The role of deubiquitinating enzymes in gastric cancer (Review)

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Abstract. The epigenetic regulation of gene expression (via DNA methylation, histone modification and microRNA interference) contributes to a variety of diseases, particularly cancer. Protein deubiquitination serves a key role in the mechanism underlying histone modification, and consequently influences tumor development and progression. Improved characterization of the role of ubiquitinating enzymes has led to the identification of numerous deubiquitinating enzymes (DUBs) with various functions. Gastric cancer (GC) is a highly prevalent cancer type that exhibits a high mortality rate. Latest analysis about cancer patient revealed that GC is sixth deadliest cancer type, which frequently occur in male (7.2%) than female (4.1%). Complex associations between DUBs and GC progression have been revealed in multiple studies; however, the molecular mechanism underpinning the metastasis and recurrence of GC is yet to be elucidated. Generally, DUBs were upregulated in gastric cancer. The relation of DUBs and tumor size, classification and staging was observed in GC. Besides, 5-yar survival rate of patients with GC is effeccted by expression level of DUBs. Among the highly expressed DUBs, specifically six DUBs namely UCHs, USPs, OTUs, MJDs, JAMMs and MCPIPs effect on this survival rate. Consequently, the association between GC and DUBs has received increasing attention in recent years. Therefore, in the present review, literature investigating the association between DUBs and GC pathophysiology was analyzed and critically appraised.

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1. Introduction

Epigenetic mechanisms are implicated in tumorigenesis and cancer progression, and are defined as heritable changes that do not affect the DNA sequence. Examples include DNA methylation, histone modification and microRNA (miR) interference (1). Histone modification serves an important role in transcriptional regulation, DNA repair and replication, and chromosomal condensation. Several studies have indicated that histone modifications typically occur at the N-terminus, primarily in the form of acetylation, methylation, phosphorylation or ubiquitination (2,3).

Ubiquitination describes a post-translational modification of proteins under the conditions of normal homeostasis or disease, which involves the addition of the evolutionarily conserved small protein ubiquitin (4) or UBLs (ubiquitin-like proteins) (5) that tag the protein for proteasomal degradation or non-degradative processes (6). Ubiquitin is a 76-amino acid polypeptide that can covalently conjugate with protein substrates via a mechanism involving three enzymes: Ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin ligase (E3). The ubiquitination of a specific protein substrate requires the selective recruitment of E1, E2 and E3 (7-9). In eukaryotic cells, the structure of ubiquitin is highly conserved and the protein responds to certain chemical signals (such as phosphorylation, oxidation, misfolding and damage to the ubiquitinated protein) to induce the ubiquitin-proteasome degradation pathway (10). Notably, the activity of deubiquitinating enzymes (DUBs) directly influences the turnover rate, activity, regeneration and localization of various proteins in cells. In addition, DUBs serve an important role in homeostasis (11), the stabilization and degradation of proteins, and signal transduction pathways (11). Changes in protein structure, abnormal spatial and temporal expression, and uncontrolled activity can result in the development of certain conditions, including arthritis, neurodegenerative and cardiovascular diseases, and tumors. In humans, DUBs can serve a role in the genesis of tumors as either oncogenes or tumor suppressor genes.

Key words: deubiquitinating enzymes, gastric cancer, survival
The DUB protein family reportedly comprises 103 members, the majority of which are cysteine proteases. As a result of similarities in their amino acid sequences and molecular structures, these proteins can be divided into the following six families: Ubiquitin C-terminal hydrolases (UCHs) (12), ubiquitin-specific proteases (USPs), ovarian tumor-related proteases (OTUs), Machado-Joseph disease protein domain proteases (MJDs), JAB1/MPN domain-associated metalloproteinase (JAMM) domain proteins and monocyte chemotactic protein-induced proteins (MCPIPs) (13). To further summarize and stratify the aforementioned proteins, subfamilies are also detailed in Fig. 1. USP6 (14), USP6NL (15), ubiquitin thioesterase otulin (OTULIN) (16) and family with sequence similarity 105 member A (FAM105) (17) were also recently discovered. The majority of these DUBs are associated with tumor progression and several studies have revealed the association between DUBs and gastric cancer (GC) (18,19). Of note, GC is the second leading cause of cancer-associated mortality and the fourth most common cancer type worldwide (20,21).

The lack of a comprehensive understanding of the molecular mechanism underpinning GC metastasis and recurrence suggests that further investigation is required. Thus, DUBs and their potential association with the progression of GC were the primary focus of the present review. Within the present study, subsequent data analyses were performed using the Gene Expression Profiling Interactive Analysis (GEPIA) website (http://geopia.cancer-pku.cn), which primary collates data from The Cancer Genome Atlas and the Genotype-Tissue Expression project databases. The name of each target gene was input into the GEPIA website and the corresponding data was extracted (22).

2. UCHs and GC

The enzymes of the UCH protein family contain a conserved catalytic domain known as the UCH domain, which comprises ~230 amino acids (23). This protein family includes four members, including UCHL1/protein gene product 9.5, UCHL3, UCHL5/UCH37 and BRCA1 associated protein-1 (BAP1) (24-27). The activities of these proteins have been associated with the occurrence and development of cancer, and several studies have identified that UCHL1, UCHL5 and BAP1 are specifically involved in the formation of GC (24-26).

Using data extracted from GEPIA, the gene expression profiles of UCHs between GC samples and the paired normal tissues are presented in Fig. 2. The gene expression levels of UCHL3 and UCHL5 in tumor tissues were upregulated >2-fold compared with normal tissues. To the best of our knowledge, no studies have reported the link between UCHL3 and GC; however, UCHL5 has been identified as a potential biomarker of GC with novel prognostic value. For elderly patients with dysregulated protein homeostasis, high levels of UCHL5 inhibited proteasome activity, and were determined to promote the apoptosis of cancer cells (28). Regarding UCHL1, research has shown that it could be a candidate biomarker and therapeutic target for GC metastasis, as UCHL1 promoted this process via the Akt and Erk1/2 pathways (29). BAP1 expression is downregulated in gastric carcinoma and its decreased expression was associated with a malignant phenotype (histological grade) and a more advanced TNM stage (30). Furthermore, low BAP1 expression was revealed to be associated with poor prognosis in patients with gastric adenocarcinoma and GC (30).

Associations between UCHs and certain clinicopathological features, and the 5-years survival rates of patients with GC are presented in Table I. High expression levels of UCHs in patients with GC were predominantly associated with tumor size and TNM stage, but not sex or age. Analysis of these expression levels indicated that the higher the degree of positive BAP1 and UCHL5 expression in GC, the higher the 5-year survival rate of patients. Conversely, increased expression of UCHL1 was revealed to reduce the survival rate of patients.

3. USPs and GC

USPs are the most diverse family of DUBs and the USP subclass represents the majority of DUBs encoded by the human genome. Consequently, numerous studies have investigated their function, substrates and mechanisms of action in various diseases. The discovery of gene mutations and the upregulation of USPs in various types of cancer, and their potential for targeted small molecule-mediated inhibition, indicates USPs as a promising therapeutic target. There is also increasing interest in the development of USP-specific inhibitors as antiviral and anticancer agents (31). In the present study, the USP family was stratified into 10 subgroups comprising USPs 1-10. The gene expression profile of USPs was compared between GC and paired normal tissues (Fig. 3).

USP1s and GC. The USP1 subfamily includes 11 members: USP1 (32), USP10-13 (33-36), USP14-16 (37-39), USP17L2 (40), USP18 (41) and USP19 (42). Of the USP1 subfamily members investigated, the expression levels in CG tissues was higher compared with those in the adjacent normal tissues (Fig. 3). The expression levels of USP13 and USP18 were <10 Transcripts Per Million (TPM), which were relatively low compared with the other USPs investigated (which were expressed at levels >10 TPM). USP17L2 expression was not detected. The highest levels of expression were noted for USP10, followed by USP14 and USP11, which exhibited expression levels >20 TPM.

The expression of the majority of USP1s has been associated with tumor growth, though studies into GC have predominantly investigated USP10, USP14 and USP15 (43). USP10 and USP14 are independent predictors of prognosis for patients with GC, and the increased expression of USP10 in GC has been associated with the 5-year survival rate of patients. A previous study demonstrated that the downregulation of USP10, as well as the absence of USP14 expression in GC cells had significant effects on gastric wall invasion and lymph node metastasis, increased malignant biological behavior and reduced survival rate, as determined from a large number of clinical samples (44,45). Conversely, vimentin expression was upregulated in human GC tissues and cell lines as a result of deubiquitination, following interactions with USP14 and miR-320a, which may contribute to the aggressiveness of GC cells (46). It was also reported that the direct targeting of USP14 and vimentin by miR-320a inhibited GC cell proliferation, migration and invasion. miR-320a not only directly suppresses vimentin expression, but also binds to USP14, indirectly downregulating vimentin in GC tissues.
Therefore, a high positive expression rate of USP14 correlates with a high recurrence rate in patients with GC (44, 45).

**USP2s and GC:** The 10 USP2 family members are: USP2 (47), USP20 (48), USP21 (49), USP22 (50), and USP24-29 (26, 51-55).
Table I. Association between DUBs and clinicopathological variables and survival in patients with gastric cancer.

| DUB     | Expression | Cases | Age, years | Sex | Tumor size, cm | Lauren classification | TNM stage | 5-year survival |
|---------|------------|-------|------------|-----|----------------|-----------------------|-----------|----------------|
|         |            |       | <60 | ≥60 | M | F | <5 | ≥5 | Intestinal | Diffuse | I and II | III and IV | Patients, n | Rate (%) |
| BAP1 (30) | Positive | 211 | 124 | 87 | 145 | 66 | 42 (<3) | 169 (≥3) | 51 | 117 | 91 | 74 | 136 | 65 |
|         | Negative  | 263 | 144 | 119 | 180 | 83 | 20 (<3) | 243 (≥3) | 43 | 174 | 120 | 189 | 100 | 38 |
|         | P-value    | 0.381 | 0.948 | 0.001 | 0.042 | (Mix= 0.001) | 0.01 | 0.001 |
| UCHL1 (29) | Positive | 87 | 37 | 50 | 67 | 20 | 23 (<3) | 64 (≥3) | NF | NF | 25 | 62 | 26 | 30 |
|         | Negative  | 109 | 59 | 50 | 80 | 29 | 43 (<3) | 66 (≥3) | NF | NF | 53 | 56 | 66 | 61 |
|         | P-value    | 0.107 | 0.561 | 0.038 | NF | 0.004 | 0.001 |
| UCHL5 (28) | Positive | 379 | 181 (<66) | 198 (≥66) | 188 | 191 | 139 | 240 | 181 | 198 | 150 | 229 | 258 | 65 |
|         | Negative  | 111 | 51 (<66) | 60 (≥66) | 54 | 57 | 50 | 61 | 34 | 77 | 40 | 71 | 42 | 38 |
|         | P-value    | 0.747 | 0.914 | 0.173 | 0.004 | 0.001 | 0.108 |
| USP10 (45) | Positive | 198 | 95 (≤57) | 103 (>57) | 137 | 61 | 83 (<4) | 115 (≥4) | 111 | 87 | 108 | 90 | 106 | 64 |
|         | Negative  | 167 | 85 (≤57) | 82 (>57) | 118 | 49 | 60 (<4) | 107 (≥4) | 72 | 95 | 69 | 98 | 79 | 40 |
|         | P-value    | 0.758 | 0.761 | 0.182 | 0.060 | NF | 0.004 | 0.003 |
| USP14 (44) | Positive | 62 | 36 | 26 | 49 | 13 | NF | NF | NF | NF | 17 | 45 | NF | NF |
|         | Negative  | 51 | 32 | 19 | 44 | 7 | NF | NF | NF | NF | 21 | 30 | NF | NF |
|         | P-value    | NF | NF | 0.124 | NF | NF | NF |
| USP20 (57) | Positive | 52 | 21 | 31 | 37 | 15 | 39 | 13 | NF | NF | 30 | 22 | 23 | 45 |
|         | Negative  | 37 | 18 | 19 | 24 | 13 | 11 | 26 | NF | NF | 13 | 24 | 8 | 20 |
|         | P-value    | 0.439 | 0.529 | 0.001 | NF | 0.036 | 0.003 |
| USP22 (58) | Positive | 125 | 55 | 70 | 88 | 37 | 56 | 69 | NF | NF | 23 | 102 | 23 | 18 |
|         | Negative  | 94 | 42 | 52 | 74 | 20 | 39 | 45 | NF | NF | 59 | 35 | 45 | 48 |
|         | P-value    | 0.920 | 0.165 | 0.283 | NF | 0.004 | 0.001 |
| USP3 (71) | Positive | 67 | NF | NF | 42 | 25 | NF | NF | 37 | 30 | 16 | 51 | 13 | 20 |
|         | Negative  | 80 | NF | NF | 25 | 27 | NF | NF | 61 | 19 | 50 | 30 | 48 | 60 |
|         | P-value    | NF | 0.653 | NF | 0.007 | NF | 0.001 | 0.001 |
| USP33 (72) | Positive | 58 | 24 (<55) | 34 (>55) | 32 | 26 | 38 | 20 | NF | NF | 34 | 24 | 40 | 68 |
|         | Negative  | 63 | 23 (<55) | 40 (>55) | 19 | 32 | 32 | 31 | NF | NF | 12 | 51 | 26 | 42 |
|         | P-value    | 0.583 | 0.095 | 0.182 | NF | 0.001 | 0.001 |
| USP39 (74) | Positive | 26 | NF | NF | NF | NF | NF | NF | NF | NF | 6 | 24 |
|         | Negative  | 27 | NF | NF | NF | NF | NF | NF | NF | NF | 18 | 62 |
|         | P-value    | NF | NF | NF | NF | NF | NF | NF | NF | NF | 0.019 |
Table I. Continued.

| DUB       | Expression | Cases | Age, years | Sex | Tumor size, cm | Lauren classification | TNM stage | 5-year survival |
|-----------|------------|-------|------------|-----|----------------|------------------------|-----------|-----------------|
|           |            |       | <60        | ≥60 | <5             | ≥5                     |           |                 |
|           |            |       | M          | F   |                |                        |           |                 |
| USP42 (85)| Positive   | 45    | 15 (<55)   | 30 ≥55 | 36         | 9                    | 25        | 20              | 49 NF 41 NF 49 NF 41 NF 49 NF 41 NF |
|           | Negative   | 45    | 11 (<55)   | 34 ≥55 | 31         | 14                   | 14        | 31              | 18 NF 27 NF 18 NF 27 NF 18 NF 27 NF |
|           | P-value    |       | 0.486      | 0.334 | 0.033         |                        |           |                 | 0.006 NF 0.006 NF 0.006 NF 0.006 NF |
| USP44 (86)| Positive   | 90    | NF         | NF   | 60             | 30                     | NF        | NF              | 32 NF 58 NF 32 NF 58 NF 32 NF 58 NF |
|           | Negative   | 117   | NF         | NF   | 78             | 39                     | NF        | NF              | 51 NF 66 NF 51 NF 66 NF 51 NF 66 NF |
|           | P-value    |       | NF         | 1    |                |                        |           |                 | 0.440 NF 0.440 NF 0.440 NF 0.440 NF |
| USP9X (97)| Positive   | 43    | 31         | 12   | 34             | 9                     | 29        | 14              | 11 NF 32 NF 11 NF 32 NF 11 NF 32 NF |
|           | Negative   | 25    | 15         | 10   | 18             | 7                     | 12        | 13              | 16 NF 9 NF 16 NF 9 NF 16 NF 9 NF |
|           | P-value    |       | 0.304      | 0.508 | 0.114         |                        |           |                 | 0.006 NF 0.006 NF 0.006 NF 0.006 NF |
| OTUB1 (105)| Positive  | 78    | 33         | 45   | 56             | 22                    | 35        | 43              | 10 NF 68 NF 10 NF 68 NF 10 NF 68 NF |
|           | Negative   | 78    | 40         | 38   | 64             | 14                    | 56        | 22              | 22 NF 56 NF 22 NF 56 NF 22 NF 56 NF |
|           | P-value    |       | 0.261      | 0.128 | 0.001         |                        |           |                 | 0.017 NF 0.017 NF 0.017 NF 0.017 NF |
| EIF3F (133)| Positive  | 66    | 33         | 33   | 49             | 17                    | 34        | 32              | 53 NF 13 NF 53 NF 13 NF 53 NF 13 NF |
|           | Negative   | 129   | 51         | 78   | 94             | 36                    | 80        | 49              | 46 NF 90 NF 46 NF 90 NF 46 NF 90 NF |
|           | P-value    |       | 0.170      | 0.870 | 0.160         |                        |           |                 | 0.020 NF 0.020 NF 0.020 NF 0.020 NF |

The expression of DUBs in GC and normal tissues was not significantly associated with sex or age, but was associated with tumor size, tumor stage, grading and 5-year-survival. Positive expression refers to the positive expression of a certain protein in gastric cancer. All expression was detected by immunohistochemistry. BAP1, BRCA1 associated protein-1; DUBs, deubiquitinating enzymes; EIF3F, eukaryotic translation initiation factor 3 subunit F; NF, not found; OTUB1, otubain 1; TNM, tumor-node-metastasis; UCH, ubiquitin C-terminal hydrolase; USP, ubiquitin-specific protease. *P<0.05.
As depicted in Fig. 3, the protein expression level of the USP2 subfamily in GC tissues were typically higher compared with those in normal gastric tissues in 9/10 cases, although the opposite was true for USP20. Notably, USP26 and 29 were not detected in gastric tissues, yet USP22 was expressed at levels as high as 60.31 TPM.

USP20, USP22 and USP28 have been previously determined to be associated with GC. Compared with normal tissues, high expression levels of USP28 were detected in GC tissues, and were also associated with the distant metastasis of tumors. Conversely, USP28 downregulation may significantly inhibit the proliferation and migration of GC cells; however, the
effects of USP28 expression on the proliferation and migration of gastric epithelial mucosal cell lines were not significant (46). The aforementioned findings provide a novel insight for the development of therapeutic strategies to treat GC via the regulation of USP28 (56). USP20 also serves an important role in gastric tumorigenesis and progression. A negative association between USP20 expression and tumor size, tumor invasion, and TNM stage has previously been reported (Table I). It was revealed that USP20 expression negatively correlated with patient prognosis and its anti-tumor activity. The mechanism underlying the effects of USP20 included the positive regulation of claspin stabilization in GC, thus, USP20 represents a promising molecular target for the development of novel therapeutic drugs (57). USP22-mediated protein stabilization of B cell-specific Moloney murine leukemia virus integration site 1 promotes the stemness of GC stem cells as well as GC progression, and its expression may also serve an important role in gastric carcinoma (58-60). Yang et al. discussed that USP22 expression is correlated with cancer progression. Where they found that around 57% of gastric cancer tissues showed high expression of USP22 comparing with normal connective tissue. This overexpression of USP22 consequently effect on tumor size, invasion and metastasis (60). Additionally, both USP20 and USP22 expression are positively correlated with the 5-year survival rate of patients with GC (57,60).  

**USP3s and GC.** The USP3 subfamily represents the largest family of USPs and consists of the following 12 members: USP3 (61), USP30 (62), USP31 (63,64), USP32, USP32P2 (22), USP33 (64), USP34 (65), USP35 (66), USP36 (67), USP37 (68), USP38 (69) and USP39 (70). As shown in Fig. 3, excluding USP32P2 and USP35, the expression of each member was upregulated in GC tissues compared with normal gastric tissues. The highest expression levels were exhibited by USP34 (37.21), while the lowest were reported for USP32P2 (0.33). The expression levels of USP30, USP31, USP32P2, USP35, USP37 and USP38 were <10 TPM.  

USP3 s may also serve as useful biomarkers to predict the prognosis of patients with GC. Studies investigating USP3s revealed their ability to influence cell proliferation, cell cycle regulation and transfer-related protein expression (61). In vivo experiments revealed that USP3s promoted the growth and metastasis of GC. Additionally, the high expression levels of these proteins imparted a lower survival rate in patients (71). Studies have also discovered that tumor location, tumor infiltration depth and TNM stage are all associated with USP33 upregulation, and affect the overall survival rate and prognosis of patients with GC. USP33 may also be linked with the prognosis of GC (62), and its high expression levels indicated longer survival times in patients (72).  

It was also determined that short hairpin RNA-mediated downregulation of USP39, another member of the USP3 subfamily, inhibited GC cell proliferation and colony formation. USP39 inhibition also induced G2/M phase arrest and increased poly (ADP-ribose) polymerase cleavage (Asp214) suggesting that USP39 is critical for GC cell proliferation. As USP39 is upregulated in certain types of cancer, and hyper-proliferation is a hallmark of cancer, USP39 may represent a potential therapeutic target for the treatment of several cancer types (73). By contrast, miR-133a expression was inversely correlated with USP39, which it directly targets by binding at the 3′-untranslated region; the high expression rate of USP39 indicated a longer survival time for patients (74).  

**USP4s and GC.** The USP4 subfamily has a total of 11 members: USP4 (75), USP40 (76), USP41 (77), USP42 (78), USP43 (79), USP44, USP45 (80), USP46 (80), USP47 (80), USP48 (81) and USP49 (82). Generally, the expression of USP4 s in GC tissues was increased compared with those in normal adjacent tissues; however, USP40, USP44, USP45 and USP47 were downregulated (Fig. 3). The expression levels of the seven upregulated members were all <10.  

Studies into GC have investigated USP42, USP44 and USP47. It has been reported that USP47 may represent a drug resistant target for GC. Additionally, it was determined that miR-204-5p was downregulated in GC, and may inhibit the proliferation of GC cells by targeting USP47 and RAB22A, thus serving a role in suppressing cancer development. Therefore, the recovery of miR-204-5p expression may be a potential therapeutic strategy for the treatment of GC (83,84). In vitro analyses also demonstrated that USP42 silencing suppressed cell proliferation by inducing G1/G0 arrest, and inhibited cellular invasion via matrix metalloprotease and epithelial-mesenchymal transition regulation. The increased expression of USP42 may be important in tumor progression and the metastasis of GC, and may serve as a prognostic marker (85). The combination of USP44 expression and DNA ploidy status may also serve as an independent prognostic marker in GC. Notably, the expression rate of USP44 in GC is negatively correlated with the 5-year survival rate of patients (86).  

**USP5s and GC.** The USP5 subfamily comprises six members, including USP5 (87), USP50 (88), USP51 (89), USP52 (90), USP53 (91) and USP54 (92). The expression of USP5s in GC and normal tissues differed (Fig. 3). Notably, the expression of USP52 in GC tissues was upregulated 3-fold compared with that in normal gastric tissues, and USP52 was differentially expressed compared with USP5. The expression levels of USP50 and USP51 were <1 in normal and gastric tumor tissues, and although USP5s have been associated with multiple cancer types (93), no studies have reported the association between USP5s and GC.  

**USP6s and GC.** At present, the USP6 subfamily comprises only two members, USP6 (94) and USP6NL (15). As presented in Fig. 3, the two members, particularly USP6, were not highly expressed in either GC or normal tissues. However, USP6 has been reported to contribute to the progression of colon cancer and may therefore represent a valuable prognostic biomarker for patients. USP6NL (also known as RN-tre) is a GTPase-activating protein involved in the regulation of endocytosis and signal transduction. USP6NL upregulation results in increased glycolysis in breast cancer cells and highlights a point of metabolic vulnerability for the targeting of certain therapeutic agents in a subset of aggressive basal-like breast tumors. The association between the USP6 subfamily and GC progression requires further investigation (15,95).  

**USP7s and GC.** USP7 is currently the only member of the USP7 subfamily. Its expression levels in GC tissues are
higher than those in normal tissue (46.63 TPM and 28.04 TPM, respectively; Fig. 3). Studies investigating USP7 and its relation to GC are yet to be performed; however, H. pylori was reported to affect the expression of the USP family via alternative H. pylori-specific mechanisms distinct from the conserved signaling pathways, during the activation of the innate immune response (18).

**USP8s and GC.** The roles of USP8 and its substrate (epidermal growth factor) have been evaluated in cancer therapy, and their possible targeting for the treatment of Cushing’s disease has been investigated (96); USP8 is the only member of the USP8 subfamily. As shown in Fig. 3, USP8 expression in GC tissues was increased ~2-fold compared with that in normal tissues.

**USP9s and GC.** The USP9 subfamily comprises two members, USP9X and Y. As presented in Fig. 3, the expression of USP9X in GC tissues was upregulated 2-fold compared with that of normal tissues. By contrast, the expression of USP9Y in normal tissues was higher than that of cancerous tissues, though its overall expression was notably lower than that of USP9X. Upregulation of the deubiquitinating enzyme USP9X in GC suggested that it may be associated with certain oncogenes, and it was also significantly associated with reduced survival rate (97). A link between USP9Y and GC has not yet been confirmed, although its expression has been revealed to correlate with certain breast cancer characteristics (98).

**Other proteins and GC.** Additional USP family members include CYLD lysine 63 deubiquinase (CYLD) and USPL1. Their expression in GC tissues was notably increased compared with normal tissues (Fig. 3). The CYLD signaling pathway serves a biological function similar to that of the oncogenes in gastrointestinal tumors, and has been associated with the occurrence and development of GC (99,100). Moreover, genetic variations affecting USPL1 expression have been linked to breast cancer (101).

Analysis of USP gene expression in GC and normal tissues (Fig. 3) revealed that their expression in tumor tissues is markedly upregulated compared with that in normal tissues; the majority of GC and normal tissues exhibited detectable basal levels of USP expression. Of note, the expression of certain genes was upregulated >2-fold; increased expression of USP52 (tumor=43.5; normal=13.6) was reported in normal tissues compared with GC samples. However, whether USPs may be considered as reliable prognostic indicators of GC requires further investigation. As presented in Table 1, associations between USPs, and the clinicopathological features and prognosis of GC were reported. In addition, the increased expression of the majority of USPs in GC tissues was associated with poor prognosis. It was also revealed that the expression profiles of USP10, USP20 and USP33 were the opposite of those aforementioned.

### 4. OTUs and GC

A total of 18 OTU family DUBs exist in humans, the majority of which have been associated with the prognosis of patients with tumors. OTUs can be divided into four categories: OTUBs, OTUDs, A20s and OTULINs (102). The gene expression profiles of OTUs in GC samples and paired normal tissues were presented in Fig. 4.

**OTUBs and GC.** The OTUB family comprises two members, OTUB1 (103) and OTUB2 (104), which are expressed in the majority of tissues. In the present study, their expression was determined to be increased 2-fold compared with that of normal tissues. Additionally, the expression of OTUB1 in gastric tissues was markedly higher than that of OTUB2 (which was almost undetectable), yet the expression levels of OTUB1 in GC tissues were as high as 93.09, which was twice that exhibited in normal tissues (Fig. 4). OTUB1-isoform 2 was reported to be a predictor of poor prognosis and to promote tumor progression in patients with GC (95). However, its potential clinical application as a marker of tumor invasiveness requires further investigation. Poor prognosis of patients with GC was revealed to correlate with high expression of OTUB1-isoform 2 (105); the association between OTUB2 and GC remains to be further studied.

**OTUDs and GC.** OTUDs are the largest class of DUBs, which comprises the following nine members: OTUDI-5 (106-110), OTUD6A (111) and B (112), UDP-N-acetylglucosamine transferase subunit ALG13 homolog (ALG13) and hematological and neurological expressed 1 protein (HIN1 L) (102). Using data extracted from GEPIA, the expression levels of both of the OTUD subfamily members in GC and normal tissues were determined to be relatively low. OTUD6A and HIN1L were undetectable, although the expression levels of OTUD4 and OTUD5 were >10 in GC tissues. Further investigation is required to determine the pathophysiological role of OTUDs in GC progression.

**A20s and GC.** The A20 subfamily contains five members: A20, Cezanne (113), Cezanne2 (114), Ubiquitin thioesterase ZRANB1 (TRABID) (115) and ubiquitinating protein VCIP135 (VCPIP) (102). As exhibited in Fig. 4, the expression of VCPIP in GC and normal tissues was notably high, yet low expression levels of other A20s were detected. Additionally, to the best of our knowledge, no data regarding the expression of TRABID has yet been reported. Inhibition of A20 expression or overexpression of miR-200a may prevent the polydialylation of receptor interacting serine/threonine kinase 1, and promote caspase-8 lysis and tumor necrosis factor-related apoptosis inducing ligand-associated apoptosis (102). A20 is able to induce apoptosis in GC cells, thus may be considered as a potential therapeutic target for GC (116). In the current study, the expression levels of A20s in GC tissues were not high, yet notable levels of VCPIP were detected, suggesting that further study into the prognostic value of A20s in GC is required.

**OTULINs and GC.** The OTULIN subfamily comprises only two members, OTULIN and FAB105A (102). The role of OTULIN in immune homeostasis and inflammation has been reported to result in certain autoimmune and cancer-associated defects (117). Data analysis in the present study indicated that OTULIN and FAB105A expression in GC tissues was increased compared with that in normal tissues; however, the levels of expression remained low (Fig. 4). Conversely, the
expression levels of OTUB1, OTUD5, ALG13 and VCPIP were markedly increased. In particular, OTUB1 expression in GC tissues was 93.09, which is >2-fold higher than the expression level observed in healthy tissues. Moreover, certain studies have revealed that the high expression rate of OTUB1 in GC tissues was associated with poor prognosis (105,118).

The association between the prognosis of patients with GC and the expression of other members of the OTU subfamily remains unclear; thus further investigation is required.

5. MJDs and GC

Ataxin (ATXN)3, ATXN3L, Josephin domain containing (JOSD)1 (119) and JOSD2 (120) all belong to the MJD subfamily. In the present study, JOSD1 and 2 were revealed to be expressed in both GC and normal tissues; however, the expression of ATXN3L was not detected (Fig. 5). The expression levels of ATXN3 and JOSD1 in GC tissues were increased compared with normal tissues. Notably, the expression level of JOSD2 was downregulated.
in GC samples. Furthermore, the expression of ATXN3 in GC was determined to be associated with tumor cell proliferation and infiltration (121). Therefore, the association between MJDs and the prognosis of patients with GC requires further analysis.

6. JAMMs and GC

The JAMM subfamily comprises 12 members, including COP9 signalsome subunit (CSN5), 26S proteasome non-ATPase regulatory subunit 14 (POH1) (122), BRCA1/BRCA2-containing complex subunit 3 (BRCC3) (123), MPN domain containing (MPND) (124), myb-like SWIRM and MPN domains 1 (MYSM1) (125), eukaryotic translation initiation factor 3 subunit (EIF3)H, CSN6 (126), 26S proteasome non-ATPase regulatory subunit 7 (PSMD7) (127), EIF3F, anti-Müllerian hormone (AMSH) (128), AMSH-LP (129) and pre-mRNA-processing-splicing factor 8 (PRPF8) (130). The data presented in Fig. 6 demonstrate that the expression levels of JAMMs in GC tissues were upregulated compared with those in normal tissues, particularly EIF3H and EIF3F, in which the expression levels were >120. The expression of BRCC3 was not detected. These findings suggest that the inhibition of CSN5 may result in a significant increase in p53 levels, indicating that CSN5 may be a crucial regulator of p53 and its associated intracellular signaling pathway, via CSN5-mediated cell activity. Moreover, upregulation of CSN5 has been significantly associated with the progression of GC; therefore, CSN5 may represent a novel target for the treatment of this disease (131). EIF3H was also reported to influence the progression of GC (132), and therefore, may serve as a potential therapeutic target. In particular, the strategy of inhibiting EIF3H expression may suppress the progression of GC and improve patient prognosis (131). Furthermore, EIF3F was determined to serve an important role in the recurrence of GC; increased expression rates of EIF3F in GC were associated with higher 5-year survival rates of patients (133).

7. MCPIPs and GC

The MCPIP subfamily includes MCPIP1 (134), MCPIP2-4 (135), MCPIP5 (136), MCPIP6 and 7 (137). The expression data of the MCPIP subfamily in GC and normal tissues are presented in Fig. 7. MCPIPs were expressed at markedly low levels in GC.
and normal tissues; and only MCPIP1 was expressed at levels >10. It has been demonstrated that MCPIP3 serves a negative role in the migration of human colorectal cancer cells (138). In the same study, researchers demonstrated that overexpression of MCPIP3 inhibit cell migration, which confirmed by downregulation of E-cadherin (Marker of EMT). Alternately, mutated MCPIP3 was responsible for enhancing cancer cell migration; However, MCPIP3 expression could not inhibit the cell growth and proliferation (138). Though none of the MCPIP family members were determined to be associated with the 5-year survival rate of patients with GC. In addition, the expression profiles of MCPIP5-7 in GC and normal tissues have not yet been determined. Therefore, the association between MCPIPs and GC should be further evaluated in the future.

8. Conclusions and future perspectives

According to global cancer statistics in 2018 (125), 18.1 million new cancer cases and 9.6 million cancer-associated mortalities were reported worldwide, and the incidence of GC was ranked sixth; the incidence of GC was 5.7% (18.1 million) and the mortality rate was 8.2% (9.6 million) of the total cancer cases. Furthermore, the incidence of GC in males was 7.2% (9.5 million), and the mortality rate was 9.5% (5.4 million), compared with an incidence of 4.1% (8.6 million) and mortality rate of 6.5% (4.2 million) in female patients (139). The high prevalence and mortality rates suggest that novel therapeutic strategies are required to treat this disease. The present review focused on the association between GC and DUBs. The present study reported that DUBs are typically upregulated in the majority of GC tissues (79%). A total of 25% of the reported GC cases exhibited a ≥2-fold increase in DUB expression compared with that of normal tissues. Only 19% of healthy tissues exhibited enhanced USP32P2 and USP52 expression, in which this expression was twice the level of that in GC tissues (Fig. 8D). Notably, USP17L2, USP26 and USP29 expression was detected in both GC and normal tissues. On the contrary, the number of DUBs associated with GC was determined to be 29%. Following analysis of data from previously published studies (Table I), the expression of DUBs in GC and normal tissues was not determined to be associated with either sex or age; however, an association between DUBs and tumor size, classification and staging was observed. In addition, the expression level of DUBs was significantly associated with the 5-year survival rate of patients with GC. Among the upregulated genes in GC, six DUBs were linked to a high 5-year survival rate, though the difference between the two was not significant. Thus, DUBs may serve a dual role in the prognosis of GC. However, further investigation is required. Providing that DUBs can be divided into two categories according to the prognosis of GC, the common features associated with this disease and DUBs may be identified, in which DUBs may be considered in the development of treatments for GC.

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Authors' contributions
JS, XS and YG conducted literature searching and wrote this review. JS conducted the data analysis. The language of the review was edited by MAAM.

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Competing interests
The authors declare that they have no competing interests.

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