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Review article

Research advancements on the involvement of E3 ubiquitin ligase UBR5 in gastrointestinal cancers

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ABSTRACT

E3 ubiquitin ligases comprise a family of ubiquitination-catalyzing enzymes that have been extensively researched and are considered crucial components of the ubiquitin-proteasome system involved in various diseases. The ubiquitin-protein ligase E3 component n-recognition 5 (UBR5) is an E3 ubiquitin-protein ligase that has garnered considerable interest of late. Recent studies demonstrate that UBR5 undergoes high-frequency mutations, chromosomal amplification, and/or abnormalities during expression of various malignant tumors. These alterations correlate with the biological behaviors and prognoses of malignancies, such as tumor invasion, metastasis, and resistance to chemotherapeutic agents. This study aimed to comprehensively elucidate the biological functions of UBR5, and its role and relevance in the context of gastrointestinal cancers. Furthermore, this article expounds a scientific basis to explore the molecular mechanisms underlying gastrointestinal cancers and developing targeted therapeutic strategies for their remediation.

The ubiquitin-proteasome system (UPS) is a typical post-translational modification pathway [1–3] that assumes a pivotal role in the regulation of cell survival and differentiation together with intracellular protein homeostasis to maintain normal cellular activities and modulate signaling pathways. UPS dysfunction can induce aberrations in the expression levels, interactions, and/or subcellular localization of substrate proteins. In recent years, numerous studies demonstrated the occurrence of abnormal protein ubiquitination modifications in various diseases, including cancer [4–7]. Three key enzymes catalyze the ubiquitin pathway: E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases [8–10]. E3 ubiquitin ligases are indispensable to the ubiquitination pathway and can be used as potential targets for therapeutic intervention, owing to their ability to selectively identify target proteins and simultaneously degrade the ubiquitin transferred to the substrate [11–14]. Currently, over 650 E3 ubiquitin ligases are discovered in the human body, among which UBR5 has garnered contemporary focus as a progestin-induced protein. In this review, we focused on novel findings regarding the function of UBR5 in gastrointestinal cancers and its potential as a biomarker and prognostic factor.

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1. Structure and function of UBR5

UBR5 is a mammalian ortholog of the Drosophila hyperplastic disc tumor suppressor gene that encodes a ubiquitin ligase [15]. Human UBR5 was first discovered in breast cancer cells, where it functions as a tumor suppressor gene [16]. The human UBR5 gene encodes an mRNA of approximately 10 kbp that translates into a protein of >300 kDa. It is highly conserved in multicellular organisms and comprises five structural domains: an N-terminal ubiquitin-associated domain, two predicted small β-barrel domains (SBB1 and SBB2), a UBR-box domain, an MLLE domain that was previously known as the poly(A)-binding protein (PABC) domain, and a C-terminal homologous to the E6AP C-terminus (HECT) domain [17,18]. The HECT domain consists of an N-terminal and a C-terminal that are connected by a flexible linker. MLLE inserts into the N-lobe of the HECT domain. The N-terminus binds E2, whereas the C-terminus carries a catalytic cysteine that accepts ubiquitin from E2 to generate an E3 ubiquitin complex [19]. However, the HECT domain of UBR5 is characteristically distinct compared to other HECT ligases. Neither the C-terminus nor the N-terminus presents non-covalently bound ubiquitin surfaces [20,21]. According to another recent study,the UBA domain facilitates the enlistment of Ub-loaded E2 (E2∼Ub) to UBR5. The flexibility of the hinge region enables rotations in the HECT domain, which likely enable the engagement of E2∼Ub with the HECT domain N [22](Fig. 1). Furthermore, based on cryo-electron microscopy(Cryo-EM) observations, two latest studies found that two crescent-shaped UBR5 monomers assemble head-to-tail to form the dimer, and the dimer interface is further stabilized by a domain-swapped dimerization loop (DSD loop). Subsequently,two dimers bind face-to-face to form the cage-like tetramer [18,22].

Numerous studies confirm that UBR5 (functioning as an E3 ligase) assumes a remarkably significant role in the UPS enzymatic cascade reaction and mediates the regulation of many cellular processes: DNA damage repair, metabolism, transcription, apoptosis [23–25] (Fig. 2). UBR5 is required for the correct maturation of ribosomal RNA [26]. Furthermore, UBR5 plays an important role in disassembling mitotic checkpoint complexes [27]. The ongoing advancements in research have depicted that UBR5 modulates the emergence and proliferation of various types of cancer through protein interaction. Moreover, UBR5 undergoes mutations (including point and frameshift mutations) and/or overexpression in tumor cells [28]. Point mutations are prevalent in the UBR5 open reading frame. Conversely, frameshift mutations are predominantly localized in the PABC/HECT region of UBR5 and lead to the loss of E3 Ub ligase activity. These mutations aid further speculation regarding the involvement of UBR5 in malignancies.

2. Research advancements pertaining to the role of UBR5 in gastrointestinal cancers

The latest statistics from the National Cancer Center of China have documented approximately 4.064 million emergent cases of cancer and 2.4135 million cancer-related fatalities nationwide in 2016. Among them, malignant tumors of the digestive system accounted for 69.3 % of the mortalities [29]. Moreover, a growing body of evidence reveals that the expression level of UBR5 is intricately related to the malignant phenotype and poor prognosis associated with multiple cancers [30,31] (Fig. 3).

2.1. Esophageal cancer

An extant literature survey revealed a limited number of studies on the involvement of UBR5 in esophageal cancer. The transcription factor sex-determining region SRY-box 2 (SOX2) notably contributes to the maintenance of the self-renewal of cancer stem cells and plays a crucial role in cancer stem cell formation. SOX2 gene amplification is implicated as a driver of various cancers, including esophageal cancer, and it enhances the stem cell properties of esophageal cancer [32]. UBR5 promotes its degradation by ubiquitinating SOX2 at lysine 115, and the SOX2 level increases after UBR5 knockdown that promotes tumor formation. Simultaneous knockdown of UBR5 and SOX2 inhibits tumor formation, which indicates that UBR5 regulates the proliferation and cancer stem cell properties of esophageal cancer cells through SOX2 [33].

2.2. Gastric cancer

Current worldwide morbidity and mortality rates of gastric cancer are high; however, its pathogenesis is not fully elucidated. Researchers on the function of UBR5 in gastric cancer provided a scientific basis to further elucidate the pathogenesis of gastric cancer. Studies have depicted that UBR5 mRNA and protein are highly expressed in gastric cancer tissues compared to adjacent tissues, and

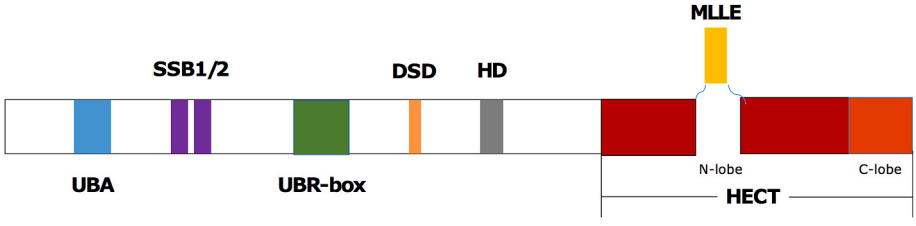

Fig. 1. Functional domains and known post-translational modification sites of UBR5. UBR5 domains include: Homologous to the E6AP Carboxyl Terminus(HECT); The ubiquitin activation (UBA); Two predicted small β-barrel domains (SBB1 and SBB2); Ubiquitin recognition box (UBR-box); Poly(A)-binding protein (PABC/MLLE domain); A domain-swapped dimerization loop(DSD); Dimerization helix(DH).

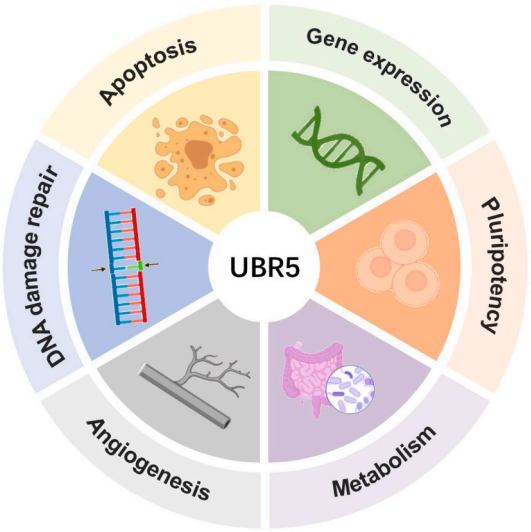

Fig. 2. Summary of known functions of UBR5.

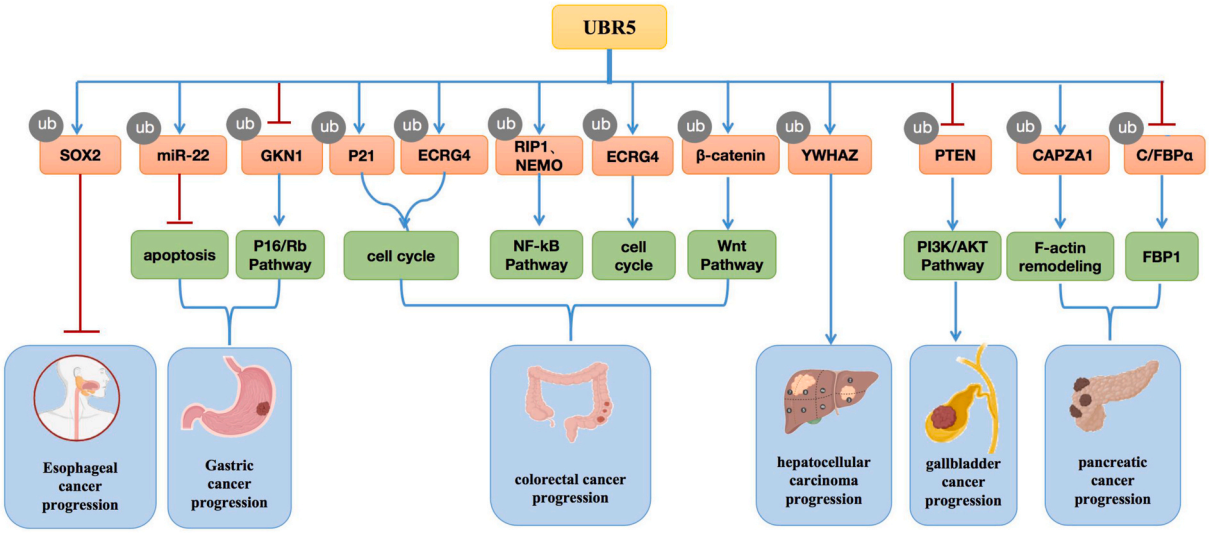

Fig. 3. Role of UBR5 in different types of gastrointestinal cancers (esophageal, gastric, colorectal, liver, gallbladder, and pancreatic cancers). Solid and flat arrows symbolize activation and inhibition, respectively.

their expression levels are related to tumor size, TNM stage, and lymph node metastasis. High UBR5 expression indicates a poor prognosis in gastric cancer patients. In vitro experiments show that UBR5 knockdown inhibits the proliferation, invasion, and migration of gastric cancer cells. Therefore, UBR5 is a potential biomarker to evaluate the prognosis of gastric cancer [34]. In addition, knocking down UBR5 promotes apoptosis in gastric cancer cells. The role of UBR5 in regulating the growth and apoptosis of gastric cancer cells is related to its PABC domain, which targets miR-22 [35]. UBR5 binds to the tumor suppressor motilin 1 (GKN1) and increases its ubiquitination, thereby affecting the protein stability of GKN1. GKN1 promotes the in vitro colony formation and in vivo growth of gastric cancer cells. However, knocking out both GKN1 and UBR5 does not affect the in vitro colony formation and in vivo growth of gastric cancer cells. This indicates that GKN1 promotes the growth of UBR5 in human gastric cancer cells. In summary, UBR5 plays an important role in gastric cancer and is expected to be a potential diagnostic and therapeutic target for gastric cancer [36].

2.3. Colorectal cancer

Many studies have shown that the occurrence of colorectal cancer is related to dietary habits, inflammation, and gene mutations; however, its specific pathogenesis requires further exploration. Ji et al. [37] found that in colon cancer, UBR5 is highly expressed at both mRNA and protein levels. Further, UBR5 can promote the degradation of P21 through ubiquitination, thereby promoting the

growth of colon cancer cells, inhibiting apoptosis, and inducing UBR5 mRNA upregulation and UBR5 gene amplification. Patients with high nuclear UBR5 protein levels demonstrated poor prognosis. Further analysis found that the expression of UBR5 can be used as an independent predictor for evaluating the prognosis of colorectal cancer patients. In addition, after knocking down UBR5, the proliferation, invasion, migration, and colony formation of colorectal cancer cells was inhibited. Further, experiments with animal models confirmed that the knockdown of UBR5 inhibited the growth of colorectal cancer [38]. Wang et al. [39] also studied the mechanism by which UBR5 promoted the progression of colorectal cancer and found that UBR5 directly binds to the esophageal cancer-related gene 4 protein (ECGR4) and promotes ECGR4 ubiquitination to reduce the protein stability of ECRG4. In addition, some researchers have found that the development of colorectal cancer in patients with inflammatory bowel disease is driven by chronic inflammation, and that these patients have a higher mutation rate of UBR5 than other colorectal cancer patients [40]. The above studies systematically demonstrated that UBR5, a novel regulator of colorectal cancer progression, has an important clinical and biological significance. In conclusion, UBR5 acts as an oncogenic factor and plays an important role in the diagnosis and prognostic assessment of colorectal cancer.

2.4. Liver cancer

Liver cancer has the fourth highest mortality rate among all cancers in the world [41]. Although research on clinical diagnosis and treatment has made significant progress, its prognosis remains unsatisfactory [42]. Therefore, there is an urgent need to identify biomarkers associated with the prognosis of patients with liver cancer. Accumulating evidence indicates that many structural or functional disturbances in E3 ligases are associated with liver cancer [43]. UBR5 is highly expressed in the tissues of patients with liver cancer and high UBR5 expression is significantly correlated with older age, a higher tumor grade, lymph node metastasis, and a lower survival rate [44]. In addition, elevated UBR5 levels are directly associated with overexpression of tyrosine 3/tryptophan 5 monooxygenase-activating protein Z (YWHAZ), and UBR5 promotes liver cancer cell proliferation by affecting YWHAZ expression. ECRG4 is a potential tumor suppressor gene, and ECRG4 can increase the expression of P21 by interacting with UBR5, thereby inhibiting the migration and invasion of liver cancer cells [45].

2.5. Gallbladder cancer

Although the incidence of gallbladder cancer is lower than that of the aforementioned gastrointestinal cancers, its mortality rate is higher [46]. Therefore, research on the molecular mechanisms of gallbladder cancer is helpful in predicting the prognosis of the disease and in performing targeted therapy. UBR5 is highly expressed in gallbladder carcinoma tissues and high expression of UBR5 correlates with tumor size, histology, tumor differentiation, and patient prognosis. Knockdown of UBR5 considerably inhibits cancer cell proliferation and colony formation, which may increase the phosphorylation of protein kinase B by degrading phosphatase and tensin homologs, thereby promoting the growth of gallbladder cancer [47]. Therefore, UBR5 may be an important biomarker to predict the prognosis of gallbladder cancer patients.

2.6. Pancreatic cancer

Pancreatic cancer is often diagnosed at an advanced stage, with an average survival period of only 6–9 months after diagnosis [48,49], and approximately 80–85 % of the patients die because of metastasis [50,51]. Ubiquitination-/de-ubiquitination-related genes are key factors in the development of pancreatic cancer [52–54]. A recent study found that UBR5 was significantly upregulated in pancreatic cancer tissues and increased expression of UBR5 is associated with lymph node metastasis and a poor prognosis. In addition, UBR5 significantly enhances the migration and invasion abilities of pancreatic cancer cells in vitro. Collectively, this study revealed that UBR5 is a novel key regulator of pancreatic cancer metastasis and highlights the potential of the UBR5-CAPZA1 axis as a therapeutic target to prevent metastasis in patients with pancreatic cancer, especially those with elevated UBR5 expression [55]. Another study showed UBR5 promotes the growth of pancreatic cancer cells by inducing aerobic glycolysis. Fructose-1,6-bisphosphatase (FBP1) negatively regulates aerobic glycolysis in various cancers, and UBR5 knockdown increases the level of FBP1, confirming UBR5-induced aerobic glycolysis-dependent FBP1 in pancreatic cancer cells [30]. These findings provide new insights into the role of UBR5 in the adaptation of pancreatic cancer cells to metabolic stress and provide new ideas for related studies on pancreatic cancer progression.

3. Conclusions

In recent years, numerous studies documented that UBR5 assumes a pivotal role in the pathogenesis and progression of various malignancies; nevertheless, current research in this discipline area remains at a nascent stage. UBR5 is an E3 ubiquitin ligase that mediates its functions in cancer through ubiquitination of its substrates. Extant literature pertaining to UBR5 and its involvement in gastrointestinal cancers predominantly focuses on its degradation of specific substrates and the correlation between its expression level and the clinical prognoses of gastrointestinal cancers; however, the precise mechanism of action remains ambiguous. Therefore, the following gaps in apprehension warrant delineation: uncertainty concerning the classification of UBR5 as either an oncogene or a tumor suppressor gene; potential interrelation between the distinct mechanisms of action of UBR5 in different gastrointestinal cancers; and efficacy of the UBR5 gene-dependent regulatory mechanism network. Furthermore, the candidature of UBR5 as a potential target for the treatment of gastrointestinal cancers and the distinct effects of UBR5 on specific substrates necessitate investigation. In

conclusion, an in-depth study of UBR5 will aid in the enunciation of the mechanisms of action of UBR5 in various gastrointestinal cancers and the assessment of potential biomarkers and novel therapeutic targets to facilitate their diagnosis and remediation.

Ethics statement

Review and approval by an ethics committee was not needed for this study because this was a literature review and no new data were collected and analysed. For the same reason, informed consent was not required.

Data availability statement

No data was used for the research described in the article.
No additional information is available for this paper.

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Consent for publication

All authors approved the final manuscript and the submission to this journal.

CRediT authorship contribution statement

Rong Qin: Writing – review & editing, Funding acquisition, Conceptualization. **Xirui Fan:** Writing – original draft. **Rui Ding:** Resources. **Yadan Qiu:** Writing – review & editing, Resources. **Xujia Chen:** Resources. **Yanting Liu:** Resources. **Minjuan Lin:** Resources. **Hui Wang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ECGR4	esophageal cancer-related gene 4 protein
FBP1	fructose-1,6-bisphosphatase
NLS	nuclear localization sequence
SSB	small β-barrel domains
PABC	poly(A)-binding protein
UBA	ubiquitin activation
UBR	ubiquitin recognition box (UBR)
UBR5	ubiquitin protein ligase E3 component n-recognition 5
UPS	ubiquitin-proteasome system
YWHAZ	tyrosine 3/tryptophan 5 monooxygenase-activating protein

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