Review

UPF1: a potential biomarker in human cancers

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TABLE OF CONTENTS

1. Abstract

Recently, Up-frameshift protein 1 (UPF1) is reported to be downregulated in various cancers and its low expression is closely correlated with poor prognosis. UPF1 is well known as a master regulator of nonsense-mediated mRNA decay (NMD), which serves as a highly conserved mRNA surveillance process protecting cells from aberrant toxic transcripts. Due to dysfunction of UPF1, NMD fails to proceed, which contributes to tumor initiation and progression. This review shows a brief summary of the aberrant expression, functional roles and molecular mechanisms of UPF1 during tumorigenesis. Increasing evidence has indicated that UPF1 could serve as a potential biomarker for cancer diagnosis and treatment for future clinical applications in cancer.

2. Introduction

Nonsense-mediated mRNA decay (NMD) is a highly conserved mRNA surveillance process that eliminates aberrant transcripts which contain premature termination codons (PTCs) [1, 2]. In this role, NMD serves as a quality control pathway that protects cells from the toxic effects of the truncated protein products arising from PTC-containing mRNAs [3, 4]. Additionally, NMD has been shown to be involved in regulating the expression of 1–10% normal physiological mRNAs [5]. By controlling the levels of endogenous mRNAs, NMD can regulate various biolog-

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ical processes including embryonic development and brain development [6].

As a master regulator of NMD, Up-frameshift protein 1 (UPF1), initially reported in 1996, is located at chromosome 19p13.2-p13.11 [7, 8]. Accordingly, UPF1 is evolutionarily conserved and ubiquitously expressed phosphoprotein with RNA/DNA-dependent ATPase and RNA helicase activity [7]. The ability of NMD to selectively target PTC-containing mRNAs depends on the ATPase and helicase activities of UPF1 [9]. Mechanically, UPF1 acts in associated with the peptide release factors eRF1/eRF3 to recognize aberrant translation termination events and triggers degradation of mRNA in a subsequent step together with UPF2 and UPF3, which bind to the CH-domain of UPF1 and cause a conformational change, activating the ATPase or helicase activity of the UPF1 protein [10, 11]. UPF1 is thought to mediate the degradation of NMD substrates through a phosphorylation/dephosphorylation cycle [12]. Phosphorylation of UPF1 facilitates the assembly of degradation factor, consequently, triggers the degradation of NMD sensitive mRNAs [13–15]. Previous researches have revealed that UPF1 is phosphorylated by SMG1 [14, 15]. Further, Zhu and colleagues found that SMG1-mediated phosphorylation could be inhibited by SMG8-SMG9 complex [16]. In addition to its relationship with NMD, UPF1 is also involved in several biological roles. For instance, UPF1 is required for S phase progression and genome stability [17]. UPF1 also contributes to embryonic development and survival [18, 19], while loss of UPF1 also causes embryonic lethality in zebrafish and flies [19, 20]. Feng *et al*. describes a role for UPF1 in regulated protein decay, wherein UPF1 acts as an E3 ubiquitin ligase to repress human skeletal muscle differentiation [21].

Currently, this molecule is known to play a critical role in cell proliferation and differentiation by promoting a proliferative, undifferentiated cell state [22]. Further, accumulating studies have been reported that UPF1 is dysregulated and plays important role in various cancers, including hepatocellular cancer [23–27], colorectal cancer [28–31], gastric cancer [32], lung adenocarcinoma [33, 34], pancreatic cancer [35], inflammatory myofibroblastic tumor [36], thyroid cancer [37], ovarian cancer [38], glioma [39] and prostate cancer [40] (Table 1).

Herein, we summarize recent studies on the role of UPF1 in cancers, including those focused on its aberrant expression, biological functions, and associated clinical features, in addition to its regulatory network, and further debate the prognostic and therapeutic values of UPF1 in human cancers.

3. Expression of UPF1 in cancer

Currently, several researches have reported that UPF1 act as tumor suppressor and was downregulated in various cancers. Liu *et al*. [35] found that level of UPF1 expression was downregulated in pancreatic adenosquamous carcinoma (PASC) due to commonly genomic mutations in the UPF1, comparing to normal pancreatic tissue and non-ASC pancreatic as well as lung tumors. UPF1 downregulation has also been consistently revealed in a great diversity of other tumor types, including hepatocellular cancer (HCC) [23, 25–27], gastric cancer (GC) [32], inflammatory myofibroblastic tumors (IMT) [36], thyroid cancer (TC) [37], ovarian cancer (OC) [38] and glioma [39]. These studies demonstrated that UPF1 has a tumor-suppressive role. Furthermore, the expression level of UPF1 in most cell lines of these mentioned cancers are also downregulated.

Although Cao *et al*. [33] reported that UPF1 level was downregulated in 160 lung adenocarcinoma (LADC) tissues compared with matched adjacent normal tissues, a recent study uncovered by Han and colleagues also focused on the biological role of UPF1 in LADC, and confirmed an inconsistently obvious upregulation of UPF1 in LADC cells [34]. Interestingly, Bokhari *et al*. [31] found that expression level of UPF1 was higher in primary microsatellite instable (MSI) CRC compared to microsatellite stable (MSS) CRC. So we speculate that the discrepancy of UPF1 expression might be related to different pathological types. These findings indicate that UPF1 may have different roles in tumorigenesis. The biological roles of UPF1 in cancers are not clear yet. Maybe the contributors to dysregulated expression of UPF1 in cancers are various, including tumor cell, pathological type and so on, which still need further investigations.

4. Regulation mechanisms of UPF1 expression

4.1 Epigenetic alterations

Studies had shown hypermethylation of tumor suppressor genes contribute to tumorigenesis [41]. Utilizing CpG island prediction software, Li *et al*. [32] found that the CpG island was enriched in a putative promoter region of UPF1 in gastric cancer. Mechanistic study indicated a representative methylation pattern of the CpGs putative promoter region [32]. Furthermore, Chang *et al*. [27] found that fragment [18831624 ~ 18832749 in chromosome19, NC_000019.10] was rich in CpG dinucleotides and predicted as a putative promoter region. 26 CpG dinucleotides in this fragment were amplified from genomic DNA isolated from HCC and normal tissues. Accordingly, 53.85% [14/26] CpGs were hypermethylated in tumors compared to 15.38% (4/26) in normal tissues [27]. In addition, following treatment with increased concentrations of the DNA-demethylating agent 5-Aza-2'-deoxycytidine (5-Aza-dC), the mRNA and protein expression levels of UPF1 were gradually increased in both GC and HCC cells [27, 32]. Although these findings demonstrated that CpG hypermethy-

Table 1. Functional characterization of UPF1 in various tumors.

Cancer type	Aberrant expression	Role	Associated clinical feature	Biological function	Target	Reference
HCC	down	anti-cancer	tumor size, lymph node metastasis, Edmondson-Steiner grade, Barcelona Clinic Liver Cancer stage, portal vein tumor thrombus, OS and recurrence rates	cell proliferation, colony-forming ability, invasion, migration, cell stemness, EMT, glycolysis, cell apoptosis, sorafenib sensitivity	UCA1, ABCC2, Smad7, SNHG6 TGF-β	[23, 25–27]
CRC	up (in MSI)	Oncogenic (in MSI)	-	cell proliferation (in MSI)	-	[31]
	unknown	-	-	Wnt activity	SNHG6, NR4A1	[28–30]
GC	down	anti-cancer	survival time	cell proliferation, cell cycle progression, migration, invasion apoptosis, EMT, chemotherapeutical sensitivity	MALAT1	[32]
LADC	down	anti-cancer	histological type, TNM stage, lymphatic metastasis, distant metastasis, histological types, OS, recurrence rates	EMT	TGF-ß	[33]
	up	-	-	-	ZFPM2-AS1	[34]
pancreatic ASC	down	-	-	somatic mutations in UPF1	-	[35]
IMT	down	-	-	somatic mutations in UPF1	-	[36]
TC	down	-	-	-	DLX6-AS1	[37]
OC	down	anti-cancer	-	cell proliferation and migration	DANCR	[38]
glioma	down	anti-cancer	-	cell proliferation and migration	PVT1	[39]
prostate cancer	-	-	Gleason score, metastasis	-	-	[40]

lation downregulated UPF1 expression in GC and HCC, the underlying mechanism between dysregulation of UPF1 and DNA methylation in other cancers have not been reported yet, which need more researches.

4.2 Genomic alteration

In addition to epigenetic alterations, it is reported that genomic alteration also play an vital role in UPF1 expression in cancers. Previous study by Liu *et al.* [35] reported somatic genomic mutations in the UPF1 gene in pancreatic adenosquamous carcinoma from 18 of 23 patients, the first gene known to be selectively mutated in PASC. According to what Liu and his colleagues found, the point mutations in the PASC were nearly equally distributed in the exons and introns of UPF1 gene, leading to disrupt intronic splicing enhancers and exonic splicing enhancers, and thus triggering alternative splicing of UPF1 pre-mRNA. As a result, the level of UPF1 expression was downregulated in PASC compared to adjacent normal tissue [35]. Additionally, Lu *et al.* [36] also reported the identification of somatic mutations in UPF1 gene in 13 of 15 pulmonary inflammatory myofibroblastic tumor samples. Sequence analysis revealed that these UPF1 mutations occurred in a specific region (the exon10-intron 10-exon 11 region), which elicited exon skipping, thus resulting in reduced UPF1 protein levels in IMTs. Accumulating researches have established that UPF1 is downregulated in various cancers. However, whether UPF1 mutations is a common molecular alteration associated with cancers still determine to be clarified in the following research.

5. Aberrant splicing of UPF1 in cancers

It has been established that NMD serves as a surveillance process that protects cells from the toxic effects of the truncated protein products arising from PTC-containing mRNAs. The perturbation of NMD could dysregulate ~3 to 10% of mRNAs in human cells and organisms [5, 42, 43], which might promote the tumorigenesis. And the biological function of NMD largely depends on UPF1. In fact, UPF1 exon 10 and intron 10 are unusually short (169 and 85 nt, respectively) and have a high GC content (59% and 73%, respectively), both of which could weaken RNA splicing [44]. However, mutations in UPF1 will disrupt these regions, leading to aberrant splicing more easily. Aberrant splicing of UPF1 caused by mutations in the exon 10/11 region disrupt a part of essential UPF1's RNA helicase domain [43], while mutations in the exon 21/23 region truncate the carboxy-terminal region of UPF1, which contains (S/T)Q motifs phosphorylated by SMG1, a serine/threonine kinase necessary for NMD [45]. As the essential functional domains lost, these mutant of UPF1 are likely to have dominant-negative activity, resulting in NMD dysfunction. For example, NMD disruption in IMTs due to UPF1 mutation elevated expression of the pro-inflammatory molecule NIK and upregulated chemokine

expression such as IL-8, CCL20, and CXCL1, thereby inducing immune cell infiltration, the hallmark of IMTs [36]. Interestingly, the vast majority of the mutations observed in IMTs were clustered in one of the same two regions of the UPF1 gene as in PASC [35]. Therefore, the aberrant splicing of UPF1 might be a new therapeutic target for human cancers.

6. Function of UPF1 in cancer

Over the last decades, the functions of UPF1 in cancers have been studied with the aim to access its role in biological progress of tumors. Several studies have reported that knockdown UPF1 via UPF1-siRNA transfection increased cell proliferation, invasion and migration in GC [32], HCC [23, 27], LADC [33], OC [38] and glioma [39], while overexpression of cellular UPF1 significantly showed the opposite function and increased apoptosis in HCC [27]. Another study from Bordonaro *et al*. revealed that UPF1 overexpression enhances butyrate-mediated Wnt activity, which correlates to induction of apoptosis in CRC [29]. Additionally, cell cycle analysis showed that UPF1 downregulation increased the percentage of cells in the S phase in HCCLM9 and Huh7 HCC cells [27]. Furthermore, UPF1 upregulation could significantly weaken the sphere-forming ability characterized as the decreased size of tumor sphere [25] and remarkably decrease the expressions of HCC tumor stemness markers, CD133, CD90 and CD13 [46, 47], as well as decrease the expressions of cancer stem cell (CSC)-related markers (sox2 and oct4), thus inhibits HCC cell stemness [25]. Moreover, decrease in UPF1 also enhanced the colony-forming ability and glycolysis HCC [23].

In addition to an anti-oncogenic role, UPF1 might also act as an oncogene. Bokhari *et al*. found that expression level of UPF1 was higher in primary MSI CRC compared to MSS CRC [31]. Further, inhibition of UPF1 caused decreased cell proliferation in the MSI CRC cell lines, whereas no effect was seen in the MSS CRC [31].

Taken together, UPF1 act as a tumor suppressor but also an oncogene in cancer, playing a vital role in inhibiting or promoting biological processes, including proliferation, migration, invasion, apoptosis and colony-forming ability as well as CSC-like characteristics.

7. The involvement of UPF1 in EMT

It is reported that epithelial-mesenchymal transition (EMT) contributed to tumor metastasis and is regulated by different signaling pathways and various growth factors [48, 49]. TGF-β signaling is one of the most important signaling pathways in EMT and induces EMT by activating downstream Smad signaling, Smad2 and Smad3 [50, 51]. A study by Cao *et al*. elucidated that inhibiting NMD via downregulating the UPF1 expression could induce LADC cells to undergo EMT and acquire a fibroblast-like and mesenchymal morphology, while upregulating UPF1 suppresses EMT [33]. UPF1 knockdown could downregulate epithelial marker E-cadherin, while upregulate mesenchymal markers vimentin and Zeb1 [33], which was the same as that found in hepatocellular cancer and gastric cancer [25, 32]. Mechanically, UPF1 regulated EMT by targeting the TGF-β signaling pathway through two non-mutually exclusive ways [33]. On the one hand, upregulating UPF1 inhibited the TGF-β signaling via decreasing the expression of Smad2/3 proteins [33]. On the other hand, overexpression of UPF1 directly inhibited MIXL1 and SOX17, the TGF-β signaling component genes [33]. Interestingly, a slight UPF1 upregulation greatly inhibited TGF-β signaling through decreasing the upregulation of MIXL1 and SOX17, whereas suppressing UPF1 enhanced TGF-β signaling required high doses [33]. Overall, UPF1 could regulate EMT by targeting the TGF-β signaling pathway.

8. Mechanistic model of UPF1

Long noncoding RNAs (lncRNAs) are a class of little or no protein-coding potential RNAs that are more than 200 nucleotides in length [52]. Accumulating reports revealed that lncRNAs are involved in various regulations of many cancer processes [53, 54]. Recently, researches have demonstrated that UPF1 could exert oncogenic or tumor-suppressive function in various cancers through interacting with lncRNA and MicroRNA, including UCA1 [23], miR-1468 [24], SNHG6 [26–28], NR4A1AS [30], MALAT1 [32], ZFPM2-AS1 [34], DLX6-AS1 [37], DANCR [38] and PVT1 [39]. Better understanding of the mechanistic model of UPF1-lncRNA in human cancers may shed new light on tumor pathogenesis and molecular treatment (Fig. 1).

8.1 Linc-ASEN/UPF1/p21

Lee *et al*. [55] have clarified that UPF1 could represses cellular senescence through *Linc-ASEN*/UPF1/p21 axis. Mechanistic study showed that *Linc-ASEN* could directly bind to UPF1 to suppress p21 transcription by recruiting Polycomb Repressive Complex 1 (PRC1) and PRC2 to p21, leading to the failure of interaction between transcriptional activator p53 and p21 promoter. Moreover, the *Linc-ASEN*-UPF1-DCP1A (a decapping enzyme) complex repressed p21 expression posttranscriptionally by enhancing p21 mRNA decay via directly binding to 3′UTR of p21 mRNA. In summary, UPF1 associates with *Linc-ASEN* and represses cellular senescence by reducing p21 production transcriptionally and posttranscriptionally.

8.2 LncRNA SNHG6/UPF1/Smad

Chang *et al*. elucidated that UPF1 could suppress HCC invasion, migration and proliferation through activating the TGF-β/Smad pathway by binding to SNHG6

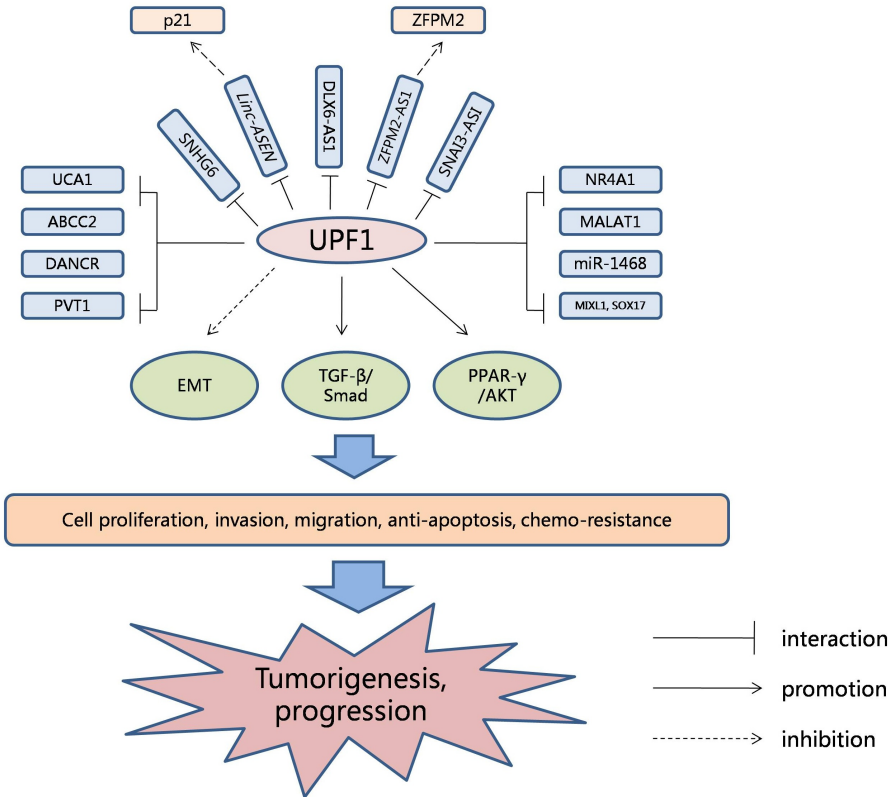

Fig. 1. The signaling pathways of UPF1 in tumorigenesis and progression. UPF1 exerts oncogenic or tumor-suppressive effects through interacting with lncRNA and MicroRNA (UCA1, miR-1468, SNHG6, NR4A1AS, MALAT1, ZFPM2-AS1, DLX6-AS1, DANCR and PVT1). UPF1 associates with *Linc-ASEN* and then reduces p21 production transcriptionally and posttranscriptionally. UPF1 induces EMT not only through regulating EMT markers E-cadherin and Zeb1, but also through inhibiting the expression of MIXL1 and SOX17. UPF1 is a direct downstream target of miR-1468 and promotes PPAR-γ/AKT pathway, while alteration of PPAR-γ or AKT phosphorylation could abolish the biological effects of miR-1468. Direct co-function between SNHG6/ SNAI3-AS1 and UPF1 decreases the expression level of the core factors of TGF-β/Smad Pathway. Therefore, UPF1 involves in cellular proliferation, invasion, migration, and apoptosis as well as chemo-resistance in tumors.

[26, 27]. Mechanistic study showed that there was an inverse correlation between UPF1 and Smad7, and knockdown of UPF1 increased expression of Smad7, the key role in the TGF-β pathway [27]. Furthermore, UPF1 played a role in TGF-β pathways through altering phosphorylation of Smad2/3 but not total Smad2/3 expression level [27]. Interestingly, subsequent researches by Chang and colleagues confirmed direct co-function between SNHG6 and UPF1. Of note, SNHG6 inhibited Smad7 protein expression, and thus induced phosphorylation of Smad2/3 [26]. Consistently, Wang *et al*. also uncovered that the expression of UPF1 protein, and the Smad7 downstream TGF-β pathway proteins, such as p-Smad2 and p-Smad3, were decreased with SNHG6 knockdown whereas total Smad2 and Smad3 expression level was not significantly altered in CRC tissues [28]. Taken together, the SNHG6/UPF1/Smad axis may open a new window for understanding the hidden aspects of HCC and CRC.

8.3 LncRNA SNAI3-AS1/UPF1/Smad

Li *et al*. [56] reported that UPF1suppressed tumorigenesis of HCC through SNAI3-AS1/UPF1/Smad network. Mechanistic study showed that UPF1 could directly interact with SNAI3-AS1, which could exert oncogenic function in HCC. Inhibition of UPF1 could partially restore the inhibitory effects on cell invasion mediated by SNAI3-AS1. Moreover, silencing of UPF1 increased, while up-regulated UPF1 decreased the expression level of Smad7. Of note, SNAI3-AS1 knockdown significantly decreased phosphorylation of Smad2/3. Both of Smad7 and Smad2/3 served as the core factors of TGF-β/Smad Pathway. All these results demonstrated that SNAI3-AS1 promotes HCC tumorigenesis by binding UPF1, regulating Smad7 expression, and inducing activation of the TGF-β/Smad pathway.

8.4 LncRNAZFPM2-AS1/UPF1/ZFPM2

Han *et al*. [34] elucidated that lncRNA ZFPM2-AS1could stimulate LADC cell proliferation through ZFPM2-AS1/UPF1/ZFPM2 axis. Accordingly, RIP assay and pulldown assay confirmed the interaction of ZFPM2-AS1 with UPF1. Further mechanistic study showed that UPF1/ZFPM2-ASI shortened the half-life of ZFPM2 mRNA via binding at its 3'UTR region. However, there is non-effect of ZFPM2-AS1 on the luciferase activity

of ZFPM2 promoter reporter, demonstrating that ZFPM2-AS1 might regulate ZFPM2 at post-transcriptional level. And then they found that overexpression of UPF1 reduced, while silence of UPF1 induced the expression of ZFPM2 at mRNA and protein levels. Taken together, these findings first demonstrated a role for the ZFPM2-AS1/UPF1/ZFPM2 axis in LADC progression.

8.5 MicroRNA miR-1468/UPF1, CITED2/PPAR-γ/AKT

One of the key regulatory mechanisms linked to HCC is the miR-1468/UPF1, CITED2/PPAR-γ/AKT network revealed by Liu *et al*. [24]. CITED2 and UPF1 were identified as direct downstream targets of miR-1468 in HCC cells, and were inversely correlates with miR-1468. Restoration of CITED2 or UPF1 expression reversed the promotive effects of miR-1468 on cell proliferation, colony formation, cell cycle progression and apoptosis on HCC cells. Moreover, CITED2 or UPF1 overexpression promoted PPAR-γ/AKT pathway. Intriguingly, alteration of PPAR-γ or AKT phosphorylation could abolish the effects of miR-1468 on cell cycle and apoptosis-related proteins. In summary, these findings supported that the notion of miR-1468/UPF1, CITED2/PPAR-γ/AKT in HCC tumorigenesis and represents a promising therapeutic strategy for HCC patients.

9. Clinical application of UPF1

9.1 UPF1 as a prognostic marker

As a prognostic biomarker, UPF1 expression is correlated to cancer progression. Chang *et al*. found that aberrant expression of UPF1 in HCC was closely correlated with Edmondson-Steiner grade, Barcelona Clinic Liver Cancer stage, portal vein tumor thrombus, tumor size and lymph node metastasis and overall survival as well as recurrence rates [23, 27]. Another study focusing on lung cancer demonstrated that LADC patients with negative or weak UPF1 expression had a higher rate of distant metastasis (35/51, 68.6%) than those with high UPF1 expression levels (16/51, 31.4%) [33]. Patients with higher UPF1 expression had better overall survival and lower recurrence rates compared with those with weak UPF1 expression level [33], but has no significant correlation with patient age or gender, tumor size, or smoking. Interestingly, the cellular localization of UPF1 seemed to be related to prostate cancer progression and metastasis [40]. Yang and colleagues reported that prostate tumors with Gleason score 3–6 showed increased nuclear expression for UPF1, while in tumors with Gleason score 7–10 UPF1 expression seemed to be replaced by enrichment in the cytoplasm. In addition, in metastatic tumors the cellular localization of UPF1 seemed to be shifted to a more cytoplasmic pattern, although this was not statistically significant [40].

9.2 Potential therapeutic target

This review shows a brief summary of oncogenic or anti-oncogenic biological function of UPF1 during tumorigenesis. In hepatocellular cancer, UPF1 serves as anti-oncogene. When pcDNA3.1-UPF1-transfected HCCLM9 cells were inoculated into the oxter of male nude mice, tumor growth was dramatically inhibited and the number of pulmonary metastatic nodules decreased markedly compared with controls [27]. Interestingly, UPF1 serves as oncogene in MSI CRC. Bokhari and colleagues demonstrated that both inhibition of UPF1 and NMD inhibitor amlexanox caused decreased cell proliferation in the MSI CRC cell lines (HCT116 and RKO), whereas no effect was seen in the MSS cell lines (LS513 and SW480) [31]. In addition, amlexanox led to a significant antitumor effect in xenografts of MSI CRC cells by targeting NMD [31]. However, whether the inhibitor of UPF1 could also suppress tumorigenesis in MSI CRC, such as NMDI-1, which inhibits the dephosphorylation of UPF1 and thereby keeps it in a non-active state [57], should be further investigated.

Ectopic expression of UPF1 also increase chemotherapeutical sensitivity. Li *et al*. found that BGC-823 and SGC-7901 cells with UPF1 overexpression displayed high doxorubicin sensitivity in GC. When treated with doxorubicin, cells with UPF1 overexpression decreased a larger percentage of cells in the S phase. Meanwhile, upregulating UPF1 in GC cells obviously promoted apoptosis induced by doxorubicin treatment [32]. Another research uncovered by Zhang and colleagues also focused on HCC cell sensitivity to chemotherapeutic agent, sorafenib. UPF1 overexpression enhanced sorafenib-mediated inhibition on HCC cell proliferation and promotion on apoptosis. Notably, UPF1 could enhance the sensitivity of sorafenib via interacting with ABCC2 in HCC cells [25].

In summary, these data open a new window for understanding the biological function of UPF1 in cancer treatment and more efforts should be devoted to clarifying the potential of UPF1 as a promising therapeutic strategy.

10. Concluding remarks and future perspectives

UPF1 has been reported to be dysregulated in multiple types of human malignancy, and its expression trends in various cancers are not completely consistent. Several researches showed that UPF1 was significantly downregulated and acted as a tumor suppressor in most types of cancer including HCC, GC, TC, OC and glioma. However, the expressions of UPF1 in LADC tissues reported by two research teams were completely opposite to each other. In addition, the somatic mutations in UPF1gene were clarified in IMTs and pancreatic ASC. Moreover, the aberrant expression of UPF1 influenced cancer cell prolifera-

tion, apoptosis, migration and invasion as well as poor prognosis, revealing its potential as an effective biomarker for cancer diagnosis and treatment. Mechanistic study showed that UPF1 co-functioned with lncRNA (i.e., DLX6-AS1, DANCR, ZFPM2-AS1, SNHG6, PVT1, *Linc-ASEN*) and was involved in some signaling pathways essential for cancer, including EMT, TGF-β/Smad pathway, and PPAR-γ/AKT pathway.

In summary, UPF1 can serve as an independent prognostic indicator with clinical potentials in many cancers. However, the expression pattern of UPF1 in several cancer tissues compared to matched normal tissues is not clear, such as prostate cancer and colorectal cancer. In the future, larger sample size in different ethnic groups is still needed to further confirm the expression pattern of UPF1 in diverse cancers and further clarify the correlation between UPF1 level and clinicopathological parameters, as well as the prognostic value of UPF1. Additionally, the lack of animal experiments is a common defect for existing published papers of UPF1. Meanwhile, further investigations into the molecular mechanism between UPF1 and lncRNA should provide more mechanistic insights. And more efforts are warranted to facilitate translation of UPF1 from basic science into clinical utility.

11. Author contributions

HMW and BLC contributed equally to this work. (I) Conception and design: All authors, (II) Collection of data: HMW, BLC and XSL, (III) Data analyze and manuscript writing: HMW and BLC, (IV) Final approval of manuscript: All authors.

12. Ethics approval and consent to participate

Not applicable.

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15. Conflict of interest

The authors declare that they have no competing interests.

16. References

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Abbreviations: 3'UTR, 3' untranslated regions; 5-Aza-dC, 5-Aza-2'-deoxycytidine; CCL20, CC chemokine ligand 20; CD, leukocyte differentiation antigen; CITED2, carboxy-terminal domain 2; CSC, cancer stem cell; CXCL1, chemokine (C-X-C motif) ligand 1; DANCR, differentiation antagonizing noncoding RNA; DCP1A, mRNA-decapping enzymes 1a; DLX6-AS1, lncRNA DLX6 antisense RNA 1; Erf, Eukaryotic release factor; EMT, epithelial-mesenchymal transition; IL-8, Interleukin-8; lncRNA, long non-coding RNA; Linc-ASEN, long intergenic noncoding RNA associated with senescence; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MIXL1, The Mix1 homeobox-like; MSI, microsatellite instable; MSS, microsatellite stable; NIK, NF-kappaB-inducing kinase; NMD, nonsense-mediated mRNA decay; NR4A1, Nuclear receptor subfamily 4 group A member 1; NR4A1AS, Nuclear receptor subfamily 4 group A member 1 antisense RNA; OCT4, Octamer-binding protein 4; PASC, pancreatic adenosquamous carcinoma; PCR, Polycomb Repressive Complex; PPAR-γ, peroxisome proliferator-activated receptor-γ; PRC1, Polycomb Repressive Complex 1; PTCs, premature termination codons; PVT1, plasmacytoma variant translocation 1; *siRNA*, Small interfering RNA; SNAI3-AS1, The Snail Family Gene Snai3 antisense RNA 1; SNHG6, small nucleolar RNAs host gene 6; SOX2, sex-determining region Y-box 2; Sox 17, Sry-related high-mobility-group box 17; TGF-β, Transforming growth factor beta; UCA1, urothelial cancer associated 1; UPF1, up-frameshift protein 1; ZEB1, Zinc finger E-box binding homeobox 1; ZFPM2, Zinc finger protein multitype 2; ZFPM2-AS1, Zinc finger protein multitype 2 antisense RNA 1.

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