

Role of E3 ubiquitin ligases in gastric cancer

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Abstract

E3 ubiquitin ligases have an important role in carcinogenesis and include a large family of proteins that catalyze the ubiquitination of many protein substrates for targeted degradation by the 26S proteasome. So far, E3 ubiquitin ligases have been reported to have a role in a variety of biological processes including cell cycle regulation, cell proliferation, and apoptosis. Recently, several kinds of E3 ubiquitin ligases were demonstrated to be generally highly expressed in gastric cancer (GC) tissues and to contribute to carcinogenesis. In this review, we summarize the

current knowledge and information about the clinical significance of E3 ubiquitin ligases in GC. Bortezomib, a proteasome inhibitor, encouraged the evaluation of other components of the ubiquitin proteasome system for pharmaceutical intervention. The clinical value of novel treatment strategies targeting aberrant E3 ubiquitin ligases for GC are discussed in the review.

Key words: E3 ubiquitin ligases; Gastric cancer; Oncogene; Tumor suppressor gene; Target therapy

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Core tip: E3 ubiquitin ligases are a large family of proteins that catalyze the ubiquitination of many protein substrates for targeted degradation by the 26S proteasome. They play an essential role in a variety of biological processes, including cell cycle regulation, proliferation and apoptosis. They are often found overexpressed in gastric cancer (GC) and their deregulation has been shown to contribute to GC development. The mechanisms of E3 ubiquitin ligases in the regulation of biological functions and their exact roles in carcinogenesis can help to develop specific E3 ubiquitin ligase inhibitors to improve the treatment strategies for GC patients.

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies worldwide, as well as one of the leading causes of cancer-related death^[1]. More than half of these cases occur in Eastern Asia. It is well known that GC is highly invasive and metastatic, which is the main

factor contributing to the high mortality rate of GC patients^[2-4]. Although there are many studies of novel diagnostic and therapeutic interventions, the prognosis of patients with advanced GC remains poor^[5]. It is well known that GC is a multifactorial and multistep disease which involves activation of oncogenes and inactivation of tumor suppressor genes during GC progression^[6]. Genetic and epigenetic alterations, occurring in genes and molecules, occur in proliferation, invasion and metastasis of GC and influence its prognosis^[7-10]. An understanding of these alterations may be critical for improvements in the diagnosis, treatment or prediction of prognosis of GC.

The ubiquitin-proteasome system (UPS) plays a key role in the regulation of many cellular pathways by controlling the abundance, activity and localization of an enormous variety of cellular proteins^[11-14]. The UPS targets a variety of proteins, including those that are misfolded, mutated, or otherwise damaged - the cellular version of quality control^[15]. The attachment of ubiquitin to target proteins is mediated by three enzymes: E1, E2, E3. E1 involved in the ubiquitination process. E1 is the ubiquitin-activating enzyme recruiting ubiquitin. E2 is the ubiquitin-conjugating enzyme that transfers the ubiquitin to the targeted protein. E3 is the ubiquitin ligase acting as a scaffold protein that interacts with the E2 enzyme and transfers ubiquitin to the target protein^[16,17]. This process is reversible through the action of deubiquitinases (DUBs) that remove ubiquitin chains linked to the target protein^[18]. DUBs are also involved in ubiquitin processing and recycling^[19]. In this process, E3 ubiquitin ligases perform a critical role through the selective binding of protein substrates. This review will focus on the role of E3 ubiquitin ligases in GC and their potential as a novel anticancer target.

E3 UBIQUITIN LIGASES

More than 600 E3 ubiquitin ligases are expressed in the human genome, allowing for the specificity of the ubiquitination system^[20]. E3 enzymes are divided into subclasses based on their biochemical and structural features: HECT (homologous to E6-AP carboxy terminus), RING (a very interesting new gene) fingers, and U-box domains^[21]. There are about 30 proteins containing the HECT domain. The RING fingers and U-box ubiquitin ligases contain the new gene (RING) finger domain^[22]. There are over 700 proteins containing the RING finger domain, but only a small part functions as an E3 ubiquitin ligase. Unlike RING proteins, most HECT proteins, if not all, are believed to function as E3 ubiquitin ligases. RING and HECT E3 ubiquitin ligases use different catalytic mechanisms to promote the transfer of ubiquitin to targeted substrates. RING E3 ubiquitin ligases can promote the direct transfer of ubiquitin from E2 to the targeted substrate, whereas HECT E3 ubiquitin ligases interact with the cognate E2, followed by the formation of a thiolester linkage with ubiquitin and subsequent transfer of ubiquitin to the

targeted substrate^[23]. Many E3 ubiquitin ligases could be oncogenes or tumor suppressor genes because frequent deregulation of E3 ubiquitin ligases has been shown in gastric carcinogenesis. The function of E3 ubiquitin ligases in GC are discussed in detail below.

E3 UBIQUITIN LIGASES AS ONCOGENES IN GASTRIC CANCER

Some E3 ubiquitin ligases, such as MDM2 and MKRN1, have established roles in the cell cycle and apoptosis. Other E3 ubiquitin ligases, such as Cbl/Cbl-b/c-Cbl, Cullin1, and Hakai, may be similarly important in gastric carcinogenesis. These E3 ubiquitin ligases are overexpressed in GC, and their inhibition leads to cells growth arrest or apoptosis. The oncogenic E3 ubiquitin ligases in GC are discussed in detail below.

Murine double minute 2

The murine double minute 2 (*MDM2*) gene encodes an important negative regulating protein which promotes ubiquitin-dependent proteasomal degradation of P53 by functioning as an E3 ubiquitin ligase^[24,25]. SNP309, a T to G change at the 309th nucleotide in the first intron of the *MDM2* gene, has been characterized and shown to increase the affinity of the transcriptional activator Sp1, resulting in higher levels of MDM2 RNA and protein and subsequent attenuation of the p53 pathway. Numerous studies have shown that MDM2 SNP309 is associated with increased risk and poor prognosis of GC^[26-31]. Although MDM2 was characterized as a RING finger E3 for the tumor suppressor p53^[32], its interaction with Nbs1 inhibited DNA break repair, leading to chromosome instability and subsequent transformation that was independent of p53^[25,33]. MDM2 is expressed at higher levels in GC tissues than in non-cancerous gastric mucosa. In addition, MDM2 expression is associated with clinicopathologic features in patients treated only with surgery^[34]. Moreover, MDM2 is a potential predictive factor for benefit from adjuvant chemotherapy with fluorouracil-leucovorin-oxaliplatin in patients with resectable GC^[34].

Cullin1

Cullin1 is a scaffold protein of the ubiquitin E3 ligase Skp1/Cullin1/Rbx1/F-box protein complex, which ubiquitinates a broad range of proteins involved in cell-cycle progression, signal transduction, and transcription. Cullin1 is involved in the progression of several cancers^[35-37], including GC. The high expression of Cullin1 was significantly correlated with poorer overall survival and lymph node metastasis of GC^[7]. On the other hand, Korzeniewski demonstrated that Cullin1 may act as a tumor suppressor by regulating PLK4 protein levels^[38].

Cbl/Cbl-b/c-Cbl

The Casitas B-lineage lymphoma (Cbl) family of

ubiquitin ligases were identified as negative regulators of non-receptor tyrosine kinases or activated signaling pathways^[39]. Some studies showed Cbl in conjunction with epidermal growth factor receptor (EGFR) system might be associated with gastric carcinogenesis, invasion and metastasis^[40,41]. Other authors showed that cCbl, Cblb, and EGFR are highly expressed in GC tissue and their expression levels are related to the invasion and development of GC. Both cCbl and Cblb were positively correlated with EGFR, suggesting that they may interact in the proliferation, infiltration, and metastasis of GC^[42]. So Cbl, cCbl, Cblb might be deemed novel molecular markers for aggressive GC. However, another study found that the Cbl-b repressed insulin-like growth factor-1 (IGF-1)-induced epithelial to mesenchymal transition, likely through targeting the IGF-1 receptor, resulting in degradation and further inhibition of the Akt/ERK-miR-200c-ZEB2 axis in GC cells and a decrease in the risk of developing lymph node metastasis in patients with GC^[43]. Some studies demonstrated an important role of Cbl-b in reversing Pgp-mediated GC multi-drug resistance through suppression of the PI3K/Akt signaling pathway and down-regulation of P-gp expression^[44].

Hakai

Hakai was originally identified as an E3 ubiquitin-ligase for the E-cadherin complex^[45]. Hakai contains Src homology (SH)2, RING-finger, and proline-rich domains, and it is structurally and functionally related to c-Cbl, a RING-finger type E3 ubiquitin ligase for receptor tyrosine kinases^[46,47]. High expression of Hakai induced weakness of cell-cell adhesions and enhanced cell proliferation^[48]. Overexpression of Hakai in GC and colon adenocarcinomas was reported to occur in the early stages of carcinogenesis and up-regulated cell proliferation^[48,49]. Therefore, Hakai may be a valuable new biomarker or drug target for GC treatment.

Makorin ring finger protein 1

Makorin ring finger protein 1 (MKRN1) was reported to be a transcriptional co-regulator and an E3 ligase for hTERT^[50]. MKRN1 simultaneously induced p53 and p21 ubiquitination and proteasome-dependent degradation. This suggested that the presence of MKRN1 in cancer cells may affect p53- and p21-dependent apoptosis and cell growth. MKRN1 remains unique in its ability to negatively regulate the major tumor suppressors including p14ARF and p53^[51]. MKRN1 may induce gastric carcinogenesis by regulating the p14ARF-associated pathways, and thus potentially represent an important therapeutic target in GC^[52].

E3 UBIQUITIN LIGASES AS TUMOR SUPPRESSOR GENES IN GASTRIC CANCER

Numerous E3 ubiquitin ligases, including FBXW7 and

CHIP, have been shown to be tumor suppressors in GC. Frequent inactivating mutations or downregulated expression of these E3 ubiquitin ligases have been detected in GC. Several discovered E3 ubiquitin ligases, such as CHFR, ZNRF3, and RNF180, may play an important role in regulating gastric carcinogenesis. Besides mutation and gene copy loss, epigenetic alteration (*i.e.*, promoter methylation) also contributed to inactivation of these tumor suppressors. E3 ubiquitin ligases with tumor suppressor activity in GC are discussed in detail below.

FBXW7/CDC4

The *FBXW7/CDC4* gene, which maps to 4q32, encodes a ubiquitin ligase and has been implicated as a tumor suppressor gene in many tumor types, including GC. *FBXW7/CDC4* targets several oncoproteins, including cyclin-E, c-myc, c-jun, Notch 1 and Notch 4, for degradation. and its tumor suppressor function was thought to be exerted through these substrates^[53]. Loss of *FBXW7/CDC4* was seen in both early-onset GC and advanced GC^[54]. *FBXW7* inactivation contributed to poor prognosis *via* genome instability and cell cycle progression. Recent studies suggested that GC patients with inactivation of *FBXW7* had aggressive cancer and a poor prognosis^[55,56]. Loss of *FBXW7* expression could lead to MYC overexpression, and was associated with poor prognosis in GC patients^[56]. In the future, *FBXW7/CDC4* may be a potential diagnostic biomarker and therapeutic target for GC.

Ring finger protein 180

Ring finger protein 180 (RNF180), a novel member of the RING finger protein family and function as an E3 ubiquitin ligase, is well conserved among vertebrates^[57]. High expression of RNF180 suppressed cell growth and induced apoptosis, which were mediated by upregulating the antiproliferation regulators MTSS1 and CDKN2A and the proapoptotic mediator TIMP3^[58]. Promoter methylation of RNF180 was detected in 76% of primary GC and 55% of intestinal metaplasia, but was not detected in any of the normal gastric tissues, suggesting methylation of this gene was a common and early event in gastric carcinogenesis. Promoter methylation of RNF180 DNA was more frequently detected in the GC tissue samples, which led to low or loss of RNF180 expression in GC patients with poor overall survival^[58]. Our study showed that methylation of CpG sites(-116, -80, +97, and +102) in the RNF180 DNA promoter predicted poor prognosis of GC^[10].

CHIP

CHIP (carboxy terminus of Hsc70 interacting protein) was reported to be an E3 ubiquitin ligase that could induce ubiquitination and degradation of several tumor-related proteins, and acted as a suppressor of tumor metastasis. CHIP inactivation was significantly correlated with GC progression, lymph node metastasis, TNM

stage, and tumor differentiation. Therefore, CHIP inactivation was an independent prognostic marker of poor survival in GC patients as well as added significant prognostic value to the well known clinical prognostic factors^[8,59]. Moreover, CHIP suppresses GC angiogenesis by inhibiting nuclear factor (NF)- κ B activity through ubiquitin-proteasome-dependent degradation of the NF- κ Bp65 and downregulation of the proangiogenic cytokine interleukin-8^[8]. Therefore, CHIP may be as a potential diagnostic biomarker and therapeutic target for GC.

CHFR

The *CHFR* gene encodes a RING finger domain containing E3, as a tumor suppressor gene, which was shown to play an important role in mitosis through targeting key mitotic proteins Aurora A and Plk for ubiquitin-mediated proteolysis^[60,61]. Loss of *CHFR* mRNA expression was a consequence of promoter methylation, suggesting that it played a tumor suppressor role in gastric carcinogenesis^[62,63]. *CHFR* promoter methylation status may be of value in predicting malignant behavior or as a molecular diagnostic marker for GC^[64-66]. Moreover, *CHFR* promoter methylation was a sensitive marker for the effect of docetaxel in GC patients^[67].

COP1

COP1 (constitutive photomorphogenic 1, also known as RFWD2) is a p53-targeting E3 ubiquitin ligase, containing RING-finger, WD40-repeat domains, and coiled-coil^[68-70]. Whether the *COP1* gene is an oncogene or a tumor suppressor gene remains controversial. Some studies showed that *COP1* acted as a tumor suppressor^[71-73]. However, other studies indicated that *COP1* acted as an oncogene^[74]. One study showed that loss of *COP1* expression determined poor prognosis in patients with GC^[9]. However, another study showed that *COP1* overexpression was associated with poor prognosis in primary GC^[75]. Therefore, *COP1* may be worth further investigation to determine the fundamental biology of GC.

ZNRF3

ZNRF3, a unique transmembrane E3 ubiquitin ligase, suppresses the β -catenin signaling initiated by endogenous Wnt proteins^[76]. ZNRF3 was reported as a negative regulator of the Wnt pathway that inhibited cancer cell growth and promoted cell apoptosis. ZNRF3 inhibited GC cell growth and promoted the cell apoptosis by limiting the Wnt/ β -catenin/TCF signaling pathway^[77]. In the future, a novel therapeutic strategy based on ZNRF3 may be of value in patients with GC.

TARGETING E3 UBIQUITIN LIGASES FOR GC THERAPY

The success of bortezomib, a selective proteasome

inhibitor, for treating refractory myeloma and mantle cell lymphoma, showed that modulation of UPS may represent a novel strategy for GC. However, in a nonrandomized Phase II clinical trial conducted in 16 patients with advanced GC, bortezomib, at a dose of 1.3 mg/m² *i.v.* twice weekly for 2 wk (days 1, 4, 8 and 11) every 21 d, did not show any clinical activity (no patient responded and only one patient achieved stable disease as the best response)^[78]. In addition, 14 out of 16 patients experienced grade 2 or greater toxicity. Similar outcomes were obtained in another clinical trial^[79]. These studies showed that proteasome inhibition in GC should include combination therapy with targeted agents focusing on nonoverlapping oncogenic pathways.

By selectively inhibiting an E3 ubiquitin ligase, the proteins that are regulated by this E3 ubiquitin ligase can be stabilized, thereby avoiding any unwanted effects on other cellular proteins. Targeting of the E3 ubiquitin ligase has gained increasing attention, and has led to the development of high-throughput screening assays to identify inhibitors of multiple E3 ubiquitin ligases^[80]. Nutlin-3 has potent antitumor activity against human GC cells with wt p53 and has shown promise as a single agent and in combination with conventional anticancer drugs^[81]. Small molecule compounds, such as Nutlin-3a, RITA, and MI-219, have been identified as potent MDM2 inhibitors^[82-85]. These small molecule compounds disrupted MDM2-mediated p53 degradation and thus led to tumor regression by inducing p53-mediated cell cycle arrest and cell death^[82-85]. Therefore, using analogs of MDM2, or using agonists of Mdm2 with other therapeutic modalities may be of use as neoadjuvant therapy for GC within a few years.

Recognition of molecules that could promote the activity of FBXW7 and subsequently enhance the degradation of its oncogenic substrates could also be a very good anticancer treatment strategy. It has been shown that a natural dietary agent genistein inhibited miR-223 expression and subsequently up-regulated FBXW7, leading to cell growth inhibition and apoptosis in pancreatic cancer cells^[86]. Another study indicated that rapamycin suppressed FBXW7 loss-induced epithelial-mesenchymal transition and cancer stem cell-like characteristics in colorectal cancer cells^[87]. However, there are no inhibitors targeting FBXW7 that is currently being tested in preclinical and clinical trials in GC. In the future, targeting FBXW7 may be useful in patients with GC.

SCF ligases, also known as CRL (Cullin-RING ubiquitin Ligases), are the largest family of ubiquitin ligases, and promote the degradation of about 20% of UPS-regulated proteins^[88,89], including cell cycle regulatory proteins, transcription factors, oncoproteins and tumor suppressors among others^[90,91]. Post-translational neddylation of CUL, a process triggered by the NEDD8-activating enzyme E1 subunit 1 (NAE1), is required for CRL/SCF activation. Recently, MLN4924 was discovered *via* a high-throughput screen as a specific NAE1 inhibitor and first-in-class anticancer drug^[92,93]. The efficacy and

mechanism of action of MLN4924 has been tested *in vitro* and in mouse models and has shown promising anticancer activity in a wide-range of malignancies^[94-99], though these did not include GC. MLN4924 is currently in multiple phase I clinical trials for both solid tumors and hematological malignancies^[88]. We believe that MLN4924 may be used in patients with GC in the near future.

CONCLUSION

The E3 ubiquitin ligases play an essential role in a variety of biological processes including cell cycle regulation, cell proliferation, and apoptosis. Although further research is necessary to better understand the biological functions of E3 ubiquitin ligases, it has become clear that some E3 ubiquitin ligases, such as those described in this review, are promising targets for GC therapy. Perhaps the greatest challenge for scientists trying to manipulate the E3 ubiquitin ligases in GC cells will be to delineate the role of targeted proteins as tumor suppressors or oncogenes. The effect of such proteins can be influenced by many factors, some of which are still unknown. There remain other obstacles to overcome before targeting E3 ubiquitin ligases as a viable treatment option. The main obstacle is selectivity, and any new therapies must target only cancer cells and not healthy ones. While targeting of E3 ubiquitin ligases in GC therapy is still at an early stage, continued research on the E3 ubiquitin ligases should lead to the discovery of new therapeutic targets that may boost the development of more specific, less toxic, and more efficacious anti-cancer therapeutics.

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