressor genes, is a common feature of natural compounds exhibiting anti-cancer properties. J Exp Clin Cancer Res. 2011;30:41.

19. Bostick M, Kim JK, Esteve PO, Clark A, Pradhan S, Jacobsen SE. UHRF1 plays a role in maintaining DNA methylation in mammalian cells. Science. 2007;317(5845):1760–4.

20. Achour M, Jacq X, Ronde P, Alhosin M, Charlot C, Chataigneau T, Jeannicl M, Macaluso M, Giordano A, Hughes AD, et al. The interaction of the SRA domain of ICBP90 with a novel domain of DNMT1 is involved in the regulation of VEGF gene expression. Oncogene. 2004;23(15):2187–97.

21. Achour M, Moussi M, Alhosin M, Ibrahim A, Peluso J, Muller CD, Schini-Kerth VB, Hameiche A, Dhe-Paganon S, Bronner C. Epigallocatechin-3-gallate up-regulates tumor suppressor gene expression via a reactive oxygen species-dependent down-regulation of UHRF1. Biochem Biophys Res Commun. 2013;430(1):208–12.

22. Baijsnyky P, Jankevicus G, Jurkowska RZ, Niazi A, Ljocht A. The UHRF1 protein stimulates the activity and specificity of the maintenance DNA methyltransferase DNMT1 by an allosteric mechanism. J Biol Chem. 2014;289(7):4016–10.

23. Al-Kaabi A, van Bockel LW, Potnen AH, Willems SM. p16INK4A and p14ARF gene promoter hypermethylation as prognostic biomarker in oral and oropharyngeal squamous cell carcinoma a review. Dis Markers. 2014;2014:305649.

24. Wang F, Yang YZ, Shi CZ, Zhang P, Meyer MP, Zhang HZ, Zou Y, Qin HL. UHRF1 promotes cell growth and metastasis through repression of p16(ink4a) in colorectal cancer. Ann Surg Oncol. 2012;19(8):2753–62.

25. Daskalos A, Oleksiewicz U, Filia A, Nikolaidis G, Xinarianos G, Gosney JR, Malliri A, Field JK, Liloglou T. UHRF1-mediated tumor suppressor gene hypermethylation. Cancer Biol Ther. 2015;16(8):1248–51.

26. Boukli A, Alhosin M, Bronner C, Sagini K, Truchot C, Sick E, Schini-Kerth VB, Andre P, Mely Y, Moussi M, et al. CD47 activation-induced UHRF1 over-expression is associated with silencing of tumor suppressor gene p16(ink4a) in glioblastoma cells. Anticancer Res. 2015;35(5):1497–50.
39. Jeanblanc M, Mousli M, Hopflner R, Bathami K, Martinet N, Abbadly AQ, Siffert JC, Mathieu E, Muller CD, Broncer C. The retinoblastoma gene and its product are targeted by ICBP90: a key mechanism in the G1/S transition during the cell cycle. Oncogene. 2005;24(49):7337–45.

40. Liu W, Qiao RH, Wang DM, Huang XW, Li B, Wang D. UHRF1 promotes human osteosarcoma cell invasion by downregulating the expression of Ecadherin in an RB-dependent manner. Mol Med Rep. 2016;13(1):315–20.

41. Chen H, Zhang C, Sheng Y, Yao S, Liu Z, Zhang C, Zhang T. Frequent SOCS3 and 30ST2 promoter methylation and their epigenetic regulation in endometrial carcinoma. Am J Cancer Res. 2015;5(1):180–90.

42. Jin W, Chen L, Chen Y, Xu SG, Di GH, Yin WJ, Wu J, Shao ZM. UHRF1 is associated with epigenetic silencing of BRCAl in sporadic breast cancer. Breast Cancer Res Treat. 2010;123(2):2359–73.

43. Zhang Y, Huang Z, Zhu Z, Zheng X, Liu J, Han Z, Ma X, Zhang Y. Upregulated UHRF1 promotes bladder cancer cell invasion by epigenetic silencing of KISS1. PLoS One. 2014;9(10):e104252.

44. Sheng Y, Wang H, Liu SB, Zhang C, Deng Y, Fang Z, Zhang T, Zhang C. Methylation of tumor suppressor gene CDH13 and SHP1 promoters and their epigenetic regulation by the UHRF1/PRMT5 complex in endometrial carcinoma. Gynecol Oncol. 2016;140(1):114–51.

45. Tae S, Karkhanis V, Velasco K, Yaneva M, Erdjument-Bromage H, Tempst P, Sif S. Bromodomain protein 7 interacts with PRMT5 and PRC2, and is involved in transcriptional repression of their target genes. Nucleic Acids Res. 2011;39(13):5424–38.

46. Li M, Chen D, Shiloh A, Luo J, Nobeliev AY, Qin J, Gu W. Deubiquitination of p53 by HAUSP is an important pathway for p53 stabilization. Nature. 2002;416(6881):458–53.

47. Qin W, Leonhardt H, Spada F, Usp7 and UHRF control ubiquitination and stability of the maintenance DNA methyltransferase Dnmt1. J Cell Biol. 2011;192(2):439–44.

48. Felle M, Joppien S, Nemeth A, Diermeier S, Thalhammer V, Dobner T, Kiimmerer E, Kappler R, Langst G. The USP7/Dnmt1 complex stimulates the DNA methylation activity of Dnmt1 and regulates the stability of UHRF1. Nucleic Acids Res. 2011;39(19):8355–65.

49. Ma H, Chen H, Guo X, Wang Z, Sowa ME, Zheng L, Hu S, Zeng P, Guo R, Diao J, et al. Methylation phosphorylation of the epigenetic regulator UHRF1 regulates its physical association with the deubiquitylase USP7 and stability. Proc Natl Acad Sci U S A. 2012;109(13):4828–33.

50. Zhang ZM, Rothblat SB, Allison DF, Cai Q, Harrison JS, Li L, Wang Y, Strahl BD, Wang GG, Song J. An allosteric interaction links USP7 to deubiquitination and chromatin targeting of UHRF1. Cell Rep. 2015;12(9):1400–6.

51. Ramakrishna S, Suresh B, Baek KH. The role of deubiquitinating enzymes in apoptosis. Cell Mol Life Sci. 2011;68(1):15–26.

52. Dac C, Shi D, Gu W. Negative regulation of the acetyltransferase TIP60-p53 complex by HAUSP is an important pathway for p53 stabilization. Nucleic Acids Res. 32(12):33(Suppl):S8.

53. Achour M, Fuhrmann G, Alhosin M, Ronde P, Chataigneau T, Mousli M, Kaghad M, Bonnet H, Yang A, Creancier L, Biscan JC, Valent A, Minty A, Boominathan L. Some facts and thoughts: p73 as a tumor suppressor gene involved in transcriptional repression of their target genes. Nucleic Acids Res. 2011;39(19):8355–65.

54. Siff S. Bromodomain protein 7 interacts with PRMT5 and PRC2, and is involved in transcriptional repression of their target genes. Nucleic Acids Res. 2011;39(13):5424–38.

55. Felle M, Joppien S, Nemeth A, Diermeier S, Thalhammer V, Dobner T, Kiimmerer E, Kappler R, Langst G. The USP7/Dnmt1 complex stimulates the DNA methylation activity of Dnmt1 and regulates the stability of UHRF1. Nucleic Acids Res. 2011;39(19):8355–65.

56. Achour M, Fuhrmann G, Alhosin M, Ronde P, Chataigneau T, Mousli M, Kaghad M, Bonnet H, Yang A, Creancier L, Biscan JC, Valent A, Minty A, Boominathan L. Some facts and thoughts: p73 as a tumor suppressor gene involved in transcriptional repression of their target genes. Nucleic Acids Res. 2011;39(19):8355–65.

57. Haupt S, Raghu D, Haupt Y. Mutant p53 drives cancer by subverting multiple tumor suppression pathways. Front Oncol. 2016;6:12.

58. Basu S, Murphy ME. Genetic modifiers of the p53 pathway. Cold Spring Harb Perspect Med. 2016;8(4):a026302.

59. Basu S, Murphy ME. Genetic modifiers of the p53 pathway. Cold Spring Harb Perspect Med. 2016;8(4):a026302.

60. Haupt S, Raghu D, Haupt Y. Mutant p53 drives cancer by subverting multiple tumor suppression pathways. Front Oncol. 2016;6:12.

61. Murray-Njimeswski F, Lane DP, Bourdon JC. p53/p63/p73 isoforms: an orchestra of isoforms to harmonise cell differentiation and response to stress. Cell Death Differ. 2006;13(6):962–72.

62. Bisso A, Collavini L, Del Sal G. p73 as a pharmaceutical target for cancer therapy. Curr Pharm Des. 2011;17(6):578–90.
indirectly inhibit p53 in oral squamous cell carcinoma: a pilot study. Asian Pac J Cancer Prev. 2015;16(17):7619–25.

84. Bhattacharya S, Ahir M, Patra P, Mukherjee S, Ghosh S, Mazumdar M, Chattopadhyay S, Das T, Chattopadhyay D, Adhikary A. PEYglated-thymoquine-nanoparticle mediated retardation of breast cancer cell migration by deregulation of cytoskeletal actin polymerization through miR-34a. Biomaterials. 2015;51:91–107.

85. Abusnina A, Alhosin M, Keravis T, Muller CD, Fuhrmann G, Bronner C, Lukner C. Down-regulation of cyclic nucleotide phosphodiesterase PDE1A is the key event of p73 and UHRF1 deregulation in thymoquine-induced acute lymphoblastic leukemia cell apoptosis. Cell Signal. 2011;23(1):152–60.

86. Oldenberg PA. Role of CD47 in erythroid cells and in autoimmunity. Leuk Lymphoma. 2004;45(7):1319–27.

87. Brown EJ, Frazier WA. Integrin-associated protein (CD47) and its ligands.

88. Wu SM, Cheng WL, Liao CJ, Chi HC, Lin YH, Tseng YH, Tsai CY, Chen CY, Lin SL, Chen WJ, et al. Negative modulation of the epigenetic regulator, UHRF1, by thyroid hormone receptors suppresses liver cancer cell growth. Int J Cancer. 2015;137(1):37–49.

89. Barclay AN. Signal regulatory protein alpha (SIRPalpha)/CD47: structure, function, and therapeutic target. Annu Rev Immunol. 2014;32:25–50.

90. Cheng QS, Wang XB. CD47 and leukemia stem cells. Zhongguo Shi Yan Xue Za Zhi. 2010;18(4):88–91.

91. Zhang L, Huang H. Targeting the cancer biomarker CD47: a review on the therapeutic antibody target on human acute myeloid leukemia stem cells. Proc Natl Acad Sci U S A. 2011;108(45):18342–7.

92. Wang Y, Xu Z, Guo S, Zhang L, Sharma A, Hershman JM, Koch C, McLachlan R, New M, Rebar R, et al., editors. Endotext. South Dartmouth MA: MDText.com, Inc; 2000.

93. Peccoz P, Chrousos G, Dungan K, Grossman A, Hershman JM, Koch C, McLachlan R, New M, Rebar R, et al., editors. Endotext. South Dartmouth MA: MDText.com, Inc; 2000.

94. Zhao XW, van Beek EM, Schornagel K, Van der Maaden H, Van Houdt MA: MDText.com, Inc; 2000.

95. Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs Jr KD, van Rooijen N, Leitman FS, Contreras-Trujillo H, Martin R, Cohen JD, et al. The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci U S A. 2012;109(17):6662–7.

96. Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs Jr KD, van Rooijen N, Leitman FS, Contreras-Trujillo H, Martin R, Cohen JD, et al. The CD47-signal regulatory protein-alpha (SIRPa) interaction forms a barrier for antibody-mediated tumor cell destruction. Proc Natl Acad Sci U S A. 2011;108(45):18342–7.

97. Willingham SB, Vollmer JP, Gentles AJ, Sahoo D, Dalerba P, Mitra SS, Wang J, Contreras-Trujillo H, Martin R, Cohen JD, et al. The CD47-signal regulatory protein alpha (SIRPalpha) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci U S A. 2012;109(17):6662–7.

98. Eisd_O, Weiskopf K, Vollmer AK, Vollmer JP, Willingham SB, Contreras-Trujillo H, Liu J, Majeti R, West RB, Fletcher JA, et al. Antibody therapy targeting the CD47 protein is effective in a model of aggressive metastatic leiomyosarcoma. Proc Natl Acad Sci U S A. 2012;109(17):6656–61.

99. Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs Jr KD, van Rooijen N, Leitman FS, Contreras-Trujillo H, Martin R, Cohen JD, et al. The CD47-signal regulatory protein-alpha (SIRPalpha) interaction forms a barrier for antibody-mediated tumor cell destruction. Proc Natl Acad Sci U S A. 2011;108(45):18342–7.

100. Cheng QS, Wang XB. CD47 and leukemia stem cells. Zhongguo Shi Yan Xue Za Zhi. 2010;18(4):88–91.

101. Zhao XW, van Beek EM, Schornagel K, Van der Maaden H, Van Houdt MA: MDText.com, Inc; 2000.

102. Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs Jr KD, van Rooijen N, Leitman FS, Contreras-Trujillo H, Martin R, Cohen JD, et al. The CD47-signal regulatory protein-alpha (SIRPalpha) interaction forms a barrier for antibody-mediated tumor cell destruction. Proc Natl Acad Sci U S A. 2011;108(45):18342–7.

103. Kim WG, Wang JH, Jeong SY, Jeong SY, Kim JH. Shikonin causes apoptosis by up-regulating p73 and down-regulating ICBP90 in human cancer cells. Biochem Biophys Res Commun. 2015;460(1):71–6.

104. Abusnina A, Keravis T, Yougbare I, Bronner C, Lugnier C. Anti-proliferative effect of curcumin on melanoma cells is mediated by PDE1A inhibition that regulates the epigenetic integrator UHRF1. Mol Nutr Food Res. 2011;55(11):1677–89.

105. Chen H, Zhang T, Sheng Y, Zhang C, Peng Y, Wang X, Zhang C. Methylation profiling of multiple tumor suppressor genes in hepatocellular carcinoma and the epigenetic mechanism of 3OST2 regulation. J Cancer. 2015;6(8):740–9.

106. Jang SY, Hong D, Jeong SY, Kim JH. Shikonin causes apoptosis by up-regulating p73 and down-regulating ICBP90 in human cancer cells. Biochem Biophys Res Commun. 2015;460(1):71–6.

107. Abusnina A, Keravis T, Yougbare I, Bronner C, Lugnier C. Anti-proliferative effect of curcumin on melanoma cells is mediated by PDE1A inhibition that regulates the epigenetic integrator UHRF1. Mol Nutr Food Res. 2011;55(11):1677–89.

108. Chung B, Jeong SY, Jeong SY, Kim JH. Shikonin causes apoptosis by up-regulating p73 and down-regulating ICBP90 in human cancer cells. Biochem Biophys Res Commun. 2015;460(1):71–6.

109. Abu-Alainin W, Gana T, Liloglou T, Olayanju A, Herrera LN, Ferguson R, Campbell F, Andrews T, Goldring C, Kitteringham N, et al. UHRF1 inhibition of the Keap1-Nrf2 pathway in pancreatic cancer contributes to oncogenesis. J Pathol. 2016;238(3):423–33.

110. Parashar G, Capalash N. Promoter methylation-independent reactivation of PAX1 by curcumin and resveratrol is mediated by UHRF1. Clin Exp Med. 2016;16(3):471–8.

111. Yu C, Xing F, Tang Z, Bronner C, Lu X, Di J, Zeng S, Liu J. Anisomycin suppresses Jurkat T cell growth by the cell cycle-regulating proteins. Pharmacol Rep. 2013;65(2):435–44.