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E3 ubiquitin ligase HECW2: a promising target for tumour therapy

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Abstract
Ubiquitination is a prevalent post-translational modification that plays a crucial role in a wide range of pathophysiological processes, including cell proliferation, apoptosis, autophagy, immune response, and DNA damage repair. Among the enzymes involved in ubiquitination, E3 ubiquitin ligases are particularly significant, serving as key regulators of numerous diseases, including tumours. This review focuses on HECW2 (HECT, C2, and WW domain-containing E3 ubiquitin protein ligase 2, also known as NEDL2), providing a comprehensive overview of its interactors and its pathological roles in tumorous cancer and other diseases. The insights gained from this review may contribute to the development of novel treatment strategies for various diseases, particularly tumours.

Keywords E3 ubiquitin ligase HECW2, Tumours, Prognosis, Immune infiltration, Interacting proteins, Pathological roles

Introduction

Ubiquitination is the process by which ubiquitin is covalently attached to substrate proteins, a reaction that is synergistically catalysed by E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases [1]. Among these enzymes, E3 ubiquitin ligases are pivotal as they determine the specificity and extent of ubiquitination of substrate proteins [2]. Although various types of E3 ubiquitin ligases exist, the HECT- and RING-type E3 ubiquitin ligases have been extensively studied [3]. As illustrated in Fig. 1, HECT-type E3 ubiquitin ligases are classified into three groups: (1) the NEDD4 subfamily with WW domains, including HECW1, HECW2, NEDD4-1, NEDD4-2, SMURF1, SMURF2, WWP1, WWP2, and ITCH; (2) the HERC subfamily with RLD-like domains, including HERC1, HERC2, HERC3, HERC4, HERC5, and HERC6; (3) other HECT-type E3 ubiquitin ligases lacking WW and RLD domains, including E6-AP, EDD, HECTD2, HUWE1, HACE1, G2E3, and TRIP12, among others [4]. As a member of the NEDD4 subfamily, HECW2 has been implicated in numerous diseases including tumours and nervous system disorders [5, 6]. This review provides a comprehensive analysis of HECW2, addressing its subcellular localization, structural characteristics, expression patterns, prognostic significance, interacting proteins, and its roles in tumours and nervous system disorders.

An overview of HECW2

The subcellular localization and protein structure of HECW2

The foundation of function lies in structure, and in this context, we firstly reviewed the localization and structure of HECW2. The gene encoding HECW2 (Homo sapiens)

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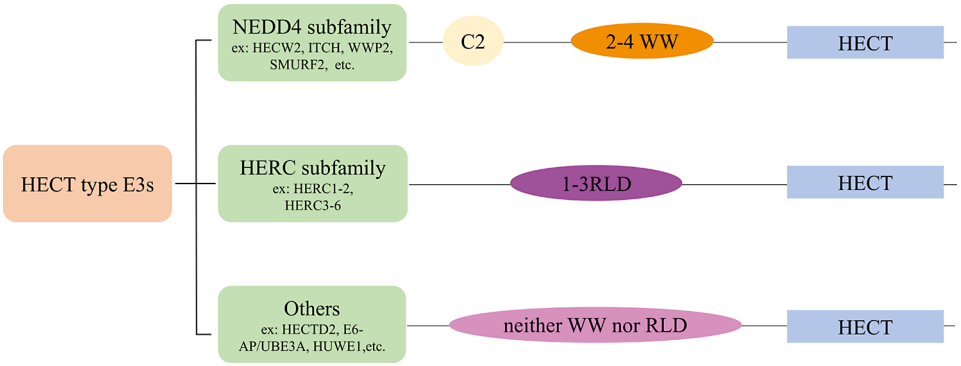

Fig. 1 HECTtype E3 ligases. HECT type E3 ligases can be classified into three subfamilies: the NEDD4 subfamily with WW domains, the HERC subfamily with RLD-like domains and other HECT-type E3 ubiquitin ligases lacking WW and RLD domains

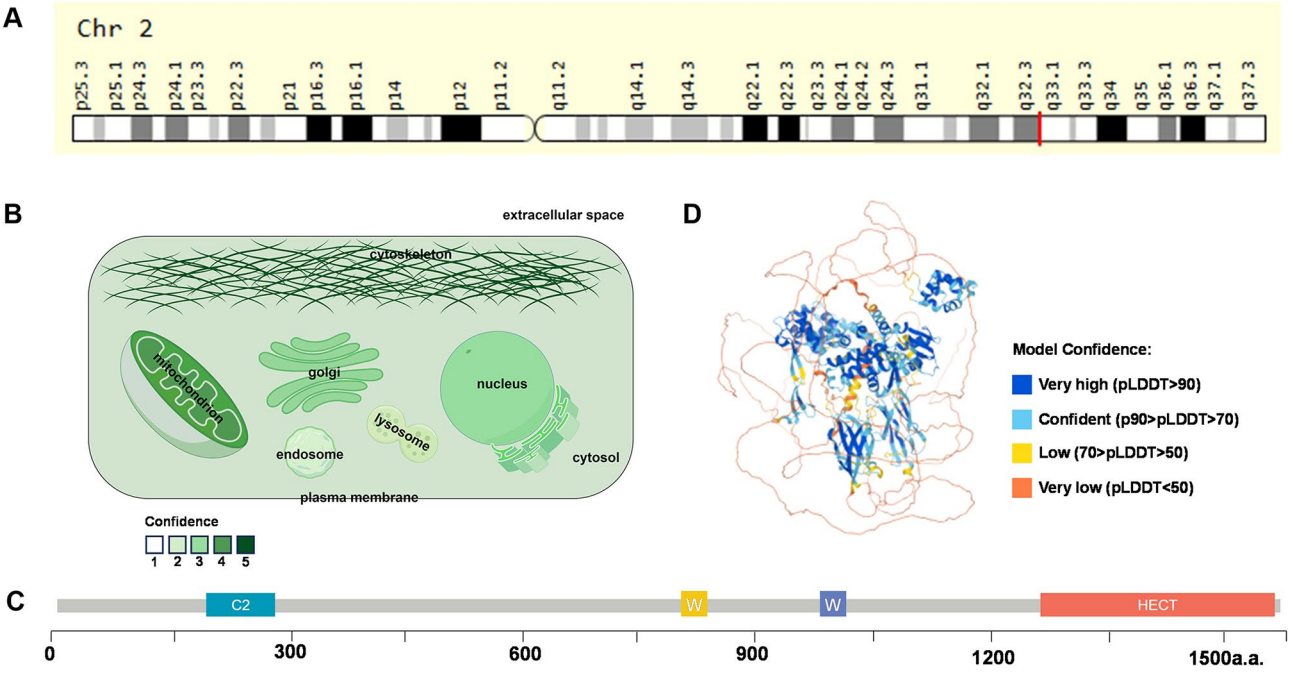

Fig. 2 Illustration of the subcellular localization and protein structure of HECW2. (**A**) The genomic position of the HECW2 gene on the chromosome from the GeneCards database. (**B**) The subcellular localization of the HECW2 protein from the GeneCards database. (**C**) The primary structure of HECW2 from the PhosphoSitePlus® database. (**D**) The advanced structure of HECW2 from GeneCards database, the PDB ID for HECW2 is 2LFE

was located on chromosome 2q32.3 (Fig. 2A), encompassing a total of 33 exons. The subcellular localization of the HECW2 protein obtained from the GeneCards database is shown in Fig. 2B. The primary and advanced structures of HECW2 are shown in Fig. 2C-D. HECW2 mainly consists of several distinctive protein domains: an N-terminal C2 domain (positioned at amino acids 192–281) and two WW domains (positioned at amino acids 809–838 and 987–1016) as well as a C-terminal HECT catalytic domain homologous to the E6AP carboxyl-terminus (positioned at amino acids 1268–1571(Fig. 2C) [4]. Each domain has a unique function. The C2 domain has Ca^{2+}/phospholipid-binding capabilities, thereby regulating the subcellular localization of substrate proteins [7]. The WW domain facilitates protein-protein interactions by recognizing the PY motifs present in substrate proteins [8]. The HECT domain mediates ubiquitin transfer to substrate proteins, primarily through thioester bond formation with ubiquitin [3, 9].

The expression levels of HECW2 in pan-cancer and their relationship with pan-cancer prognosis

HECW2 is widely expressed in various normal tissues and exhibits high relative mRNA expression levels in the lungs, spleen, testis, heart, and brain. Conversely, lower relative mRNA expression levels of HECW2 were observed in kidney, muscle, ovary, and colon tissues (Fig. 3A-C). Consistent with these findings, northern

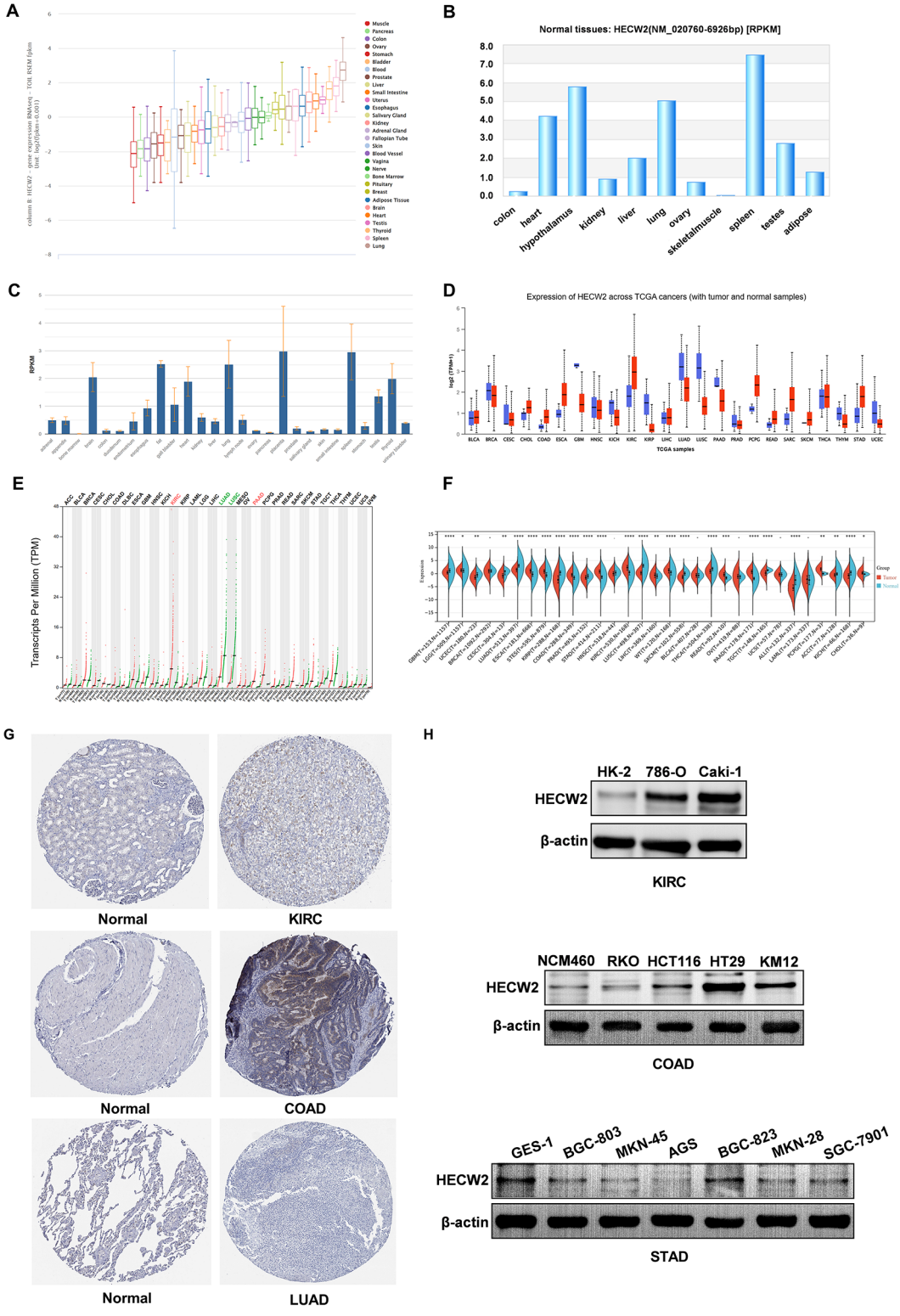

Fig. 3 The expression levels of HECW2 mRNA and protein. (**A-C**) The mRNA relative expression levels of HECW2 in normal tissues from UCSC Xena, RNA-Seq Atlas and NCBI databases, respectively. (**D-F**) The relative mRNA expression levels of HECW2 in tumour tissues from UALCAN, GEPIA, and Sangerbox databases, respectively. (**G**) The protein expression levels of HECW2 in KIRC, COAD, and LUAD from HPA database. (**H**) The protein expression levels of HECW2 in KIRC, COAD, and STAD cell lines evaluated by western blotting

blot analysis has revealed robust HECW2 expression in the adult brain, lungs, and heart [10]. In tumour tissues, HECW2 expression was higher in kidney renal clear cell carcinoma (KIRC) tissues, whereas its expression was lower in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) tissues (Fig. 3D-F). Furthermore, the Human Protein Atlas (HPA) database demonstrated elevated HECW2 protein levels in KIRC and colon adenocarcinoma (COAD) tissues but demonstrated reduced levels in LUAD tissues (Fig. 3G). At the same time, western blotting analysis results showed that HECW2 is highly expressed in KIRC and COAD cells, while lowly expressed in gastric adenocarcinoma (STAD) (Fig. 3H), which was in line with the results reported by LU [11].

Next, we assessed the association between HECW2 expression and tumour prognosis. As shown in Fig. 4A-D, patients with renal papillary cell carcinoma (KIRP) in the high-expression group exhibited significantly shorter overall survival (OS), disease-specific survival (DSS), progression-free interval (PFI), and disease-free interval (DFI) than those in the low-expression group, and patients with uveal melanoma (UVM) in the high-expression group exhibited remarkably shorter OS, DSS, and PFI. In contrast, the higher the expression level of HECW2, the longer OS, DSS, and PFI in patients with glioma (GBMLGG) and KIRC (Fig. 4A-D). These findings suggest a negative correlation between HECW2 expression levels and prognosis in KIRP and UVM, and a positive correlation between GBMLGG and KIRC. Therefore, HECW2 may be an adverse prognostic factor for KIRP and UVM, but a favourable prognostic factor for GBMLGG and KIRC.

The relationship between the expression levels of HECW2 and immune infiltration in pan-cancer

The tumour microenvironment (TME) comprises cellular compontents (such as tumour, immune, and stromal cells) and noncellular components (such as the extracellular matrix, growth factors, and chemokines) [12]. This intricate TME plays a key role in determining the survival time of patients with tumours and their sensitivity to immunotherapy [13, 14]. Using the TISIDB database, we initially examined the association between HECW2 expression and the infiltration abundance of immune cells across various tumour types. In rectal adenocarcinoma (READ), a strong positive correlation was observed between HECW2 expression and effector memory $CD4^+$T cells (Tem CD4) (r=0.6, P<2.2e-16). Conversely, in brain low grade gliomas (LGG), there was a negative correlation between HECW2 expression and CD56 bright natural killer cells (CD56 bright NK) (r=-0.54, P<2.2e-16) (Fig. 5A). Furthermore, in colorectal cancer (CRC), STAD, and LIHC, HECW2 expression levels were positively correlated with Stromal, Immune and ESTIMATE scores; however, an inverse relationship was observed for GBM(Supplemental Fig. S1).

Chemokines and chemokine receptors play crucial roles in various processes involved in tumour progression such as cell proliferation, migration, invasion, and angiogenesis [15, 16]. Consequently, they have a profound impact on the prognosis and response to immunotherapy in patients [17–20]. There was a positive correlation between HECW2 expression and the chemokines CCL2 and CCL7 in patients with COAD (Fig. 5B). This suggests that HECW2 regulates COAD development by interacting with CCL2 and CCL7. Similarly, previous studies have demonstrated that downregulation of the E3 ubiquitin ligase Fbxw7 could reduce the production of the macrophage-derived chemokines CCL2 and CCL7 in colon tissue, thereby alleviating colon inflammation [21]. Conversely, HECW2 expression levels were negatively related to CXCL17 in thyroid carcinoma (THCA) (r=-0.532, P<2.2e-16) (Fig. 5B). As depict in Fig. 5C, a notable positive correlation is observed between the expression levels of HECW2 and CCR4 (a receptor of chemokine CCL22) in head and neck squamous cell carcinoma (HNSC) (r=0.564, P<2.2e-16). In the READ, the expression levels of HECW2 exhibited significant positive correlations not only with the chemokine CXCL12 (r=0.575, P<2.2e-16), but also with the CXCL12 receptor CXCR4 (r=0.428, P=1.16e-08) (Fig. 5B-C). These findings suggest that HECW2 serves as an immunoregulatory factor in various malignancies.

Immunomodulators can be categorised into three groups: immunosuppressants, immunostimulators, and MHC molecules [22]. As shown in Fig. 6A, there was a positive correlation between the expression levels of HECW2 and the immunosuppressant KDR in many tumours, including cholangiocarcinoma (CHOL) (r=0.83, P=9.48e-08), READ (r=0.785, P<2.2e-16), and KIRC (r=0.815, P<2.2e-16). Conversely, there was a negative correlation between HECW2 expression levels and PVRL2 in TGCT (r=-0.581, P<2.2e-16) (Fig. 6A). As shown in Fig. 6B, HECW2 expression was most positively correlated with the immunostimulator TMEM173 in LIHC (r=0.629, P<2.2e-16), whereas the strongest negative correlation with C10orf54 was found in mesothelioma (MESO) (r=-0.652, P<2.2e-16). Additionally, there was a negative correlation between HECW2 and TNFRSF14 expression in COAD (r=-0.292, P=2.13e-10), READ (r=-0.466, P=3.4e-10), and KIRC (r=-0.282, P=4.11e-11) (Fig. 6B).

We then assessed the correlation between the expression levels of HECW2 and MHC molecules in the pan-cancer stage because MHC molecules play a pivotal role in tissue rejection, antigen presentation, and immune responses [23]. The expression levels of HECW2

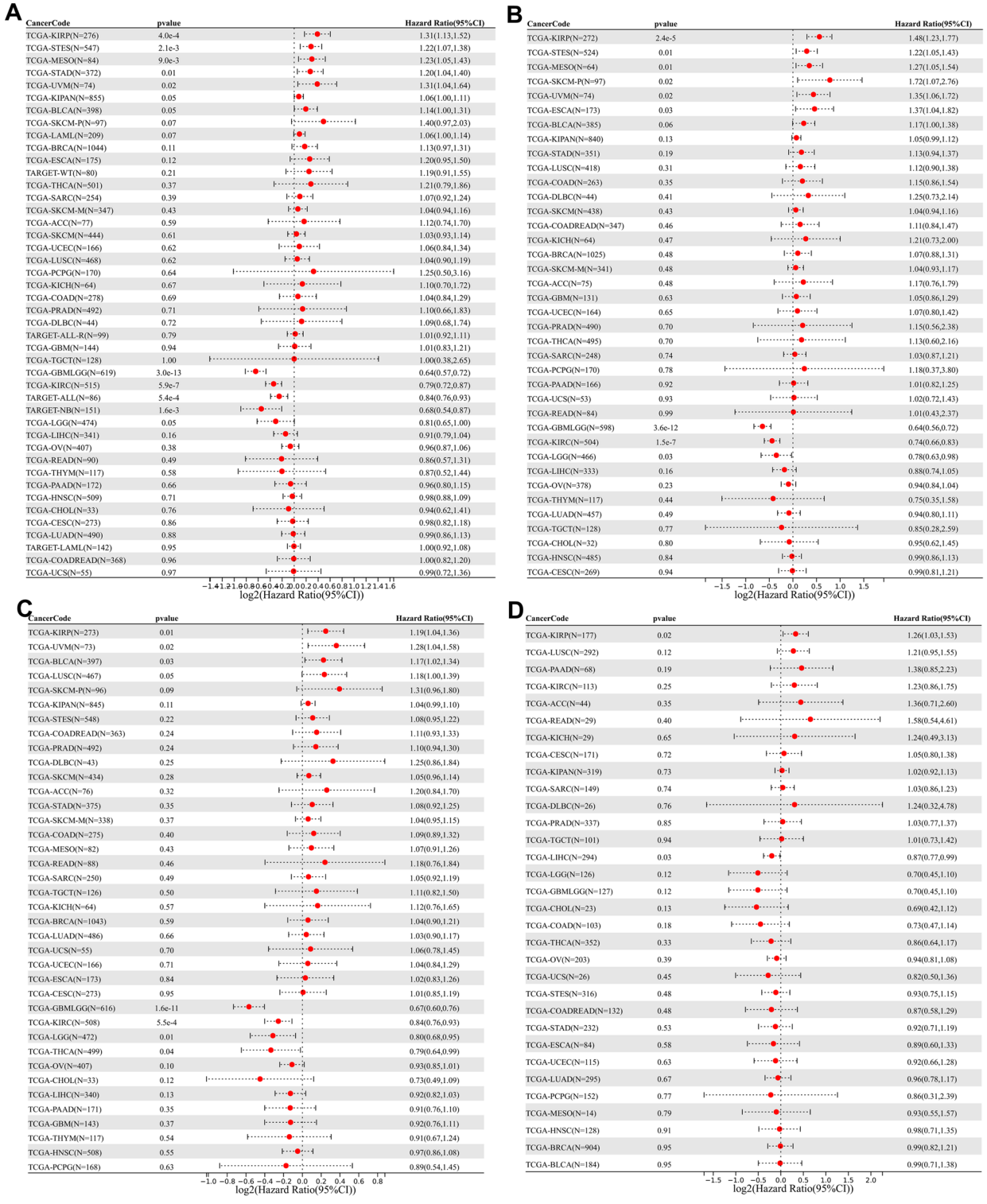

Fig. 4 The correlation between HECW2 expression levels and OS(**A**), DSS (**B**), PFI(**C**) and DFI(**D**) in pan-cancer

exhibited the strongest positive correlation with TAP1 (r=0.488, P=5.8e-06) in UVM, and exhibited the strongest negative correlation with TAPBP (r=-0.548, P<2.2e-16) in LGG(Fig. 6C). Furthermore, there was a significant positive association between HECW2 expression and HLA-DOA in COAD (r=0.343, P=5.36e-14), READ (r=0.388, P=2.78e-07), LUSC (r=0.336, P=1.58e-14), and STAD (r=0.163, P=0.000899), but a significant

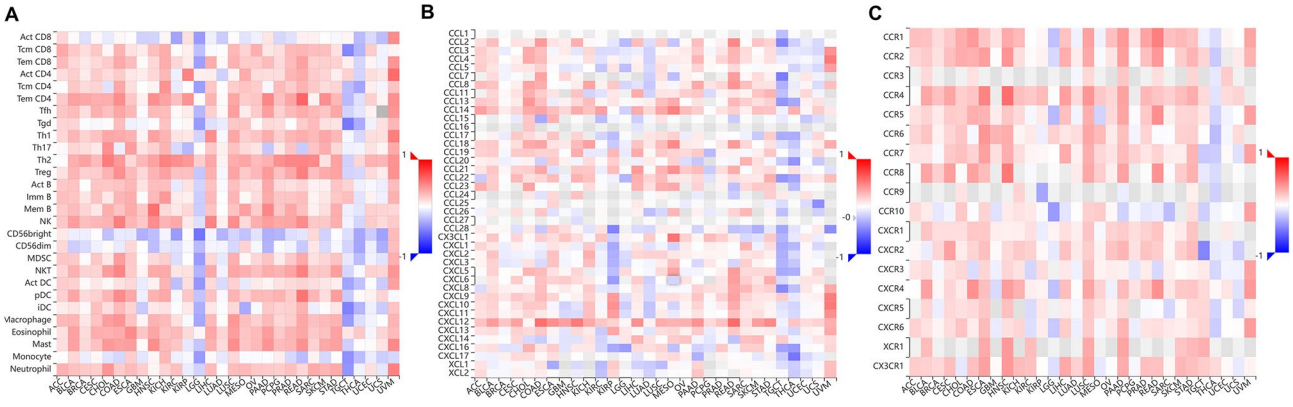

Fig. 5 The association between HECW2 expression levels and immune cell abundance(**A**), chemokines(**B**) and chemokine receptors(**C**) in pan-cancer

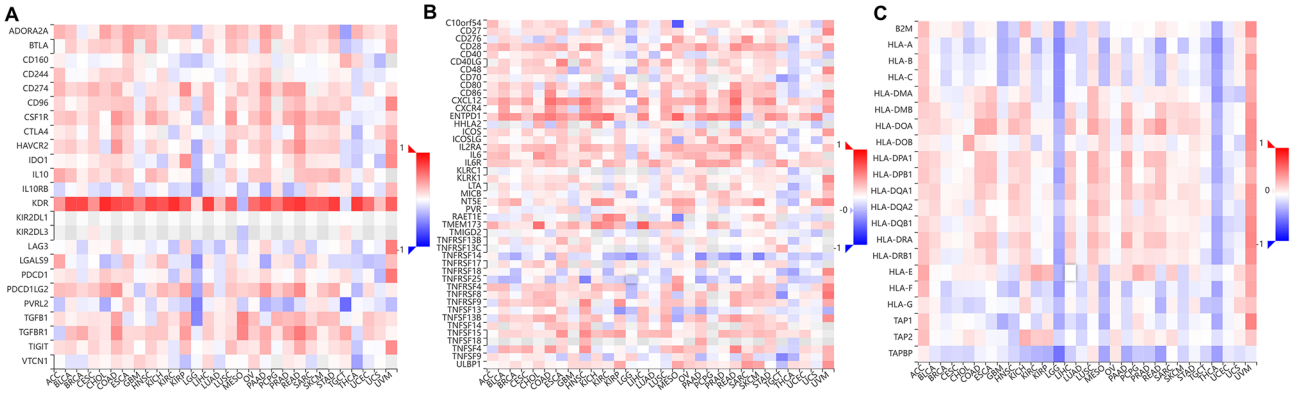

Fig. 6 The correlation between HECW2 expression levels and immunosuppressants (**A**), immunostimulators (**B**) and MHC molecules (**C**) in pan-cancer

negative correlation in THCA (r=-0.282, P=1.07e-10) (Fig. 6C).

The interactors of HECW2 protein

Interacting proteins of HECW2

Using the STRING database, we identified several proteins that interact with HECW2, including AMOTL1, ARRDC1, and UBE2L3 (Fig. 7A and Supplemental Table S1). With the help of the IntAct database, we identified additional proteins that interact with HECW2, such as ENTREP1, FBXL15, and HNRNPD (Fig. 7B and Supplemental Table S2). Moreover, FAM189A2, ARRDC3, FAM189B, and LDLRAD4 were capable of interacting with HECW2, based on the BioGrid and BioPlex databases (Supplemental Table S3). Further experimental validation is required to determine whether these interactions are direct or indirect under certain circumstances.

The candidate substrates and E3 ubiquitin ligases of HECW2

As an E3 ubiquitin ligase, HECW2 affects the stability and activity of its substrate proteins via ubiquitination. Some potential substrates of HECW2 are shown in Fig. 7C, with the top five being IGF1R, NEDD4-1, INSR, TGFBR2, and SCNN1A. On the other hand, TP73, PCNA, Lamin B1 (LMNB1), AMOTL1, HP1α/HP1β, KPNA1, and MORC4 were identified as substrates of HECW2 by experiment (Supplemental Table S4) [10, 24–28]. Additionally, several E3 ubiquitin ligases were predicted able to ubiquitinate HECW2, such as HECW1, HECW2, and NEDD4L, among others. (Fig. 7D).

The pathological roles of HECW2 in tumours and nervous system diseases

The role of HECW2 in tumours

(1) Colorectal cancer

Accumulating evidence suggests that HECW2 plays a vital role in CRC tumourigenesis and progression. For instance, KPNA1 and MORC4 can facilitate CRC progression, considering that they can be degraded by HECW2 through ubiquination modification, indicating that HECW2 may be involved in the regulation of CRC development [27, 28]. Previous studies have reported that HECW2 could mediate the ubiquitin-proteasome degradation of PCNA and LMNB1 in HEK293T cells [24]. Considering the significance of PCNA and LMNB1 in CRC development, HECW2 regulates CRC progression by mediating the ubiquitin-proteasome degradation of

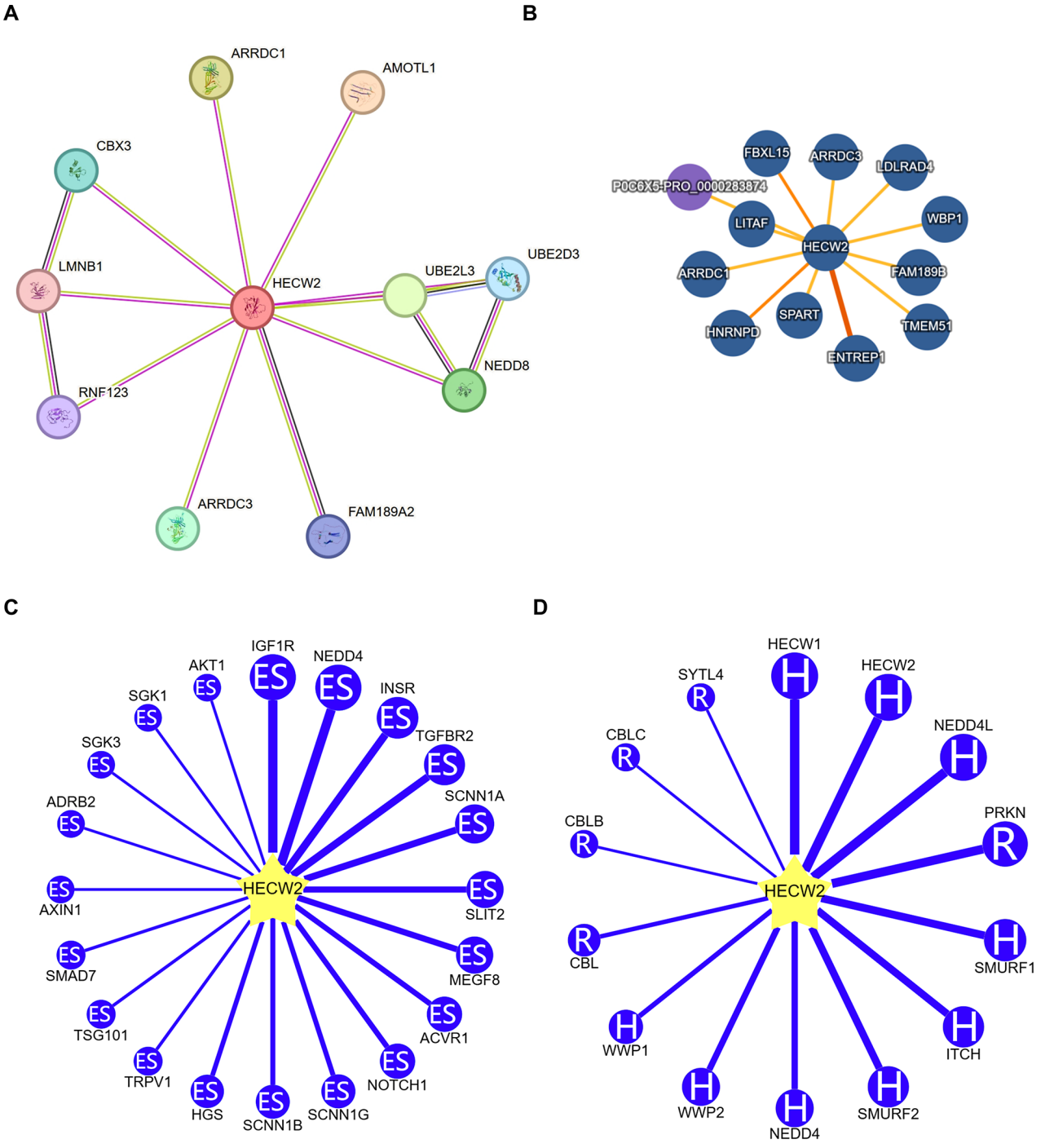

Fig. 7 The interacting proteins, candidate substrates and E3 ligases of HECW2. (**A-B**) The interacting proteins identified from STRING database and IntAct database. (**C-D**) The candidate substrates and E3 ligases of HECW2 from Ubibrowser database

PCNA or LMNB1 [29–31]. In addition to this evidence, our previous study demonstrated that HECW2 is highly expressed in both CRC tissues and cell lines [5]. HECW2 knockdown inhibits the proliferation, migration, invasion, and chemoresistance of CRC cells, whereas HECW2 overexpression yields contrasting results [5]. Moreover, we found that HECW2 might contribute to the progression and chemoresistance of CRC via activating AKT/mTOR signalling by mediating ubiquitin-proteasome degradation of LMNB1 [5] (Fig. 8).

(2) Cervical cancer

Besides CRC, HECW2 may also play a major role in the development of cervical cancer. Feng et al. found that

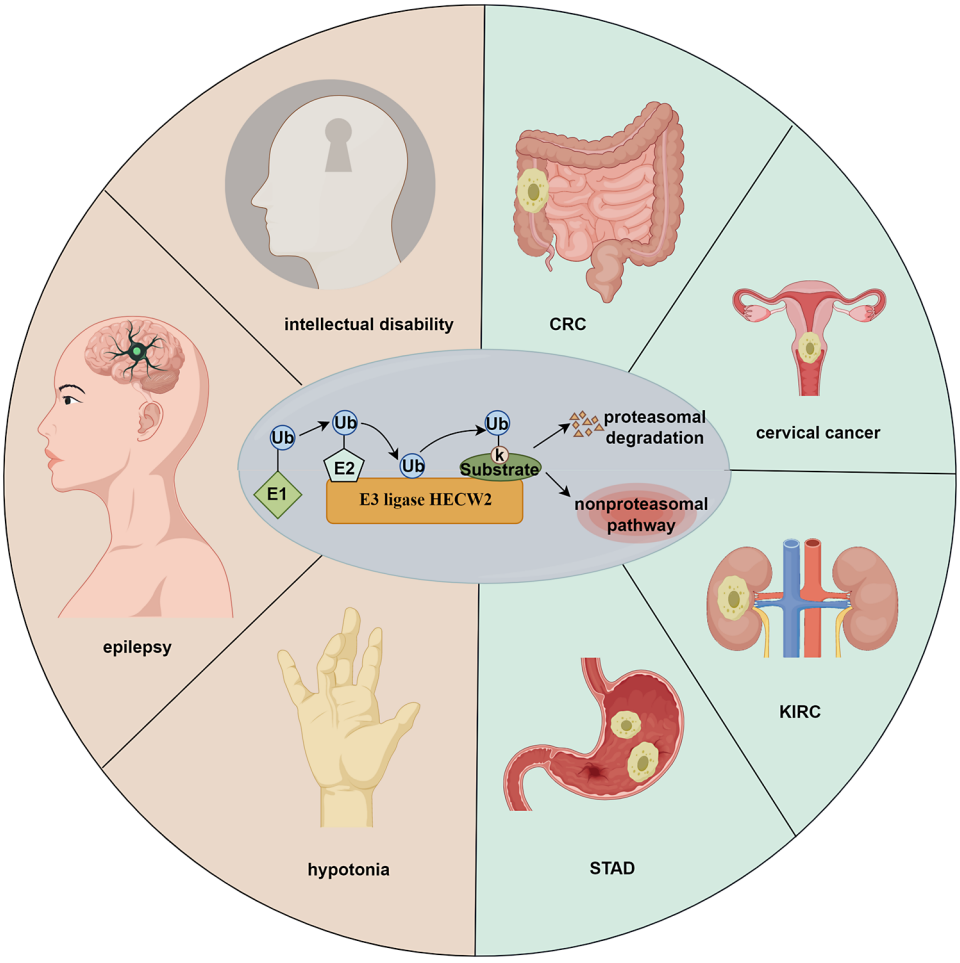

Fig. 8 The pathological implications of HECW2 in tumours and nervous system diseases

the gene integration hotspot HECW2 may be a potential carcinogenic target of HPV, which is a classical factor promoting cervical cancer progression [32]. The DNA repair capacity of cervical cancer cells expressing lamin A mutants was impaired by the depletion of ATR kinase, and HECW2 facilitated the proteasomal degradation of ATR kinase [33]. Additionally, miR-944 promotes the proliferation, migration, and invasion of cervical cancer cells by targeting HECW2 [34] (Fig. 8).

(3) Other tumours

It has been reported that patients with hamatologic malignancies in the HECW2 high expression group survived longer than those in the HECW2 low expression group [35]. HECW2 has been proposed as an independent prognostic factor and novel biomarker for prostate cancer and neuroblastoma [36]. Similarly, HECW2 is regarded as a promising candidate hub gene for targeted therapy in congenital giant melanocytic nevus [37]. In our previous study, we showed that HECW2 was highly expressed in KIRC and that knockdown of HECW2 could inhibit the proliferation and migration of KIRC cells [38]. We also showed that the higher the expression levels of HECW2, the shorter the overall survival time of STAD patients [39]. In summary, HECW2 may play different regulatory roles in different tumours, and the specific molecular mechanisms involved require further study (Fig. 8).

Nervous system diseases

Initial research on HECW2 focused on its involvement in nervous system disorders. Case reports and literature reviews have provided evidence linking HECW2 mutations to epilepsy, intellectual disabilities, hypotonia, speech disorders, and episodic ataxia [6, 40–43]. Specifically, seizures and cortical visual disturbances have been observed exclusively within the HECT domain variants of HECW2 [40, 44]. Functionally, HECW2 plays a crucial role in stabilizing P73-a key mediator of neural development and neurogenesis [41, 45]. HECW2 positively regulates the proliferation of enteric neural precursors through the GDNF/Akt signalling pathway; HECW2 deficient mice exhibited progressive bowel motility defects attributed to intestinal aganglionosis [46]. Furthermore,

HECW2 may serve as a new candidate gene for multiple malformations (a group of genetic disorders characterised by neurodevelopmental abnormalities and congenital malformations) [47] (Fig. 8).

Conclusions and perspective

In this study, we conducted a comprehensive review of the current knowledge on the E3 ubiquitin ligase HECW2, by studying various databases, literature, and our previous results. Overall, we found that HECW2 is expressed at high levels in COAD and KIRC, whereas it is expressed at low levels in LUAD. The expression levels of HECW2 are positively correlated with the prognosis of KIRC and GBMLGG, but negatively correlated with the prognosis of KIRP and UVM. Furthermore, in most tumours, the higher the HECW2 expression level, the higher was infiltration abundance of stromal and immune cells. The expression levels of HECW2 were closely related to the abundance of immune cells, chemokines, and chemokine receptors in many tumours, including COAD, STAD, and LGG. In addition, numerous interacting proteins and candidate substrates of HECW2 have been identified. HECW2 may play a crucial role in the progression of CRC, KIRC, and cervical cancer through its ubiquitination activity, and thereby holds potential as a prognostic biomarker and therapeutic target for these tumours. Inhibition of HECW2 may be a promising antitumour strategy. Notably, researchers successfully identified NSC 288,387 as a target inhibitor of WWP2 [48]. Full-length Smurf2, NEDD4-1, and WWP2 were all inhibited by heclin, a small-molecule inhibitor [49]. But so far, there are no reports about spectific small molecule inhibitors targeting HECW2. Our research group will further study the molecular mechanism by which HECW2 regulates CRC and KIRC progression and strive to screen for targeted inhibitors of HECW2.

Databases

(1) **GeneCards**: Genecards is a comprehensive database of searchable genes where we can access information on almost all known human genes (https://www.genecards.org).
(2) **UCSC Xena**: UCSC Xena is a cancer genomics data analysis platform that supports the visualization and analysis of a wide range of genomics data from cancer samples (https://xena.ucsc.edu).
(3) **RNA-Seq Atlas**: RNA-Seq Atlas is a web-based library of RNA-Seq gene expression profiling and query tools (http://medicalgenomics.org/rna_seq_atlas).
(4) **NCBI**: NCBI is the world's largest genetic database. It contains the nucleotide sequences of more than 70,000 organisms, and each record is annotated with coding region (CDS) features and includes amino acid translations (https://www.ncbi.nlm.nih.gov/).
(5) **UALCAN**: UALCAN is an effective website for online analysis and mining of cancer data, primarily based on relevant cancer data from the TCGA database (http://ualcan.path.uab.edu/index.html).
(6) **Gene Expression Profiling Interactive Analysis**: The GEPIA database includes RNA sequencing data from 9736 tumor tissues and 8587 normal tissues from the TCGA and GTEx databases, and the main functions provided are: gene expression analysis, gene correlation analysis, survival analysis, similar gene prediction, and downscaling analysis (http://gepia.cancer-pku.cn/).
(7) **Sangerbox**: Sangerbox is a web-based tool platform that allows users to perform different analyses in one friendly and interactive page (http://vip.sangerbox.com).
(8) **Human Protein Altas**: The Human Protein Atlas is a program with the aim to map all the human proteins in cells, tissues, and organs using an integration of various omics technologies, including antibody-based imaging, mass spectrometry-based proteomics, transcriptomics, and systems biology (www.proteinatlas.org).
(9) **TISIDB**: A database on tumor-immunity interactions built by integrating research articles and multiple types of high-throughput data. Users can easily find immune relationships between specific genes and the tumorigenic environment by searching the various data resources stored in TISIDB (http://cis.hku.hk/TISIDB/).
(10) **STRING**: The STRING database is a protein interaction network database based on public databases and literature information. It collects several public databases, including UniProt, KEGG, NCBI and Gene Ontology, integrates these data and generates a comprehensive protein interaction network database (https://cn.string-db.org db.org).
(11) **IntAct**: IntAct is an open source, open data database of molecular interactions consisting of data selected from the literature or directly from the data warehouse (http://www.ebi.ac.uk/intact/).
(12) **Biogrid**: The Biological General Repository for Interaction Datasets (BioGrid) is an open access database that houses genetic and protein interactions curated from the primary biomedical literature for all major model organism species and humans (https://thebiogrid.org/).
(13) **Ubibrowser**: Ubibrowser is a Web-based bioinformatics database for managing and querying a wide range of bioinformatics data such as genomes, transcriptomes, proteomes and more (http://ubibrowser.ncpsb.org/).

Supplementary Information

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Supplementary Material 1

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Author contributions
S.H. and L.F. wrote the main manuscript text, and L.F. and Z.J. supervised the main manuscript text and K.Q. and S.L. prepared Figs. 1, 2, 3, 4, 5, 6 and 7. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Conflict of interest
The authors declare no competing interests.

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