E3 ubiquitin ligase RNF40: Structure, function and its context-dependent roles in tumorigenesis (Review)

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Received January 8, 2026; Accepted March 27, 2026

DOI: 10.3892/or.2026.9126

Abstract. The ubiquitin-proteasome system, a key protein degradation machinery in humans, mediates substrate recognition and proteolysis through ubiquitin-tagged targeting of macromolecular proteins to the 26S proteasome. This evolutionarily conserved system orchestrates fundamental cell processes, including cell cycle progression, DNA damage repair, immune regulation, signal transduction and clearance of misfolded proteins. Its functional integrity is involved in the pathogenesis of various malignancies (breast and small cell lung cancer and colorectal adenocarcinoma) and degenerative diseases (Parkinson's disease). As a really interesting new gene-type E3 ubiquitin ligase, ring finger protein (RNF)40 has emerged as a key regulator of both physiological homeostasis and disease progression. The present review systematically examines RNF40 structural architecture and its multifaceted roles in ubiquitination-dependent proteostasis, epigenetic modulation and DNA repair mechanisms, as well as its tumor-specific regulatory networks across cancer subtypes and therapeutic potential as a novel drug target.

Contents

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Key words: RNF40, ubiquitin, E3 ubiquitin ligase, cancer

1. Introduction

As the second leading cause of global morbidity and mortality, cancer is a critical public health challenge with notable implications for human health and societal wellbeing (1,2). The global incidence of cancer continues to rise at an accelerating trajectory, with the growing prevalence of early-onset cancer (diagnosed in patients aged <50 years) of particular concern (2-4). In response, the identification of novel therapeutic targets and the development of effective treatment strategies have become central objectives in the era of precision oncology. Carcinogenesis is a multistep pathological process driven by dynamic interactions between genetic susceptibility and environmental exposure (5). Accumulating evidence highlights ubiquitination, a highly conserved post-translational modification, as a key regulator of oncogenic signaling networks and malignant transformation (6,7). Notably, E3 ubiquitin ligases have garnered increasing attention as promising candidates for targeted therapeutic intervention, owing to their inherent substrate specificity and key role in dictating protein fate (6,8,9).

As pivotal determinants of proteostasis mediated by the ubiquitin-proteasome system (UPS), E3 ubiquitin ligases are classified into the really interesting new gene (RING), homologous to the E6-AP carboxyl terminus (HECT) and U-box families based on their characteristic structural motifs (10,11). These enzymes serve a critical role in tumor biology by governing protein stability, subcellular localization and protein-protein interaction networks in tumors. The human genome encodes >600 E3 ligases, among which the RING family constitutes the largest subset, accounting for >60% (6). Defined by a zinc-coordinating RING domain (10), these ligases may serve either as monomers or as components of heteromeric complexes, exemplified by the tumor-relevant ring finger protein (RNF)20/RNF40 complex (6,12,13).

RNF40, a key member of the RING-type E3 ubiquitin ligases, forms functional complexes via its coiled-coil (CC) and RING domain. It catalyzes histone H2B K120 monoubiquitination (H2Bub1) and the ubiquitination of non-histone substrates, thereby contributing to fundamental physiological processes such as chromatin remodeling, DNA damage repair (DDR), metabolic regulation and inflammatory responses. Aberrant RNF40 expression has been reported in diverse

malignancies, including ovarian, breast cancer (BC) and colorectal cancer (CRC), exhibiting context-dependent functional duality: It may promote oncogenesis via activation of the NF-κB pathway and suppression of apoptosis, or, alternatively, function as a tumor suppressor (12,14,15). Therapeutically, preclinical studies have underscored its potential: RNF40 knockdown suppresses estrogen receptor (ER)α target gene transcription in ERα-positive BC (16); arsenite targets its RING domain to enhance tumor radiosensitivity (17); and proteasome inhibitors exhibit efficacy by modulating the RNF40-H2Bub1 axis (16). However, the subtype-specific regulatory mechanisms governing RNF40 and the obstacles to its clinical translation remain largely unexplored (18,19).

The present review summarizes RNF40, its molecular architecture, core biological functions and cancer subtype-specific regulatory networks, as well as the molecular mechanisms by which RNF40 contributes to tumorigenesis and progression, advances in RNF40-targeted therapeutic strategies and its viability as a novel therapeutic target. The present review discusses key challenges in clinical translation and proposes innovative strategies based on proteolysis-targeting chimeras (PROTACs) and covalent inhibitors to provide a theoretical foundation for the development of RNF40-targeted personalized cancer therapy. Table I summarizes RNF40 substrates along with their associated signaling pathways and disease contexts. Notably, the RNF20/RNF40 complex predominantly catalyzes monoubiquitination of its substrates, a modification that mediates regulatory functions, while promoting polyubiquitination of certain substrates, such as insulin-like growth factor 2 mRNA binding protein 2 (IMP2), thereby targeting them for proteasomal degradation. This functional duality underscores the diverse biological outcomes regulated by this E3 ligase beyond canonical proteolysis (9).

2. Molecular structure, expression status and function of RNF40

Structure of RNF40. Wen and Ao (20) identified retinoblastoma-binding protein 95 as a retinoblastoma-associated factor. Chin *et al* (21) discovered Staring, a previously uncharacterized E3 ligase that was subsequently confirmed through expressed sequence tag database mining to share 87% sequence homology with human RNF40. Kim *et al* (22) established that yeast Brefeldin A-sensitivity protein 1 (Bre1) protein functions as the cognate E3 ligase for histone H2B ubiquitination, thereby functionally linking RNF40 with chromatin regulation.

RNF40 is encoded by a gene located at 16p11.2 and spanning 19 exons. The canonical 1001-residue isoform exhibits a prototypical RING-family E3 ligase architecture: Four α-helical CC domains (residues 44-91, 189-377, 437-525 and 627-946) that mediate homodimerization and recruitment of interacting partners (23) and a C-terminal C_3HC_4-type RING finger domain (residues 950-998) coordinating two zinc ions via cysteine (Cys)/histidine (His) residues for E2 ubiquitin-conjugating enzyme docking (6,12). Three alternatively spliced isoforms exhibit distinct functional properties resulting from N-terminal truncations that affect nuclear localization signals (23,24). These CC domains fold into conserved superhelical architectures, typically comprising 2-7 antiparallel α-helices stabilized by hydrophobic interfaces with 3-4 heptad repeats (leucine zipper motifs at positions 78-85 and 215-222) (25,26). This structural configuration imparts both rigidity and dynamic plasticity, enabling allosteric regulation of protein-protein interactions through conformational switching (27).

The CC domain mediates RNF40 functional oligomerization. Heterodimerization with RNF20, mediated by reciprocal packing of their CC domains, results in the formation of an elongated scaffold that recruits the WW domain-containing adaptor protein with coiled-coil (WAC) (12,27,28). This tripartite BRE1 complex (RNF20/40-WAC) orchestrates H2Bub1 through coordinated E2 [RAD6, radiation sensitive 6 (RAD6)]-E3 (RNF40 RING) catalysis activity, an epigenetic modification essential for transcriptional elongation. Notably, the CC domain exhibits dual functionality: The C-terminal CC and RING domains form an integrated ubiquitination platform (Fig. 1) and its N-terminal segment (residues 627-720) binds the DNA-binding domain of p53 at arginine 282, stabilizing p53 tetramerization and enhancing transactivation of proapoptotic targets genes such as B-cell lymphoma 2 Associated X (BAX) and p53 upregulated modulator of apoptosis (29) (Fig. 1). This interaction has been structurally validated by cryo-electron microscopy at 3.2 Å resolution, which captures the coupled conformational dynamics of the complex during E2-Ub (ubiquitin) transfer (25). Metabolically, the CC domain of RNF40 specifically recognizes a conserved LXXLL motif (residues 45-49) within abnormal cell lineage protein 11, islet-1, mechanosensory abnormality protein 3) domain and actin-binding protein 1 (LIMA1). This initiates K48-linked ubiquitination of LIMA1, targeting it for degradation by the 26S proteasome (Fig. 1). This process suppresses peroxisome proliferator-activated receptor γ activity to regulate hepatic lipid droplet biogenesis (30).

The RING finger domain constitutes the defining structural feature of RING-family E3 ligases. It is defined by a zinc-coordinating module of 40-60 residues containing eight conserved residues (six Cys/two His) that chelate two zinc ions in a cross-brace topology, a structural configuration essential for E2-dependent ubiquitin transfer (6,24,31). The RING domain is highly conserved across species. This conservation is particularly pronounced in the RING-HC subfamily, where both structural fold and catalytic function exhibit marked consistency across orthologs (32). Although RNF40 retains the conserved architectural motifs characteristic of the RING-type E3 ligase superfamily, it exemplifies functional diversification through distinct structural innovations (23). Evolutionary pressures have driven diversity in the zinc-coordination architecture of RING ligases (33). Through heterodimerization with RNF20, RNF40 generates a functionally augmented protein interaction surface (34). This surface not only optimizes interaction with the E2-Ub conjugate, but may provide a structural framework for the recognition of diverse substrates, including nucleosomes and cytoplasmic proteins (18). Mechanistically, this domain facilitates ubiquitination by promoting E2 enzyme binding (Fig. 1). It subsequently enables ubiquitin transfer to substrate lysine residues through coordinated thioester chemistry (10).

The RNF20/RNF40 complex functions in concert with E2 ubiquitin-conjugating enzyme RAD6A (UBE2A) to mediate substrate-specific ubiquitination (35). In addition

Table I. RNF40 substrates and functions.

Substrate	Biological process	Function	Ubiquitination	Condition	(Refs.)
H2B	NF-κB signaling; HR/NHEJ; H3K4/H3K79 me3	Transcriptional and metabolic reprogramming; gene expression, DNA repair; cell proliferation and differentiation	K120 monoubiquitination	BC, CRC; Parkinson's disease	(23,28,39,43, 48,53,63,79, 83,104)
LIMA1	Cytoskeleton and vesicular transport	Promotes accumulation of triglyceride and glycerophosphate esters	Polyubiquitination	Atherosclerosis	(30)
eEF1BδL	p-TEFb recruitment	Enhances the transcription of heat shock response genes	K381 monoubiquitination	BC	(37,38)
Eg5	G2/M phase transition	Activates the cell cycle	K745 monoubiquitination	BLBC	(19,41)
STX1A	Neurotransmitter release cycle; transmission across chemical synapses	Participates in the calcium-dependent regulation of acrosomal exocytosis in sperm	Unknown	Autism	(58)
Parkin	Mitophagy	Inhibits mitophagy in cerebrovascular endothelial cells	K48-linked polyubiquitination	Hypertension	(72)
IMP2	Signaling through the USP14-IMP2-CXCL2 axis	Suppresses the efficacy of PD-1 therapy	Polyubiquitination	GC	(112)

CXCL2, C-X-C motif chemokine ligand 2; GC, gastric cancer; IMP2, insulin-like growth factor 2 mRNA binding protein 2; LIM domain-containing adapter protein 1; STX1A, syntaxin 1A; USP14: ubiquitin-specific protease 14; H2B, histone H2B; HR, homologous recombination; NHEJ, non-homologous end joining; p-TEFb, positive transcription elongation factor b; eEF1BδL, eukaryotic elongation factor 1B δ-like; Eg5, kinesin-5; BLBC, basal-like breast cancer.

to UBE2A, RNF40 also interacts with RAD6B, UbcH8 and UbcH6, indicating a broader E2 partnership (9,10,21,23). The RNF20 RING domain binds the negatively charged surface region on the nucleosome, and interacts with the negatively charged region of histone H2A-H2B through its positively charged surface. By contrast, the RNF40 RING domain specifically targets the phosphate groups of nucleosomal DNA at superhelical location 6.0, establishing electrostatic interactions (34). The Thr97-Pro98-Thr99 motif of RAD6 forms a non-canonical interaction with the RING domain of the RNF20/RNF40 complex. This ensures specific ubiquitin transfer, leading to H2B-targeted ubiquitination (34,35). The RING finger domain also mediates protein-protein interactions. Binding of arsenite induces a conformational change in the complex, markedly decreasing H2B ubiquitination levels and impairing DNA double-strand break (DSB) repair (17) (Fig. 1). Owing to its structural versatile, RNF40 orchestrates diverse biological processes, such as lipid metabolism and mitotic progression, and is regulated by multifaceted mechanisms. During DSB repair, ataxia telangiectasia mutated (ATM) kinase phosphorylates RNF40 at serine 114, triggering heterodimerization with RNF20 and recruitment of the complex to DNA damage sites, and chromatin remodeling via H2Bub1, which facilitates repair protein access to lesions (12,28,36).

In addition to the canonical substrate histone H2B, eukaryotic elongation factor 1B δ-like (eEF1BδL) is also ubiquitinated by RNF40, providing another example of the non-proteolytic function of this E3 ligase (Fig. 1). RNF20/40-mediated monoubiquitination of eEF1BδL promotes its accumulation at heat shock element-containing promoters, thereby enhancing the transcription of heat shock response genes (37,38).

Expression pattern of RNF40. RNF40 is widely expressed across human tissues and primarily localizes to chromatin regions within the nucleus (12,39). It is involved in diverse cell processes, including protein-protein and protein-DNA interactions. Studies have documented its upregulation in multiple types of cancer, including BC and CRC (16,40,41) (Fig. 2), where it promotes tumor cell proliferation, migration and progression, and is associated with poor prognosis in breast and liver cancer (12,14,42-44). RNF40 gene alterations have been identified in >20% of patients with BC (45). Recent technological advances have facilitated key discoveries in RNF40 research, elucidating its diverse functions in epigenetic regulation, oncogenesis and metabolic disorders (18,30,46).

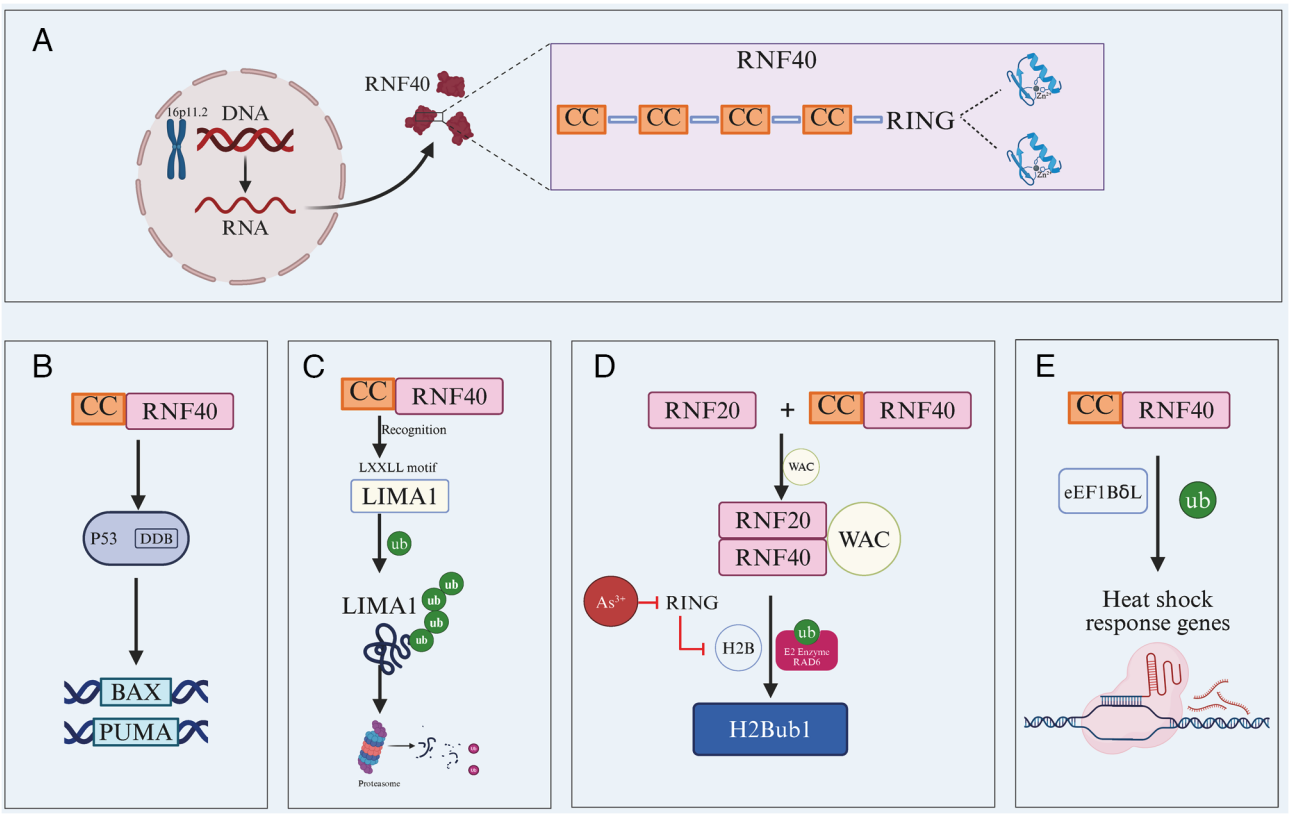

Figure 1. Protein structure of RNF40 and the functions of its domains. (A) The C-terminal CC and RING domains form an integrated ubiquitination platform. (B) The N-terminal segment (residues 627-720) binds the DBD of p53 at arginine 282, stabilizing p53 tetramerization and enhancing the transactivation of proapoptotic target genes such as BAX and PUMA. (C) The CC domain specifically recognizes a conserved LIMA1 motif, initiating K48-linked ubiquitination of LIMA1 and targeting it for 26S proteasome degradation. (D) This domain facilitates ubiquitination by promoting E2 enzyme binding. (E) RNF20/40-mediated monoubiquitination of eEF1BδL promotes its accumulation at heat shock element containing promoters, thereby enhancing transcription of heat shock response genes. Created in BioRender.com. RNF, ring finger protein; RING, really interesting new gene; CC, coiled-coil; WAC, WW domain-containing adaptor protein with coiled-coil; H2B, histone H2B; Ub, ubiquitin; RAD6, radiation sensitive 6; DDB, damage-specific DNA binding protein 1; PUMA, p53 upregulated modulator of apoptosis; LIMA, LIM domain and actin-binding protein 1; eEF1BδL, eukaryotic elongation factor 1B δ-like.

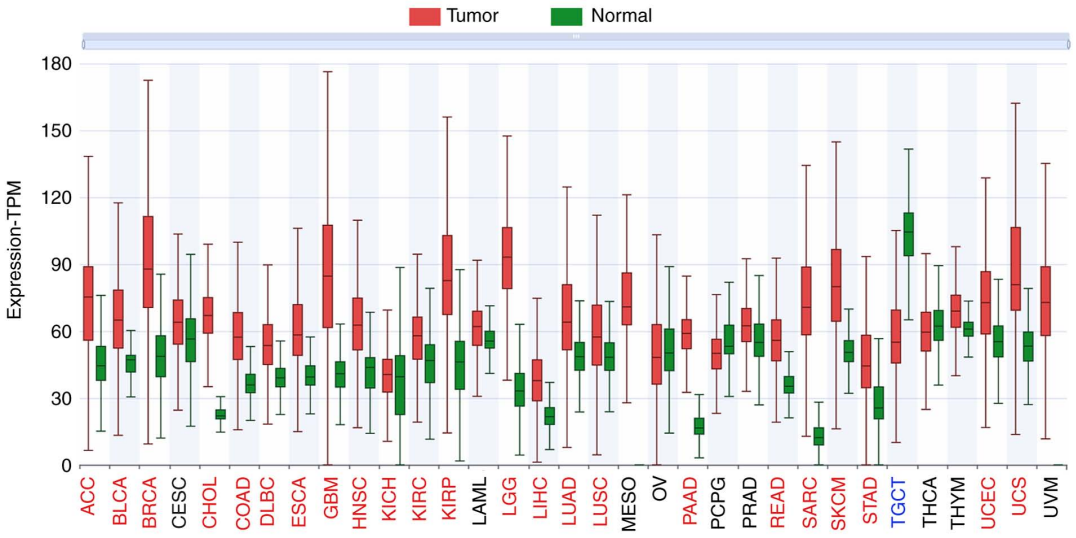

Figure 2. Expression levels of ring finger protein 40 in tumor and adjacent normal tissues. Red, high expression; blue, low expression; black, no significant difference. Data were obtained from the Gene Expression Profiling Interactive Analysis 3 database. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

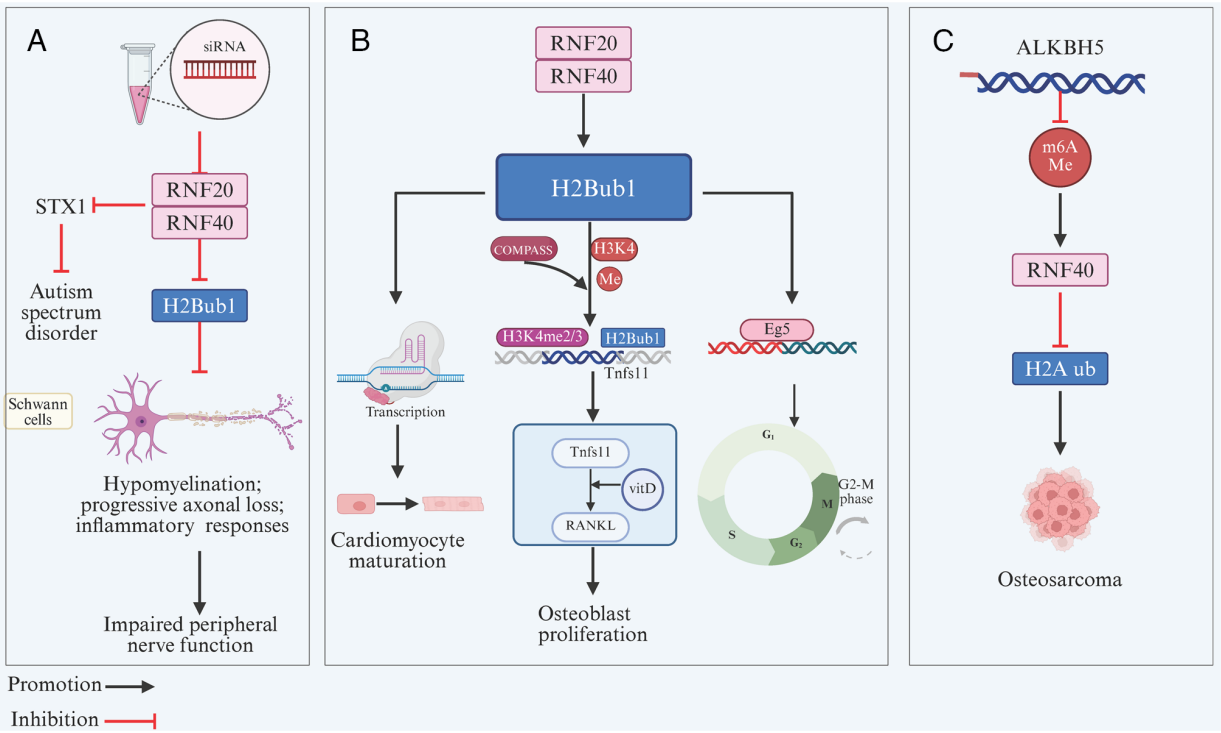

Figure 3. Epigenetic function of RNF40. (A) RNF40 expression and its downstream effects on STX1 and serotonin signaling may influence the therapeutic action of risperidone. (B) In osteoblasts, RNF20/RNF40 promote H2Bub1, which facilitates COMPASS-mediated deposition of H3K4me2/3. This epigenetic regulation controls the expression of genes such as Tnfsf11 and modulates vitamin D signaling, thereby promoting osteoblast proliferation and cell cycle progression (G1, S, and G2-M phases). (C) In osteosarcoma, RNF40 promotes tumor growth by suppressing H2A ubiquitination. This oncogenic mechanism involves ALKBH5, which is overexpressed in osteosarcoma and reduces m6A methylation, thereby upregulating RNF40 expression. Created in BioRender.com. RNF40, ring finger protein 40; H2Bub1, histone H2B K120 monoubiquitination; Eg5, kinesin-5; ALKBH5, alkylation repair homolog protein 5; si, small interfering; STX, syntaxin; COMPASS, complex of Proteins Associated with Set1; Me, methylation; Tnfs11, tumor necrosis factor ligand superfamily member 11; vitD, vitamin D.

For example, in osteosarcoma, alkylation repair homolog protein 5 (ALKBH5) enhances RNF40 stability by decreasing m6A levels (44). However, additional mechanisms regulatory remain to be fully characterized.

Functions of RNF40. RNF40 is ubiquitously expressed across human tissue (47) and functions in an epigenetically regulated, cell-type-specific manner (41). Its primary function is to mediate monoubiquitination of histone H2B at lysine 120, thereby contributing to the epigenetic regulation of biological processes, including gene expression, DDR (48), cell differentiation (49), cardiac development (15,50), lipid metabolism (30) and tumorigenesis (19). While RNF40 upregulation in liver cancer is associated with poor prognosis (14), it exhibits context-dependent functions in BC. Notably, RNF40 exerts differential effects not only across tissue but also within the same tissue, reflecting its involvement in distinct pathways. For example, in CRC, downregulation of RNF40 suppresses tumor cell proliferation, suggesting a pro-tumorigenic function (41,43), while concurrently modulating intestinal anti-inflammatory responses and calcium metabolism via maintenance of vitamin D receptor (VDR) expression (51).

Epigenetic regulation via H2Bub1. Histone H2B, a core component of eukaryotic nucleosomes, is a member of the histone family (H2A, H2B, H3, H4) that mediates chromatin organization (52). Among its post-translational modifications, H2Bub1 serves a critical role in regulating gene expression, DNA repair and other key biological processes (23,28,53). For example, H2Bub1 participates in regulation of RNA polymerase II via a feedback mechanism involving positive transcription elongation factor b and polymerase II-associated factor 1 complex (54). Notably, RNF40 deletion exhibits context-dependent effects: It selectively reduces gene expression at loci characterized by low to moderate H2Bub1 levels, while exerting minimal impact on genes with high H2Bub1 enrichment (55).

In the nervous system, conditional deletion of RNF40 in Schwann cells leads to loss of H2Bub1, leading to notable hypomyelination of peripheral nerves, accompanied by inflammatory responses and progressive axonal loss, ultimately compromising peripheral nerve function (56,57). The expression of RNF40 and its downstream effects on syntaxin 1 and serotonin signaling may influence the therapeutic action of risperidone (58) (Fig. 3). As risperidone serves as an antagonist of serotonin 5-hydroxytryptamine receptor 2A receptors, RNF40 may modulate therapeutic effects by regulating the stability of syntaxin 1, a key protein in neurotransmitter release, thereby impacting serotonergic signaling pathways (58). RNF40 is mapped to chromosome 16p11.2, a genomic locus associated with both autism and schizophrenia (59,60). This suggests that RNF40 may possess therapeutic potential for psychiatric disorders. Dysregulation of RNF40 is also associated with the pathogenesis of Parkinson's disease (61).

H2Bub1 is required for the methylation of H3K4 and H3K79, although its functional roles are not fully dependent on these H3 methylation events (55,62). RNF40-mediated H2B ubiquitination regulates transcriptional elongation at transcription start sites, influencing H3K4me3 peaks and regulating specific genes in mammal cells (39,63) (Fig. 3). Overexpression of RNF20/RNF40 suppresses the transcriptional activity of certain enhancers, especially those regulated by ERα (64). Abrogation of RNF20/RNF40 disrupts H2Bub1 deposition, inducing premature transcriptional termination and inhibiting cardiomyocyte maturation (65), which increases cardiac disease risk. Beyond cardiac development, deletion of RNF20/40 also leads to the downregulation of tissue-specific genes, including tumor necrosis factor ligand superfamily member 11 (TNFSF11), which is key for osteoblast function and bone differentiation (66) (Fig. 3). H2Bub1 mediated by RNF40 is a key regulatory factor in somatic cell reprogramming. It affects reprogramming through cell cycle-dependent (regulating proliferation-associated genes) and -independent mechanisms (balancing histone marks, regulating lineage/pluripotent genes), demonstrating the importance of chromatin dynamics in cell fate transition (67).

RNF40 and its catalytic product H2Bub1 are key for normal bone formation (66), not only affecting bone cell differentiation but also representing a notable risk factor for osteoporosis in female patients (68). During osteoblast differentiation, RNF40 exerts stage-specific regulation, promoting bone remodeling by driving TNFSF11 expression via the H2Bub1-H3K4me3 axis (66) (Fig. 3). Paradoxically, in osteosarcoma, RNF40 promotes tumor growth by suppressing H2A ubiquitination. This oncogenic mechanism involves ALKBH5, which is upregulated in osteosarcoma and decreases m6A methylation thereby upregulating RNF40 expression (44) (Fig. 3). Beyond bone biology, RNF40 is key for reprogramming mouse fibroblasts into induced pluripotent stem cells, as its deletion severely impairs this process (19,47). Collectively, these findings highlight the dual role of RNF40 in balancing cell proliferation and differentiation across biological contexts.

Roles in physiological and pathological processes. RNF40 serves as a key regulator in diverse metabolic processes, playing an essential role in maintaining cell energy balance and metabolic homeostasis (18,30). RNF40 mediates LIMA1 polyubiquitination and degradation via the UPS, decreasing cell lipid content (30) (Fig. 4). This demonstrates its capacity to exert H2Bub1-and transcription-independent E3 ligase activity by directly targeting substrates for proteasomal degradation. In basal-like BC (BLBC), RNF40 enhances glycolytic flux and malignant progression by sustaining H2Bub1 at glycolysis-related genes (hexokinase 2, lactate dehydrogenase A; Fig. 4); RNF40 knockdown suppresses lactate production and proliferation (42,69). Conversely, in streptozotocin-induced diabetic mice, RNF20/RNF40 suppresses pancreatic β cell apoptosis and inflammation while ameliorating hyperglycemia via VDR activation (51) (Fig. 4). RNF40 deficiency decreases H2Bub1 levels, impairing epigenetic regulation of insulin signaling genes (insulin receptor substrate1, AKT2) and potentially contributing to insulin resistance (30,39). Studies have demonstrated that RNF20 and RNF40 modulate β cell gene expression and insulin secretion, linking the islet-1 complex to global cell epigenetic regulation (70,71). This complex is necessary for glucose-stimulated insulin secretion and maintaining normal mitochondrial reactive oxygen species levels (70,71). In addition, in hypertension-associated pathologies such as cerebrovascular endothelial barrier dysfunction, RNF40 promotes K48-linked polyubiquitination and Parkin degradation, thereby inhibiting mitophagy and exacerbating barrier dysfunction (72) (Fig. 4).

RNF40 also plays a critical role in immune and inflammatory disorders. Ubiquitination serves a critical role in regulating tumor necrosis factor (TNF)-mediated inflammatory signaling and cell death (7). TNF activates the NF-κB and MAPK pathways to drive proinflammatory gene expression, however, RNF40 deficiency suppresses NF-κB target genes, attenuating inflammation (43). This anti-inflammatory effect has been confirmed in mouse colitis models, where RNF40 deletion markedly decreases disease severity (41,43). In CRC, RNF40 sustains a pro-inflammatory tumor microenvironment (TME) by enhancing NF-κB nuclear translocation and upregulating cytokines such as IL-6 and TNF-α (43,73) (Fig. 5). Conversely, RNF40 knockout suppresses NF-κB activity, alleviating colitis and inhibiting tumor progression (43). The RNF20/RNF40 complex also modulates inflammatory responses via VDR signaling (51). By regulating H3K4me3 enrichment and transcriptional activity at VDR target genes, this complex suppresses inflammation, a mechanism pivotal to inflammatory bowel disease (IBD) pathogenesis (51,74). Furthermore, RNF40, together with RTF1, may serve as an epigenetic regulator to promote T helper 17 cell differentiation and function, thereby contributing to the pathogenesis of IBD (75) (Fig. 5). Consistent with this, deletion of RNF20/RNF40 decreases levels of IL-6, TNF-α and IL-1β, mitigating inflammatory cascades (43,51).

RNF40 also serves a key role in DDR (17,76). Among the diverse forms of DNA damage induced by physical, chemical or biological agents, DSBs pose a notable threat to genomic integrity (77). The cellular pathways recruited to repair such lesions are collectively referred to as the DDR (77). Studies have identified RNF20/RNF40 as a novel DDR component, where its catalytic activity drives H2Bub1-dependent chromatin remodeling to orchestrate repair (49,78). Serving as a heterodimeric E3 ubiquitin ligase complex, RNF20/RNF40 plays a key role in regulating DSB repair via H2Bub1-dependent chromatin remodeling and transcriptional coordination (36,79). The dynamics of H2B ubiquitination mediated by the RNF20/40 complex are regulated by COMM domain-containing protein 4, which limits the extent of epigenetic modifications of chromatin around break sites and prevents excessive elongation of remodeled chromatin (80). RNF40 and cullin 7 (Cul7) form a HECT-type E3 ligase complex with suppressor of mec-8 and unc-52 homologs (SMU1) and damage-specific DNA binding protein 1 (DDB1), which regulates the monoubiquitination of H2B, thereby affecting cell mitosis and genomic stability (81). Similarly, RNF40 forms a Cul-RING type E3 ligase with SMU1, DDB1 and CUL7 to promote H2B ubiquitination, thereby maintaining sister chromatid cohesion during mitosis (82) (Fig. 6).

Following DNA damage, the RNF20/RNF40 complex is recruited to DSBs via interactions with ATM kinase and Nijmegen breakage syndrome 1 (Fig. 6), increasing local

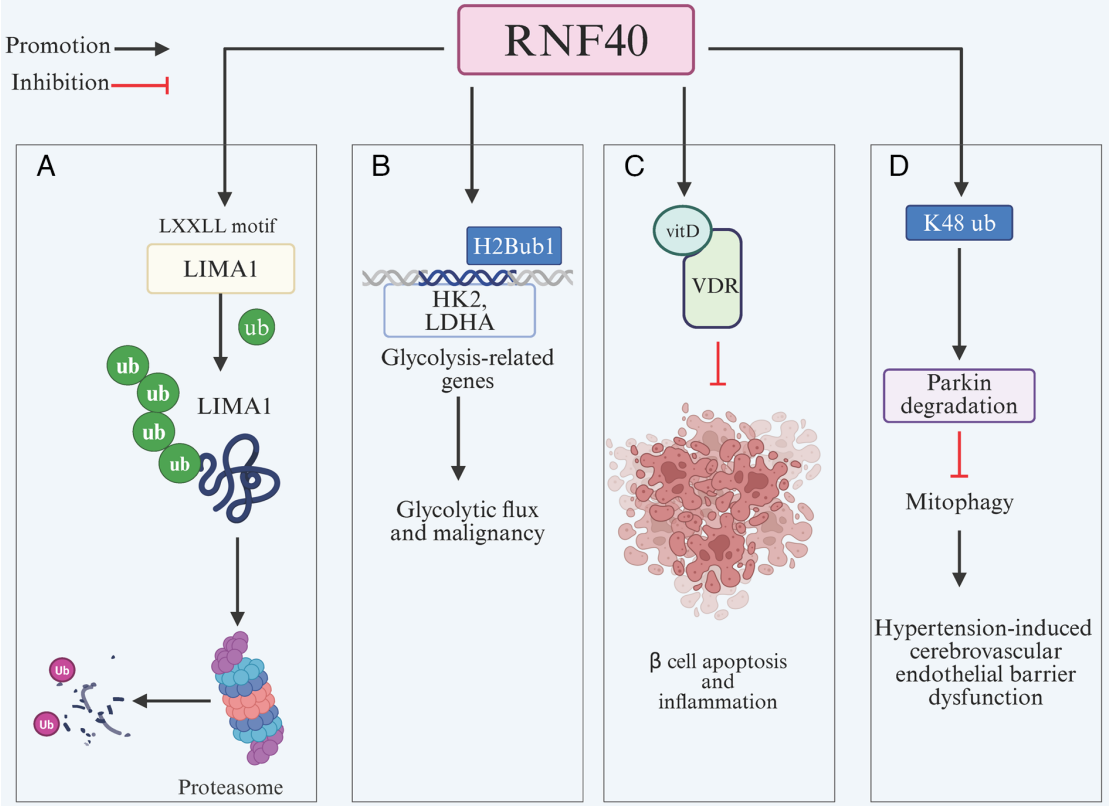

Figure 4. RNF40 ubiquitination regulates lipid and glucose metabolism. (A) RNF40 mediates polyubiquitination and degradation of LIMA1 via the UPS, reducing cellular lipid content. (B) In BLBC, RNF40 enhances glycolytic flux and malignant progression by sustaining H2Bub1 at glycolysis-related genes (e.g., HK2, LDHA). (C) RNF40 suppresses pancreatic β-cell apoptosis and inflammation while ameliorating hyperglycemia via VDR activation. (D) In hypertension-related pathologies, RNF40 promotes K48-linked polyubiquitination and degradation of Parkin, thereby inhibiting mitophagy and exacerbating hypertension-induced cerebrovascular endothelial barrier dysfunction. Created in BioRender.com. RNF40, ring finger protein 40; LIMA1, LIM domain and actin-binding protein 1; Ub, ubiquitin; H2Bub1, histone H2B K120 monoubiquitination; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; vitD, vitamin D; VDR, vitamin D receptor.

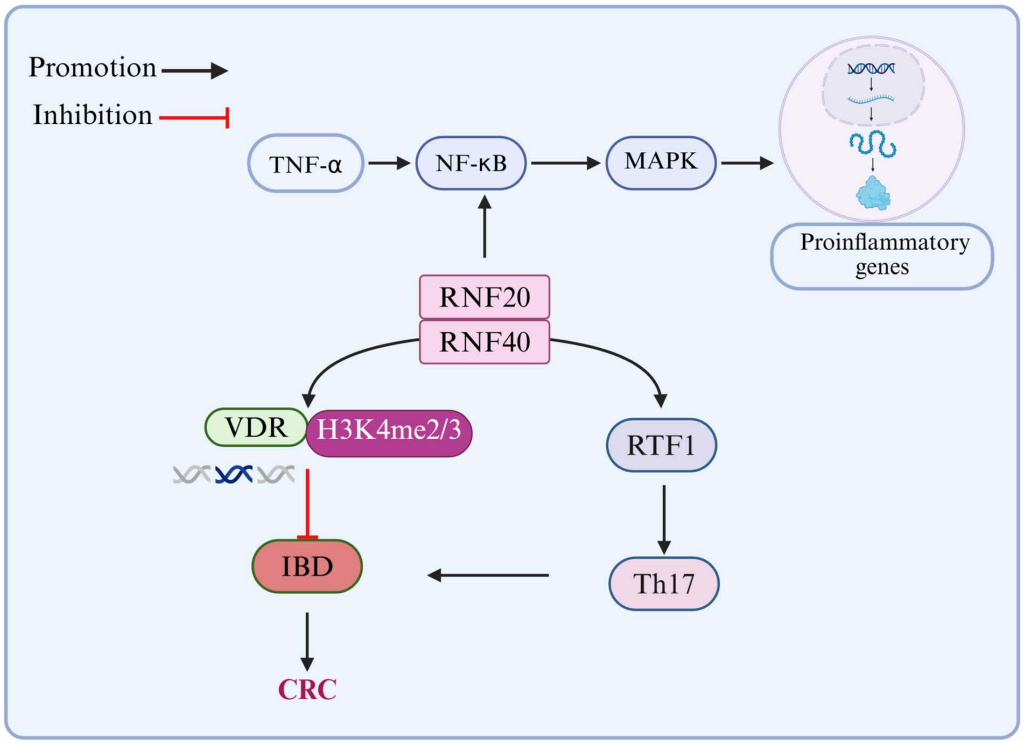

Figure 5. RNF40 maintains the pro-inflammatory tumor microenvironment, regulates the occurrence of IBD and promotes CRC by enhancing NF-κB nuclear translocation and upregulating cytokines such as IL-6 and TNF. Created in BioRender.com. RNF40, ring finger protein 40; IBD, inflammatory bowel disease; CRC, colorectal cancer; VDR, vitamin D receptor; RTF1, RNA polymerase II complex component; Th, T helper.

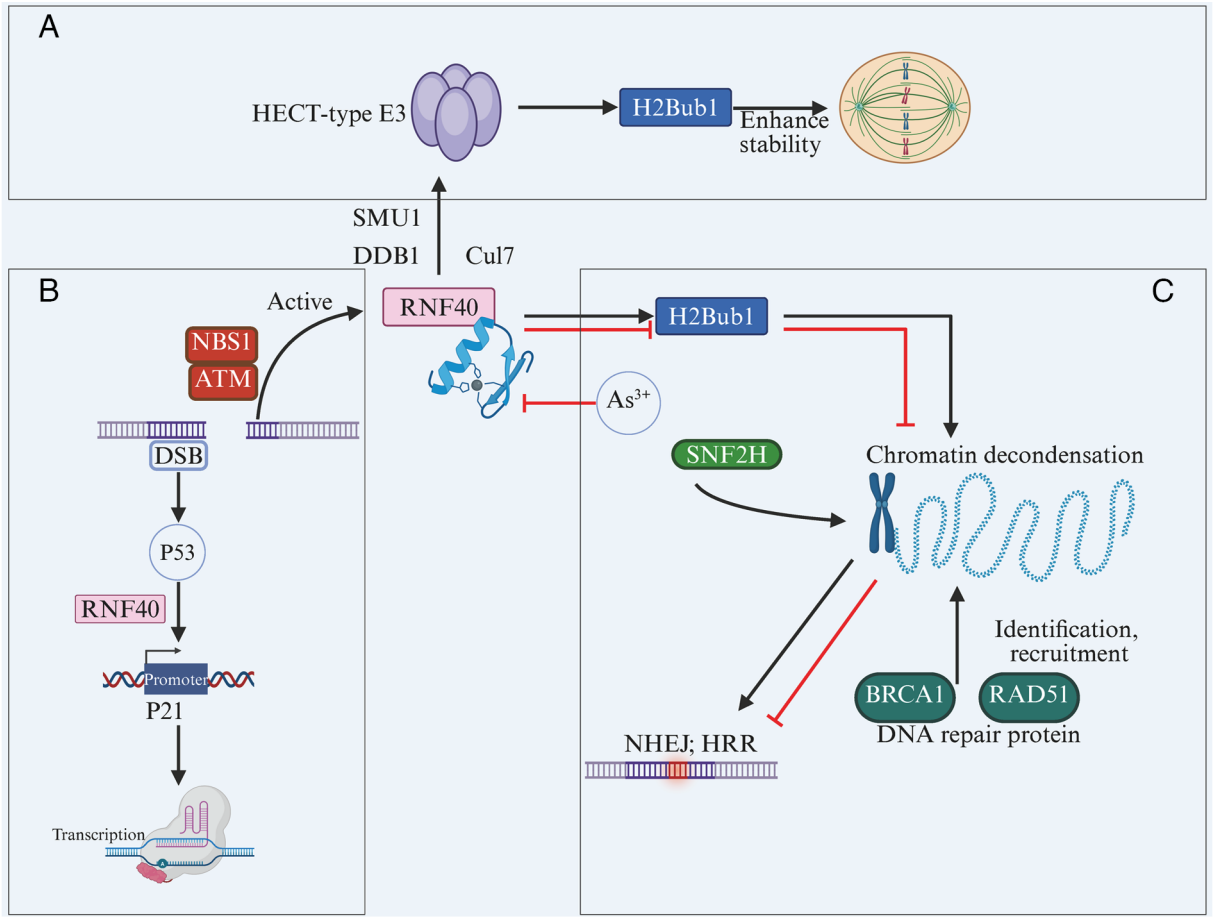

Figure 6. (A) RNF40 forms a HECT-type E3 ubiquitin ligase complex with DDB1, SMU1, and CUL7. This complex enhances the stability of H2Bub1 and helps maintain spindle dynamics during mitosis. (B-C) In response to DSBs, ATM kinase and NBS1 recruit RNF40 to the damaged sites, leading to increased local H2Bub1 deposition. This modification promotes SNF2H-dependent chromatin decondensation, which facilitates physical access of DNA repair proteins to the lesion and activates both HR and NHEJ. At DSBs, RNF40 cooperates with p53 to promote transcriptional elongation of the p21 gene. RNF40 contributes to the identification and recruitment of p53, which in turn transactivates downstream targets including BRCA1, RAD51, and p21, thereby coordinating DNA repair with cell-cycle regulation. Created in BioRender.com. RNF40, ring finger protein 40; DSB, DNA double-strand break; ATM, ataxia telangiectasia mutated; NBS1, nijmegen breakage syndrome 1; H2Bub1, histone H2B K120 monoubiquitination; HR, homologous recombination; NHEJ, non-homologous end joining; HECT, homologous to the E6-AP carboxyl terminus; DDB1, damage-specific DNA binding protein 1; SMU1, suppressor of mec-8 and unc-52 homologs; Cul7, cullin 7; SNF2H, sucrose non-fermenting protein 2 homolog; RAD51, radiation sensitive 51.

H2Bub1 levels to promote both non-homologous end joining (NHEJ) and homologous recombination (HR) repair (48,79,83). This E3 ligase catalyzes H2Bub1 deposition at DSB sites, promoting chromatin decondensation and enhancing DNA accessibility for repair factors such as BRCA1 and RAD51 (28,84). In addition, TNF receptor-associated factor interacting protein may recruit receptor-associated protein 80 to DNA damage sites via the RNF20/RNF40 complex, thereby promoting HR and NHEJ (85). The ubiquitin mark also recruits chromatin remodelers such as sucrose non-fermenting protein 2 homolog (86), which remodels nucleosomal architecture to create accessible channels for repair factors, thereby activating HR or NHEJ pathways (48,76) (Fig. 6). Importantly, deficiency of RNF20/RNF40 disrupts HR repair and class switch recombination, a process that relies on long-range DSB ligation, underscoring their key role in maintaining genomic integrity (76,79,87).

RNF40 modulates replication fork stability and interstrand crosslink repair by regulating H2Bub1 levels, thereby influencing the functional integrity of the Fanconi anemia group D2 protein complex and BRCA1/BRCC36 deubiquitinase (88). Additionally, the RNF20/RNF40 complex functions with p53 to coregulate transcriptional activation of target genes (29). Following DNA damage, p53 recruits the RNF20/RNF40 complex to the promoter of p21, increasing H2Bub1 levels to facilitate chromatin remodeling and RNA polymerase II transcriptional elongation (89) (Fig. 6).

Arsenic trioxide directly targets the RING domain of the RNF20/RNF40 complex, suppressing H2Bub1 deposition. This blocks BRCA1 and RAD51 recruitment to DNA damage sites, impairing HR and NHEJ efficiency while enhancing cell radiosensitivity (17) (Fig. 6). Dysregulation of RNF40 disrupts DNA repair fidelity, driving genomic instability and tumorigenesis (12,14,90). These dual roles as either a tumor suppressor or an oncoprotein underscore the context-dependent role of RNF40 in cancer progression and therapeutic response.

3. Mechanism of RNF40 in tumors

RNF40 exhibits tissue-specific functions across diverse organs, with its pleiotropic roles in cancer arising through three key mechanisms: Epigenetic reprogramming via H2Bub1

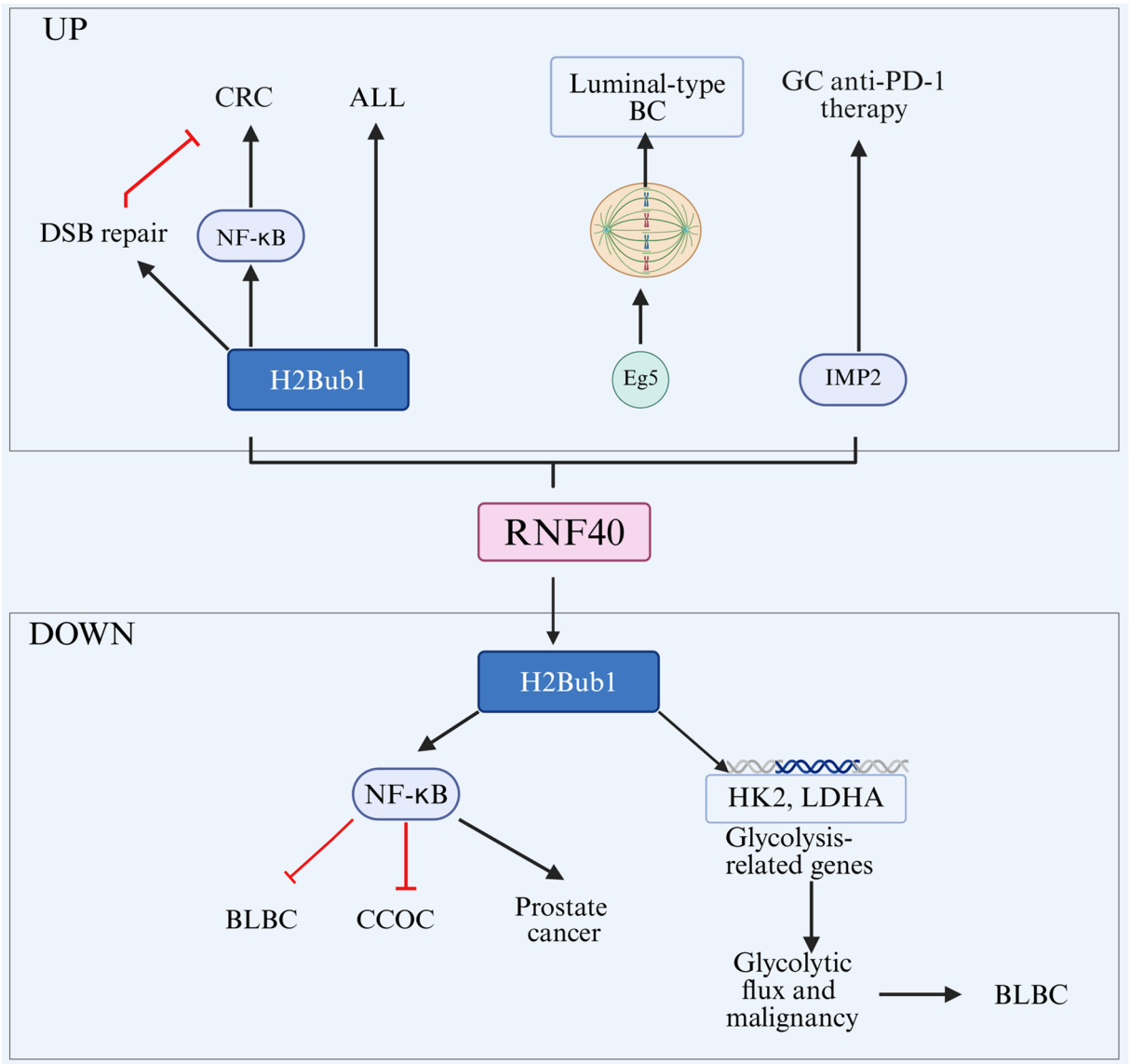

Figure 7. RNF40 promotes or suppress tumorigenesis through distinct mechanisms. Upregulation of RNF40 promotes the progression of ALL, luminal-type BC and CRC, and enhances the efficacy of anti-PD-1 therapy in GC by regulating IMP2. Conversely, downregulation of RNF40 promotes prostate cancer progression via H2Bub1 and facilitates the progression of BLBC through glycolysis-related genes (HK2, LDHA), while inhibiting the progression of both BLBC and CCOC via the NF-κB signaling pathway. Created in BioRender.com. RNF40, ring finger protein 40; BC, breast cancer; BLBC, basal-like BC; siRNA, small interfering RNA; H2Bub1, histone H2B K120 monoubiquitination; Eg5, kinesin-5; ER, estrogen receptor; Ub, ubiquitin; MCL1, myeloid Cell Leukemia 1; CRC, colorectal cancer; ALL, acute lymphoblastic leukemia; DSB, DNA double-strand break; GC, gastric cancer; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; CCOC, Clear cell ovarian cancer, IMP2, insulin-like growth factor 2 mRNA binding protein 2; PD-1, programmed cell death protein 1TME, tumor microenvironment.

modulation (91), crosstalk with oncogenic signaling pathways (19,41) and remodeling of the TME (40). Dysregulated RNF40 expression is associated with tumor progression, metastatic dissemination and therapy resistance (18,41,92). However, its functional duality as either an oncogenic driver or a tumor suppressor is dependent on cancer type and molecular context (genomic instability status, coexisting mutations) (46,91,93,94). Fig. 7 and Table II summarize the expression levels and mechanisms of RNF40 in tumors.

BC. RNF40 exhibits subtype-specific functional duality in BC, with opposing roles across molecular classifications. In BLBC, H2Bub1 acts as a tumor-suppressive modification, inhibiting disease progression (95). Conversely, luminal-type tumors exhibit improved prognosis when H2Bub1 levels are low. Mechanistically, RNF20/RNF40 stabilizes the mitotic kinesin-5 (Eg5) by catalyzing its monoubiquitination at lysine 745, ensuring proper spindle assembly and promoting BC cell survival (96). RNF40 promotes G2/M phase transition during somatic cell reprogramming by preserving H2Bub1 levels and activating cell cycle drivers such as Eg5 target genes (19,40) (Fig. 8). In ERα-positive BC, RNF40 knockdown suppresses ERα target gene transcription, exerting therapeutic effects (97). However, this intervention paradoxically activates estrogen-independent pro-survival pathways that drive metastatic migration and proliferation (42) (Fig. 8). This context-dependent antagonism underscores the dual role of RNF40 as both a vulnerability and resistance

Table II. Expression levels and mechanism of action of RNF40 in different tumors.

Cancer	Expression	Mechanism		Effect of RNF40	(Refs.)
		Substrate availability	Signaling crosstalk		
BLBC	Downregulated	H2Bub1	Glycolysis NF-κB	Oncogenic Tumor-suppressive	(42,69,96) (95)
Luminal BC	Upregulated	H2Bub1, Eg5	G2/M	Oncogenic	(20,41,96)
CRC	Upregulated	H2Bub1	NF-κB DSB	Oncogenic Tumor-suppressive	(41) (101,102)
CCOC	Downregulated	H2Bub1	Unknown	Tumor-suppressive	(91)
ALL	Upregulated	H2Bub1	RNF20/ RNF40/WAC	Therapeutic resistance	(92)
Prostate cancer	Downregulated	H2Bub1	NF-κB	Oncogenic	(105,106)
Lung	Upregulated	H2Bub1	Peroxisome function; ferroptosis	Oncogenic	(28,108,109)
Gastric	Upregulated	IMP2	USP14/IMP2/ CXCL2	Enhances the efficacy of anti-PD-1 therapy	(112)

ALL, acute lymphoblastic leukemia; BLBC, basal-like breast cancer; CRC, colorectal cancer; CCOC, clear cell ovarian carcinoma; CXCL2, C-X-C motif chemokine ligand 2; DSB, double-strand break; H2Bub1, histone H2B K120 monoubiquitination; IMP2, insulin-like growth factor 2 mRNA binding protein 2; USP14, ubiquitin-specific protease 14; WAC, WW domain-containing adapter protein with coiled-coil; RNF40, ring finger protein 40; Eg5, kinesin-5.

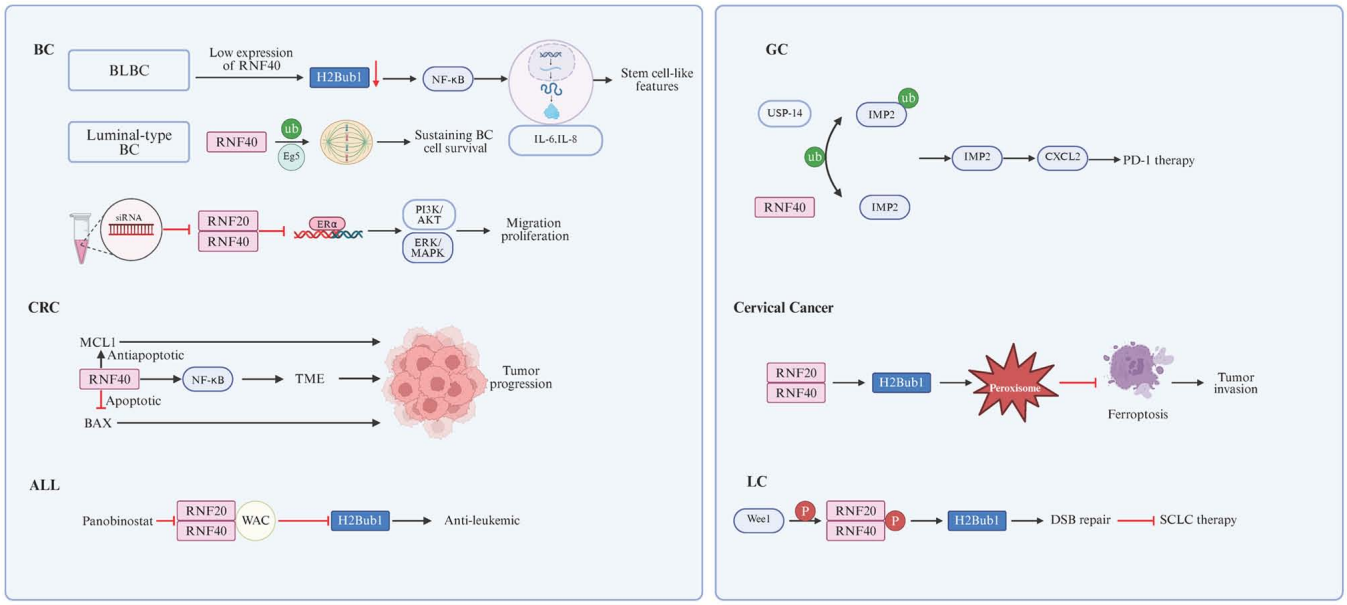

Figure 8. Roles of RNF40 in BC, CRC, ALL, GC, cervical cancer and LC and its impact on treatment. In BLBC, decreased H2Bub1 levels promote BC cell stemness. In luminal-type tumors, RNF20/RNF40 promotes BC cell survival. RNF40 promotes the progression of CRC. Created in BioRender.com. BLBC, basal-like breast cancer; H2Bub1, histone H2B K120 monoubiquitination; RNF, ring finger protein; CRC, colorectal cancer; ALL, acute lymphoblastic leukemia; WAC, WW domain-containing adapter protein with coiled-coil; GC, gastric cancer; USP, ubiquitin-specific protease; Ub, ubiquitin; IMP2, insulin-like growth factor 2 mRNA binding protein 2; Wee1, Wee-like protein kinase; DSB, DNA double-strand break; SCLC, small cell lung cancer.

factor, depending on tumor subtype and signaling network dynamics. In ER-positive MCF7 and ER-negative SUM159 human BC cells, hypoxia-induced gene expression is dependent on the histone H2A/H2B chaperone facilitates chromatin transcription complex (FACT) and H2B ubiquitin ligase RNF20/40; knockdown of FACT or RNF20/40 decreases transcription initiation and elongation of hypoxia-inducible factor 1 target genes (98). In triple-negative BC (TNBC),

Twist1 promotes cell proliferation, migration, invasion, epithelial-mesenchymal transition and angiogenesis by upregulating RNF40 transcription, facilitating the progression of the carcinogenic phenotype of TNBC cells (40). *In vivo* studies of BC using RNF40-knockdown cells confirm the multiple functions of RNF40 in different signaling pathways (19,40).

By contrast with the context-dependent duality of RNF40 in BC, H2Bub1 exhibits consistent tumor-suppressive properties, with low expression levels associated with malignant progression (12). In BC, decreased H2Bub1 levels increase the migration of non-transformed mammary epithelial and BC-derived cells (99). Notably, H2Bub1 loss occurs in 67% of breast carcinoma cases but is absent in benign tumors (100), underscoring its role as a malignancy biomarker. In HER2-positive BC, RNF40 expression is upregulated in metastatic lesions compared with primary tumors, while H2Bub1 levels decrease, a paradoxical pattern associated with aggressive disease (19). Clinically, high RNF40 expression is associated with poor prognosis, whereas low expression predicts improved survival, positioning RNF40 as both a driver of metastasis and a therapeutic vulnerability (41,46). This underscores H2Bub1 loss as a critical event in tumor evolution, mediated by RNF40 E3 ligase activity. For example, proteasome inhibitors such as bortezomib suppress ERα signaling by downregulating H2Bub1, highlighting their therapeutic potential in targeting this axis (42).

CRC. RNF40 knockout in CRC cell models exerts protective effects against local and systemic inflammation (41,43). In IBD-associated CRC, RNF40 promotes tumorigenesis by sustaining NF-κB activity, promoting the TME (43) (Fig. 8). RNF40 depletion in CRC cells markedly decreases migratory capacity while increasing apoptosis (41). Mechanistically, RNF40 suppresses apoptosis by maintaining the expression of antiapoptotic genes (myeloid cell leukemia 1) and enforcing H2Bub1-mediated transcriptional programs. Conversely, it suppresses proapoptotic genes such as BAX, and its deletion triggers cell cycle arrest and apoptosis induction (41). Collectively, these mechanisms (NF-κB activation and apoptotic evasion) position RNF40 as a key oncogenic driver in CRC progression (Fig. 8).

While caspase inhibitors partially rescue the apoptotic phenotype of RNF40-deficient CRC cells, RNF40 retains intrinsic tumor-suppressive activity independent of apoptosis regulation (41), suggesting that additional mechanisms underlie its anticancer role. In CRC, H2Bub1 serves as a tumor suppressor, with reduced levels associated with poor patient prognosis (101,102). RNF40 regulates H2Bub1 deposition via its E3 ligase activity, modulating chromatin accessibility and transcriptional programs (39). Paradoxically, RNF40 deletion elevates H2Bub1 levels, dysregulating NF-κB signaling and other oncogenic pathways, which underscores its context-dependent regulatory complexity (43). Chronic inflammation exacerbates CRC progression by remodeling the TME (103) and inducing DNA damage-driven genomic instability (104). RNF40 interplay with H2Bub1 may counteract these effects by stabilizing chromatin architecture and suppressing inflammation-associated transcriptional cascades (36). This dual capacity to regulate both epigenetic states and inflammatory signaling establishes RNF40 as a key node connecting genomic integrity, microenvironmental cues and malignant transformation (51). These findings have been corroborated by *in vivo* and *in vitro* studies using RNF40-knockdown tumor cells in CRC models (41,43).

Clear cell ovarian cancer (CCOC). H2Bub1 is markedly decreased in CCOC, with its depletion serving as an early molecular event detectable in precancerous lesions (91). RNF40, the primary E3 ligase catalyzing H2Bub1 deposition, is typically dysregulated in CCOC, either via reduced expression or functional impairment, serving as the principal driver of this tumor-suppressive epigenetic loss (91).

Prostate cancer (PC). In metastatic PC, downregulation of the E3 ligases RNF20 or RNF40 notably suppresses tumor cell proliferation, though the underlying mechanism remains elusive. This effect may involve H2Bub1-dependent chromatin remodeling or interactions with non-H2Bub1 substrates (105). Notably, the NF-κB pathway, a key driver of castration-resistant (CR)PC initiation and progression (106), is modulated by RNF40 when androgen receptor signaling is suppressed (41,43,107). These findings suggest that RNF40 influences CRPC progression and therapeutic resistance via NF-κB signaling, positioning it as a potential therapeutic target for advanced prostate malignancy.

Other types of cancer. RNF40 is highly expressed in hepatocellular carcinoma and is associated with poor patient prognosis (14). Chemotherapeutic agents such as cisplatin exert their effects primarily by inducing DNA damage, but tumor sensitivity to such drugs is modulated by RNF40 expression (29). In lung cancer (LC) models, RNF40 deficiency decreases H3K56 acetylation, disrupting chromatin flexibility and impairing DNA repair processes, which paradoxically promotes cisplatin resistance despite compromised damage resolution (28,108,109) (Fig. 8). LC cells with low H2Bub1 levels exhibit a higher proliferation rate than those with high H2Bub1 levels. Increased cisplatin resistance in LC cells is associated with downregulation of B cell lymphoma 2 modifying factor and p53, as well as upregulation of AKT (110). In small cell (SC)LC, elevated expression of Wee-like protein kinase (Wee1) promotes H2BY37ph (H2B tyrosine37 phosphorylation) to recruit the E3 ubiquitin ligase RNF20/RNF40 complex, promoting the upregulation of its phosphorylation, thereby facilitating DSB repair and contributing to therapeutic resistance in SCLC (111) (Fig. 8).

In cervical cancer, elevated expression of RNF40 increases in H2Bub1 levels, enhances peroxisome function, reinforces resistance to ferroptosis and promotes tumor invasion (46) (Fig. 8). In MLL (mixed lineage leukemia)-rearranged acute lymphoblastic leukemia, panobinostat as a single agent exhibits potent anti-leukemic effects, which prolong survival and decrease the overall disease burden. Its anti-leukemic effects is mediated through inhibition of the RNF20/RNF40/WAC E3 ubiquitin ligase complex and reducing H2B ubiquitination (92). In gastric cancer (GC), the efficacy of anti-PD-1 therapy is enhanced by inhibiting the USP14/IMP2/C-X-C motif chemokine ligand 2 (CXCL2) signaling pathway, while RNF40 dynamically balances the protein abundance of IMP2 with USP14, regulates the expression and secretion of CXCL2

and affects the efficacy of PD-1 therapy in GC (112) (Fig. 8). In bladder cancer, RNF40 contributes to tumor development, progression and prognosis by regulating alternative splicing, and its dysregulation adversely affects patient outcomes (113).

4. Conclusion

RNF40 exhibits complex and multifaceted functions across cell processes, serving key roles in cancer, metabolic disorder and immune-associated pathologies. Dysregulation of RNF40 expression or activity disrupts physiological homeostasis, resulting in notable pathological consequences. As an E3 ubiquitin ligase, RNF40 functions through two distinct mechanisms: Ubiquitination-dependent regulation of histones (H2B and H2A) and ubiquitination-independent modulation of cell pathways. Notably, its core biological function is to catalyze H2Bub1, a post-translational modification involved in chromatin remodeling, DDR and epigenetic regulation. RNF40 heterodimerizes with RNF20 through its CC domain; this RNF40/RNF20 complex serves as the primary mediator of H2Bub1. This modification is key for coordinating key biological processes, including DDR, transcriptional activation, cell cycle progression and apoptosis. The RING domain of RNF40 confers E3 ligase activity by recruiting E2 ubiquitin-conjugating enzymes (RAD6, UbcH8 and UbcH6), thereby facilitating ubiquitin transfer to target substrate proteins (23,114).

While the mechanistic role of RNF40 has been partially characterized in specific types of cancer, its functional impact across most malignancies remains largely unexplored, underscoring the need for further investigation. A key challenge lies in RNF40 integration into diverse regulatory networks, where it exhibits context-dependent duality, exerting opposing roles not only across distinct tissues but also within distinct signaling pathways of the same tissue. This functional versatility poses a barrier to the development of RNF40-targeted therapeutic strategies.

RNF40 exhibits opposing functions in BL and luminal BC. In BLBC, downregulation of RNF20, RNF40 and H2Bub1 is associated with poor prognosis (95). Decreased H2Bub1 enhances NF-κB activity and upregulates pro-inflammatory cytokines, thereby promoting tumor invasiveness, suggesting RNF40 and H2Bub1 serve as tumor suppressors (95). However, another study reported that RNF40 promotes the invasiveness of BLBC by regulating glycolysis, indicating that RNF40 acts through distinct mechanisms within the same tumor subtype (18). By contrast, in the luminal subtype, upregulation of these markers is associated with worse clinical outcomes compared with low-expression counterparts, suggesting an oncogenic function of RNF40 (95). In ER-positive BC, RNF40 knockdown activates an estrogen-dependent pro-survival pathway and accelerates tumor cell proliferation (42).

In CRC, RNF40 is highly expressed and promotes tumor progression by activating the NF-κB signaling pathway and inhibiting apoptosis, including via regulation of B cell lymphoma 2 family proteins (43). Meanwhile, H2Bub1 maintains chromatin structural stability and suppresses inflammation-associated transcriptional cascades, thereby suppressing chronic inflammation-driven tumorigenesis (73).

In CCOC, loss of RNF40 function results in a marked decrease in H2Bub1 levels, representing a key driver of this malignancy (91). In SCLC, elevated Wee1 expression promotes H2BY37ph, thereby recruiting the RNF20/RNF40 E3 ubiquitin ligase complex and enhancing its activity, which facilitates DSB repair and contributes to therapeutic resistance (111). Similarly, the anti-leukemic agent panobinostat exerts its therapeutic effects by inhibiting the RNF20/RNF40/WAC E3 ubiquitin ligase complex and decreasing H2B ubiquitination in leukemia.

Substrates of RNF40 and the signaling pathways it participates in exhibit marked differences across types of cancer, providing a molecular basis for its functional diversity. Specifically, RNF40 catalyzes the ubiquitination of its substrate proteins; these modified proteins determine the biological functions of RNF40 within specific cell contexts. The functional duality of RNF40 arises from a combination of factors, including differences in its interacting protein networks, the spatiotemporal specificity of substrate selection and the influence of the TME.

The RNF40 protein interacts with partner proteins via its CC domain to form functional complexes that regulate key biological processes, including DDR and transcriptional regulation. These mechanistic insights provide a foundation for designing therapeutic strategies, such as inhibitors or activators that target RNF40 substrate-binding or protein interaction interfaces. Given its multifaceted roles across signaling networks, combinatorial strategies integrating RNF40 modulation with pathway-specific regulators may enable novel therapeutic paradigms. Further structural and mechanistic characterization of RNF40 may reveal novel therapeutic targets and enable the development of personalized therapy for diseases associated with its dysregulation.

Given the diverse and context-dependent functions of RNF40 across types of cancer, direct targeting may disrupt key physiological processes in normal tissues and result in notable toxicity. Its broad substrate specificity further limits its utility as a biomarker, as disease relevance depends on substrate expression levels, underscoring the need for population-specific biomarker panels and evaluation criteria. Thus, rather than direct inhibition, disrupting RNF40-substrate interactions may represent a more viable strategy in certain types of cancer, such as BLBC. In this context, targeted protein degradation (TPD) offers a promising alternative.

PROTACs are heterobifunctional molecules that recruit an E3 ligase to a target protein, leading to its ubiquitination and proteasomal degradation (9). By contrast with conventional inhibitors that only block activity, PROTACs eliminate the entire protein, potentially abrogating all function and overcoming adaptive resistance. This strategy enables more precise targeting of RNF40 while decreasing off-target effects. Another emerging TPD approach involves intramolecular bivalent glues, which induce conformational changes in target proteins, enhancing recognition by endogenous E3 ligases and improving substrate specificity (9). The successful development of HER2-targeted therapy and PD-L1 inhibitors provides a paradigm for translating mechanistic insights into clinical applications, offering valuable lessons for RNF40-directed strategies. Future studies should prioritize patient stratification based on molecular biomarkers such as

RNF40 expression, H2Bub1 levels and downstream signaling activity. Drawing from advances in anticancer drug development, RNF40-targeted therapeutics, whether highly selective small-molecule inhibitors or PROTACs, hold promise for achieving enhanced specificity and efficacy.

Clinically, H2Bub has been identified as an epigenetic marker of complex DNA damage (CDD). RNF20/40 and male-specific lethal 2 may serve as potential targets for cancer radiotherapy, particularly proton radiotherapy, and enhance the efficacy of radiotherapy by regulating CDD repair (93,115). 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) inhibits the proliferation of various cancer cell lines and knockdown of RNF40 notably enhances AICAR sensitivity, which demonstrates the therapeutic potential of targeting RNF40 (116).

However, current understanding of RNF40 in disease initiation and progression remains limited (46). Most studies focus on molecular mechanisms, with a lack of clinically oriented investigations (12,30,91,92,112,117). Moreover, understanding of the molecular mechanism remains incomplete. Given the potentially opposing roles of RNF40 in different tumors, therapeutic targeting of one malignancy could increase the risk of another. Further research is essential to inform clinical strategies and expand the therapeutic repertoire.

Acknowledgements

Not applicable.

Funding

The present study was supported by Key Science and Technology Tackling Program of Henan Province (grant no. 232102311077), National Natural Science Foundation of China (grant no. 82503868), Medical Science and Technology Project of Henan Province (grant nos. LHGJ20220198, LHGJ20240104 and LHGJ20240108), Natural Science Foundation of Henan Province (grant no. 242300420578), Henan Provincial Medical Education Research Project (grant no. Wjlx2020107), National Key Clinical Discipline Construction Project (grant no. 210020116, China) and Graduate Education Reform Research and Curriculum Development Program of the Academy of Medical Sciences, Zhengzhou University (grant no. 040012023B062).

Availability of data and materials

Not applicable.

Authors' contributions

ZW wrote and edited the manuscript and conceived the study. HY edited the manuscript and conceived the study. FL, HA and ZL edited the manuscript. GC, WZhao, BB, CL and WZhu wrote and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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