Multiple roles of replication factor C family in pan-cancer (Review)

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Received July 1, 2025; Accepted September 9, 2025

DOI: 10.3892/or.2025.8998

Abstract. Due to the persistently high global incidence and mortality rates of cancer, developing novel therapeutic strategies is imperative. The replication factor C (RFC) family, a critical subset of DNA replication and repair, serves multifaceted roles in tumor progression. Despite its widely recognized importance, the pleiotropic mechanisms of the RFC family lack systematic illustration, particularly regarding each member specific contributions to cancer hallmarks. In the present review, mRNA expression of each RFC family member in pan-cancer was profiled and the associations between their expression levels and tumor types evaluated. In addition, the effect of RFC expression on patients' survival across malignancies is assessed. Furthermore, the present review summarized current research on RFC family members in various malignancies with particular emphasis on the RFC-like complexes, highlighting key findings and advancements in understanding their role in tumor biology. The signaling pathways associated with RFC family members are discussed and the molecular mechanisms elucidated. Finally, the clinical importance of RFC family members including prognosis, potential inhibitors and combination treatments are also discussed. The present review aimed to provide innovative perspectives for developing combinatorial molecular targeted therapies in the future.

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Key words: replication factor C family, pan-cancer, structure, function, signaling pathway

1. Introduction

Due to the high incidence rates and mortality burden, cancer is a notable societal, public health and economic problem. Although a variety of treatments have been proposed, the therapeutic efficiency and safety remain to be improved. There is an urgent need to develop more effective treatment strategies (1). Consequently, understanding the functional mechanisms of key genes during tumorigenesis holds notable clinical implications.

The replication factor C (RFC) family consists of five paralogous members (RFC1-5) characterized by distinct structural domains and conserved functional motifs. The sequence homology arises from the strong similarity in the sequences of these family members. RFC1 exhibits unique structural features including the exclusive RFC box I domain, while boxes II-VIII are structurally conserved across all RFC paralogs (2).

Accumulating evidence highlights the critical role of RFC family members in tumorigenesis and cancer progression. Functional experimental studies have reported the antitumor or pro-tumor effects of RFC family members, such as promoting cell apoptosis (3), inducing cell cycle arrest (4) and inhibiting epithelial-mesenchymal transition (EMT) (5). Numerous studies have also demonstrated the regulatory function of RFC family members, including microRNA (miR)-mediated translational suppression (6), post-translational modification via cascade effects (7) and epigenetic modification (8). In addition, substantial evidence suggests some RFC family members also participate in several key signaling pathways, including the Wnt/β-catenin (9), Notch pathway (10) and p53 pathways (11).

Moreover, RFC-like complexes (RLCs) also are involved in tumorigenic processes, particularly in DNA-related damage and repair. Notably, RLCs have emerged as integral components of tumorigenic processes, particularly in maintaining genomic stability through coordinated participation in DNA damage response pathways and repair mechanisms (12). Due to the multifaceted roles of RFC family in the context of cancer, its members have the potential to be biomarkers for precision oncology. However, comprehensive analyses of their contributions to tumor development and progression remain limited.

In the present review, the differential expression of RFC family members in pan-cancer was systematically evaluated using Tumor IMmune Estimation Resource (TIMER2.0) (13). As potential biomarkers for patients, the relationship between expression levels and clinical importance were investigated. Furthermore, the present review summarized current research on RFC family members in various malignancies with particular emphasis on their specific contributions to signaling pathway regulation. The present article aimed to systematically summarize the expression characteristics, functional heterogeneity and molecular mechanisms of the members of the RFC family in various cancers, and to explore their potential as diagnostic markers and therapeutic targets.

2. Overview of RFC

The replication factor C (RFC) protein, first purified from 293T cells, has been shown to interact with SV40 large T antigen during the initial phases of viral DNA replication *in vitro* (14-16). Subsequently, RFC was also purified from HeLa cells. RFC exhibits multiple activities, including its ability to participate in DNA replication in an ATP- and proliferating cell nuclear antigen (PCNA)-dependent reaction (17). Moreover, it is also involved in pleiotropic biological activities, including DNA repair, transcriptional regulation, cell cycle, apoptosis, cellular differentiation and telomere-length regulation (14).

3. Structure and expression of RFC family members in pan-cancer

The RFC family comprises of five distinct members (RFC1, RFC2, RFC3, RFC4 and RFC5) with molecular weights of 140, 40, 38, 37 and 36 kDa respectively. These proteins have been discovered in *Saccharomyces cerevisiae*, *Mus musculus*, *Homo sapiens*, *Calf thymus* and *Escherichia coli* (18-22). It has been reported that p140 (*RFC1*), p40 (*RFC2*), p38 (*RFC3*), p37 (*RFC4*) and p36 (*RFC5*) are located on human chromosomes at 4p13-p14, 7q11.23, 13q12.3-q13, 3q27 and 12q24.2-q24.3, respectively (23,24).

In humans, the five subunits of RFC complex exhibit sequence conservation across conserved regions known as RFC boxes II-VIII, which are critical for their functional interactions (2,20). The RFC box I, which is located on the large subunit p140 and consists of 89 amino acids, demonstrates sequence homology with prokaryotic DNA ligases (2). Additionally, it has been demonstrated that deletion of RFC box II domain markedly impairs DNA synthesis, which requires the RFC complex for its function (25). The highly conserved RFC box III GXXXXGK(S/T) motif contains the phosphate-binding loop (P-loop), the most evolutionarily conserved structural element within this motif. By contrast, RFC box IV exhibits limited conservation in prokaryotic proteins. RFC box V DE(V/A)D and DEAD-box proteins have similar features. Within the large subunit p140, RFC box VI is designated VIa, whereas it is referred to as VIb in the other four small subunits (14,26). RFC box VII (SRC) is conserved within the small subunits and the prokaryotic accessory proteins, but only the cysteine is present in the large RFC subunits. Notably, the HYC motif in RFC1 corresponds to box VII (27). In the human RFC family, RFC box VIII displays subunit-specific amino acid sequence variations. The characteristic sequences of RFC boxes are shown in Fig. 1.

The mRNA expression of RFC family members was evaluated in pan-cancer using TIMER 2.0 (Fig. 2) (13). According to the results, in the most types of tumors, the RFC family members are expressed at higher levels in tumor tissues compared with in normal tissues. Notably, in kidney chromophobe, the expression levels of all RFC family members are markedly lower in tumor tissues compared with in normal tissues. The underlying mechanisms warrant further investigation.

The clinical relevance of RFC gene expression across various cancer types was assessed using TIMER 2.0 (Fig. 3). For each RFC subunit, the cancer type with the highest and lowest Z score were summarized. The results are presented in Table I. Kaplan-Meier analysis was used to evaluate the overall survival (OS). The potential relationship between the mRNA expression of RFC subunits and overall survival (OS) in patients with various cancers was analyzed (Fig. 3) (28). Elevated expression levels of RFC2, RFC3 and RFC5 were associated with worse outcomes in brain lower-grade glioma (LGG). Similarly, high RFC4 expression was associated with poor survival in adrenocortical carcinoma (ACC). By contrast, reduced RFC1 expression was associated with worse outcomes in kidney renal clear cell carcinoma, while decreased RFC5 expression was associated with poor prognosis in human papillomavirus (HPV)-positive head and neck squamous cell carcinoma (HNSCC). These results indicate that RFC family members have the potential to be biomarkers for precision oncology.

4. Function of RFC subunits in human cancers

RFC1. The RFC1 gene, localized on chromosome 4, encodes the ubiquitously expressed RFC1 protein which serves as the largest subunit of the RFC family. This protein serves a critical role in DNA replication and repair processes (29). In humans, three functional homologs of RFC1 have been identified including RAD17 checkpoint clamp loader component (RAD17), chromosome transmission fidelity factor 18 (CTF18) and ATPase family AAA domain containing 5 (ATAD5). These homologs can associate with other subunits through protein-protein interactions, which facilitates the assembly of RLCs (30).

The expression of RFC1 is overexpressed in malignant nasopharyngeal carcinoma (NPC) cells (31). In breast cancer (BC), the curcumin-analog PAC markedly upregulates the expression of RFC1 which is involved in the nucleotide

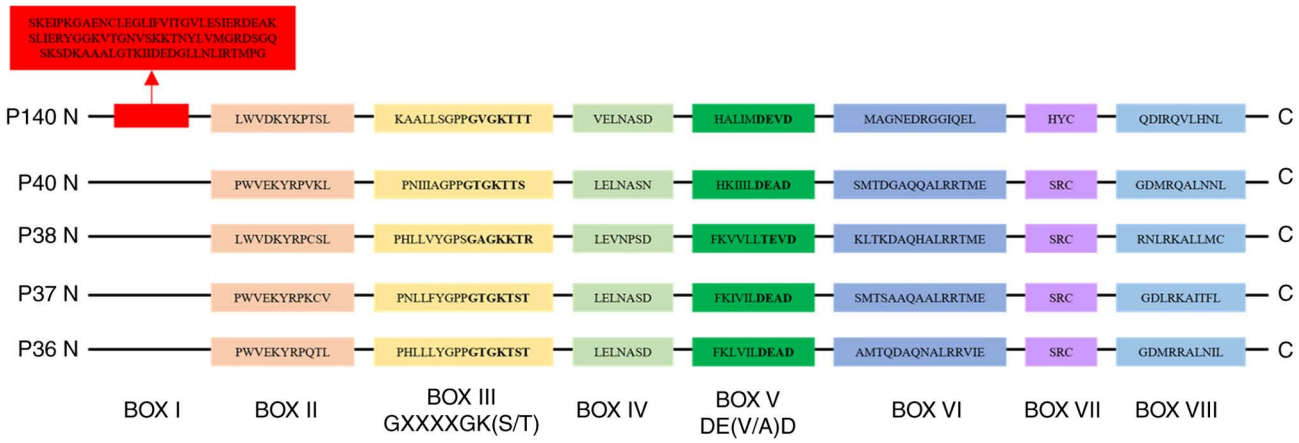

Figure 1. RFC boxes in each family member. RFC, replication factor C.

excision repair (NER) pathway (32). A study on estrogen receptor (ER)-negative MDA-MB-231 BC cells revealed that 17β-estradiol exposure downregulated RFC1 expression, leading to re-expression of ERα (33). Emerging evidence in colorectal cancer (CRC) research suggests that reduced RFC1 expression may function as a tumor suppressor mechanism. Mechanistic investigation identified post-transcriptional regulation of RFC1 via microRNA-26a-5p targeting of its 3'-untranslated region, which modulates critical DNA maintenance processes, including mismatch repair, DNA replication fidelity and NER pathway functionality (6). RFC1 demonstrates more distinctive features than the other four RFC family members, making it a promising candidate for further cancer research. Now that the notable effects of RFC1 have drawn attention in cancer research, similar focus has been directed to other members of the RFC family. Evidently, a deeper understanding of the roles of RFC family members in cancer biology is crucial, as it may facilitate the discovery of novel signaling pathways and potential therapeutic targets.

RFC2. The RFC2 gene, located on chromosome 7, encodes the unique RFC subunit that can independently unload PCNA and suppress DNA polymerase activity.

In diffuse LGG, bioinformation analysis has shown that overexpressed RFC2 is strongly associated with pivotal immune checkpoint genes [including programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), PD-L2, B7-H2 and cytotoxic T-lymphocyte associated protein 4 (CTLA4)] and serves as an independent predictor of adverse prognosis. In cell models, functional experiments demonstrate that RFC2 serves an anticancer role by promoting cell apoptosis, inhibiting proliferation and inducing cell G_2 phase arrest (3). In gastric cancer (GC), circular RNA-collagen type Iα2 chain functions as a competing endogenous RNA by sponging miR-1286, upregulating ubiquitin specific peptidase 10 expression and attenuating RFC2 ubiquitination, ultimately enhancing cell invasion and migration (8). In hepatocellular carcinoma (HCC), as a novel biomarker for the prognosis, high expression of RFC2 was associated with worse OS and disease-free survival. Functional experiments demonstrate that RFC2 knockdown inhibits malignant behaviors including proliferation and migration of HCC cell lines (34). In CRC, upregulated RFC2 expression is associated with poor clinical outcomes.

Functional studies have demonstrated that RFC2 silencing notably attenuates malignant phenotypes, including tumor cell proliferation, migration and invasion. Notably, knockdown of CAMP responsive element binding protein 5 which is the transcription factor of RFC2 markedly suppresses RFC2 expression. Moreover, RFC2 promotes aerobic glycolysis and MET/PI3K/AKT/mTOR pathway, thereby driving tumorigenesis (7). In castration-resistant prostate cancer (CRPC) cell lines, RFC2 downregulation markedly inhibits cell proliferation, induces apoptosis and aggravates DNA damage (35). Furthermore, clinical evidence demonstrates that elevated RFC2 protein expression is associated with unfavorable prognosis in patients with prostate cancer (PCa). Notably, RFC2 expression levels are markedly higher in CRPC tissues compared with localized PCa, suggesting a potential role in disease progression (35). In metastatic Ewing's sarcoma (ES), RFC2 mRNA expression is markedly upregulated. Elevated RFC2 levels are inversely associated with poor OS and event-free survival in patients with ES (36). In cervical cancer (CC), RFC2 serves a pivotal role in promoting cervical cancer progression by enhancing cell growth, regulating the cell cycle and promoting metastatic behavior (37). Therefore, RFC2 exerts pro-tumorigenic effects. Designing a targeted drug tailored to RFC2 may be a promising precision medicine approach.

RFC3. The RFC3 gene, located on chromosome 13 in humans, is involved in cell proliferation and DNA damage repair, and its abnormal activation is associated with various malignant tumors.

In HNSCC, bioinformation analysis has demonstrated that the high expression of RFC3 is notably associated with clinicopathological features, including tumor stage, grade, metastasis and patient survival (38). Additionally, it is also associated with immune cell infiltration and well-known oncogenic signaling pathways, such as MYC/MYCN, Hippo and mTOR (38). In the ER-positive BC cell line MCF-7, upregulated RFC3 is notably associated with poor prognosis, and downregulated RFC3 induces S phase arrest and attenuated cell proliferation, migration and invasion (39). The downregulation

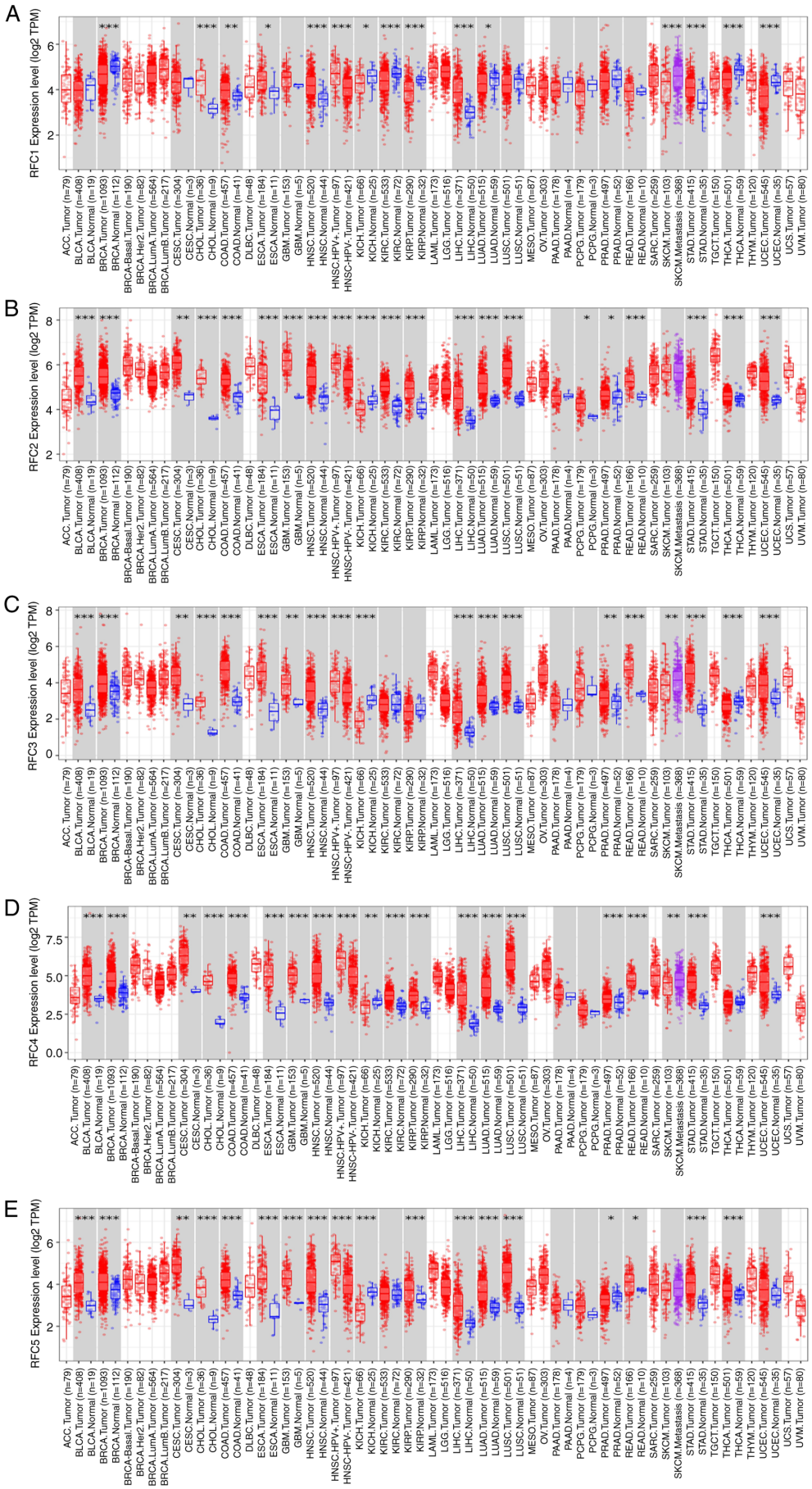

Figure 2. Differential expression of RFC subunits in various tumors. The dot plot represents the gene expression profiles of all tumor samples and paired normal tissues. The expression levels of (A) RFC1, (B) RFC2, (C) RFC3, (D) RFC4 and (E) RFC5 in pan-cancer from The Cancer Genome Atlas database were analyzed using Tumor IMmune Estimation Resource 2.0. RFC, replication factor C. *P<0.05, **P<0.01 and ***P<0.001.

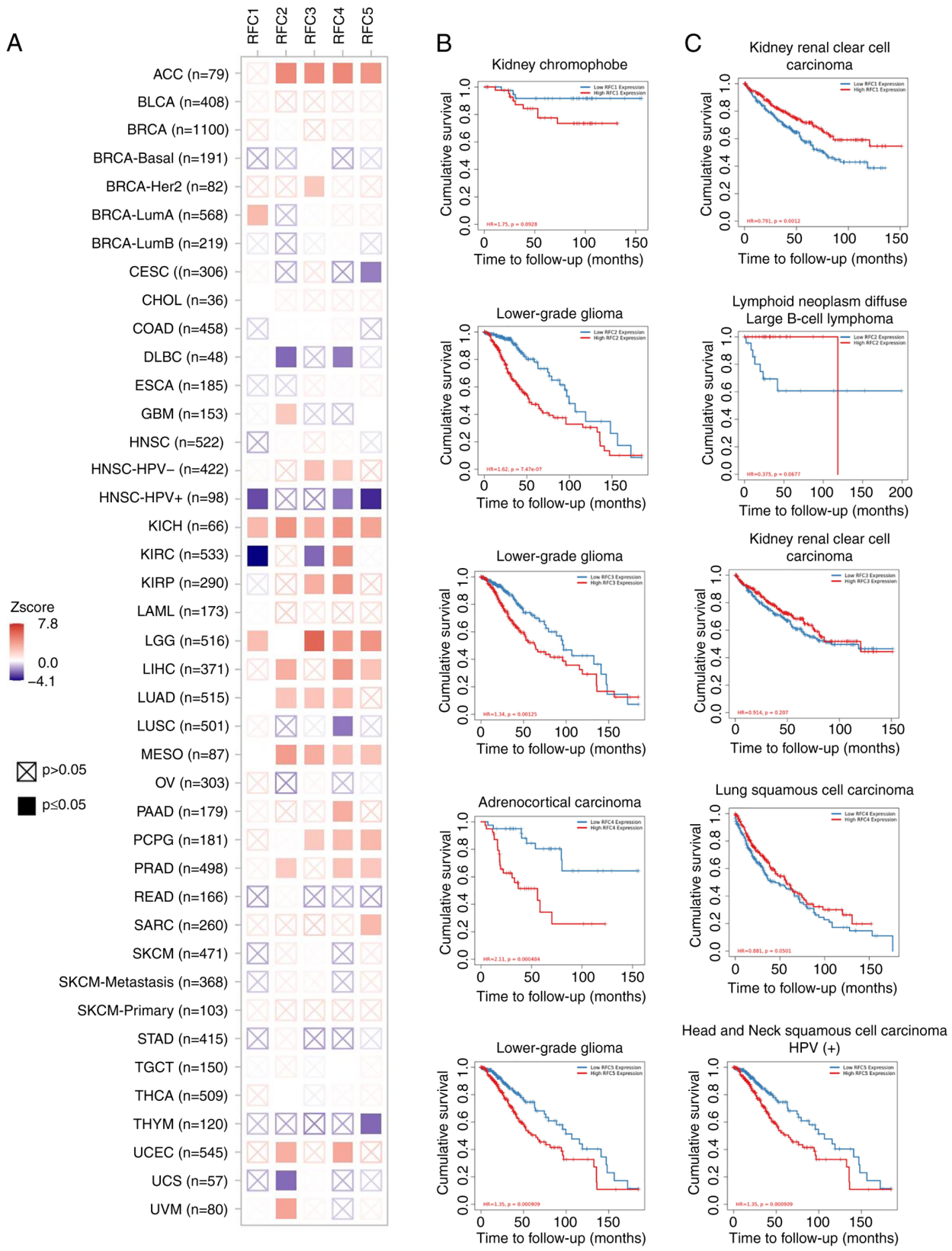

Figure 3. Clinical relevance of RFC family in pan-cancer. (A) The functional heatmap shows the clinical relevance of gene expression across various cancer types. Based on the (B) highest and (C) lowest Z scores for each cancer type, the association between each RFC subunits mRNA expression and OS in patients with various cancers was analyzed. RFC, replication factor C; OS, overall survival.

of hsa_circ_0011946 inhibits the migration and invasion of MCF-7 cells by targeting RFC3 (40). Upregulation of RFC3 is associated with poor prognostic phenotype in BC (41). In lung adenocarcinoma (LUAD), RFC3 overexpression is not only associated with poor prognosis but also facilitates cell cycle progression from G_1 to S phase, potentially contributing

Table I. Association between cancer type and the mRNA expression of RFC subunits.

Gene	Cancer	Z score	adj.p
RFC1	KICH (n=66)	2.711109947	0.047403342
	KIRC (n=533)	-4.07798685	0.000924303
RFC2	LGG (n=516)	7.83870425	0.000000000000933
	DLBC (n=48)	-2.37849173	0.091375475
RFC3	LGG (n=516)	5.892615212	0.00000039
	KIRC (n=533)	-2.39697366	0.091375475
RFC4	ACC (n=79)	4.644463897	0.00023299
	LUSC (n=501)	-2.14599312	0.142045069
RFC5	LGG (n=516)	4.114157942	0.000924303
	HNSC-HPV+ (n=98)	-3.47315808	0.005858129

RFC, replication factor C; KICH, kidney chromophobe. KIRC, kidney renal clear cell carcinoma. LGG, lower-grade glioma. DLBC, lymphoid neoplasm diffuse large B-cell lymphoma. ACC, adrenocortical carcinoma. LUSC, lung squamous cell carcinoma. HNSC-HPV+, head and neck squamous cell carcinoma HPV (+).

to tumor growth. Mechanistically, RFC3 promotes EMT through the Wnt/β-catenin signaling pathway (42). Similarly, RFC3 silencing induces cell cycle arrest at S phase, leading to proliferation inhibition in HCC (4) and CC (43). In GC, the yes-associated protein 1 (YAP1)/TEA domain family member 1 (TEAD) pathway transcriptionally activates RFC3, driving tumor progression; conversely, RFC3 depletion abolishes malignant behaviors *in vitro* and *in vivo* (5). In CRC, kinesin family member 14 upregulation counteracts the suppressive effects of RFC3 depletion on aggressive phenotypes, highlighting its functional role (44).

RFC4. The RFC4 gene, localized to chromosome 3q27 in humans, serves a critical role in DNA replication and repair. RFC4 is indispensable for the initiation of DNA template expansion by DNA polymerase δ (Pol δ) and Pol ε, essential components of the DNA replication machinery (45).

In NPC, RFC4 expression is markedly upregulated in tumor tissues compared with adjacent normal tissues. Functional studies have revealed that RFC4 knockdown induces G_2/M cell cycle arrest and inhibits cellular proliferation both *in vitro* and *in vivo*. Notably, HOXA10 has been identified as a downstream effector of RFC4, and overexpression of HOXA10 partially rescues the suppressive effects of RFC4 silencing, including impaired cell proliferation, inhibited colony formation and cell cycle arrest (46). In oral squamous cell carcinoma (OSCC), bioinformatics analysis identified high RFC4 expression is an independent prognostic factor for poor survival and associated with increased levels of MET, along with reduced levels of CD274 and CD160 (47). Knockdown of RFC4 led to G_2/M phase cell cycle arrest and inhibited the proliferation of OSCC cells both *in vitro* and *in vivo* (47).

In esophageal squamous cell carcinoma (ESCC), RFC4 overexpression may be driven by copy number alterations, which contribute to genomic instability and oncogenic activation. Notably, RFC4 is upregulated not only in early-stage tumors but also during early nodal metastasis, implying that it has a role in early dissemination. Clinically, high RFC4 expression predicts poor prognosis, independent of the presence of abundant tumor-infiltrating immune cells (such as $CD4^+$ T cells, $CD8^+$ T cells, B cells, dendritic cells and monocytes), suggesting that RFC4-mediated immune evasion or resistance may bypass immune surveillance (48). In addition, Zeng *et al* (49). collected a small sample database which comprised seven patients and the data showed that patients with low expression of RFC4 exhibited a higher tumor shrinkage rate compared with patients with high expression of RFC4. Further validation in larger cohorts is required to confirm whether RFC4 expression is indeed associated with radiotherapy response in esophageal cancer.

In CRC, RFC4 functions as a radiation resistance factor, protecting CRC cells from radiation-induced DNA double-strand breaks (DSBs) and apoptosis *in vitro* as well as in nude mouse xenograft models (50). RFC4 promotes non-homologous end joining-mediated DNA DSB repair by interacting with the Ku70/Ku80 complex. Moreover, RFC4 upregulation in tumor cells predicts reduced tumor regression and poor prognosis in patients with locally advanced rectal cancer (LARC) treated with neoadjuvant radiotherapy. Therefore, RFC4 levels might serve as an effective predictive biomarker of radiation sensitivity and a target for radio-sensitization in patients with LARC (50). Additionally, RFC4 is frequently overexpressed in CRC, driving tumor progression and poor survival outcomes. Downregulated RFC4 inhibits cell proliferation and induces S phase arrest (51). In the HCC cell line HepG2, RFC4 downregulation enhances the cytotoxic effects of doxorubicin and camptothecin, suggesting a role in chemoresistance (52). In the lung cancer cell line A549, RFC4 exhibits notable co-expression with protein kinase C-like (PKCι) and PKCι knockdown markedly suppresses RFC4 expression, suggesting a potential regulatory axis between PKCι and RFC4 (53).

Moreover, Zheng *et al* (54) reported that high expression of RFC4 was not only associated with poor prognosis but also indicated a stronger therapeutic response to immunotherapy in patients with LUAD using bioinformatics methods. Possibly because RFC4 participated in reshaping the tumor immune microenvironment (TIME), $CD8^+$ T cells and macrophages M1

were positively associated with RFC4 gene expression. In BC cell lines, silencing RFC4 inhibited cell proliferation, induced G_1 cell cycle arrest and reduced cell migratory and invasive ability (55). Moreover, knockdown of RFC4 attenuated stemness and downregulated the expression of CD44 and SOX2. RFC4 silencing inhibited migration and invasion, promoted apoptosis and improved sensitivity to radiotherapy. Regarding the mechanism, insulin like growth factor 2 mRNA binding protein 2 (IGF2BP2) can bind to the RFC4 mRNA coding sequence, and knockdown of RFC4 eliminates the effects of overexpressed IGF2BP2 on increasing cell viability, invasion, expression of stemness markers and radio resistance (56). Therefore, it also has potential to be a therapeutic target for BC.

In patients with CC, a higher expression of RFC4 is associated with an improved prognosis, possibly because RFC4 is positively associated with the expression of three immunostimulatory factors (UL16 binding protein 1, TNF receptor superfamily member 13C/18/25 and inducible T cell costimulator ligand) and three immunosuppressive factors (IL10 receptor subunit b, V-set domain-containing T-cell activation inhibitor 1 and galectin 9) (57).

RFC5. The RFC5 gene, located on chromosome 12 in humans, serves vital roles in DSB repair, DNA excision and cell cycle regulation, thereby maintaining genomic stability and influencing tumorigenesis.

Mechanistic studies have demonstrated that astrocyte elevated gene-1 (AEG-1) knockdown markedly downregulates RFC5 expression, impairing homologous recombination (HR)-mediated DNA repair following radiation exposure. This effect is associated with enhanced radiosensitivity in glioma cells, highlighting RFC5 as a critical mediator of DNA damage response (58). Clinically, high levels of AEG-1 and RFC5 are associated with poor prognosis specifically in patients with glioma undergoing radiotherapy, further supporting their roles as therapeutic targets (58). RFC5 is upregulated in HPV-negative HNSCC, where it serves a critical role in DNA damage repair pathways. This upregulation enhances the tumor cell capacity to withstand genotoxic stress, contributing to therapy resistance and poor clinical outcomes (59). RFC5 functions as an oncogene in lung cancer, where its overexpression is notably associated with poor patient prognosis. Elevated RFC5 levels are associated with aggressive clinicopathological features, including advanced tumor stage, lymph node metastasis and enhanced tumor cell proliferation, thereby promoting tumorigenesis and disease progression (60).

Bioinformatics analyses reveal that RFC5 harbors putative binding sites for serine/arginine-rich splicing factor 10 (SRSF10). Functional studies have demonstrated that RFC5 overexpression promotes CRC cell proliferation and metastasis, even when SRSF10 is silenced, suggesting an oncogenic dependency (61). Mechanistically, SRSF10 regulates alternative splicing of RFC5, preferentially excluding exon 2-AS1 (alternative splicing isoform 1 of exon 2) (61). Notably, Yao *et al* (62) confirmed that RFC5 promotes a malignant phenotype *in vitro*, and downregulation of RFC5 markedly suppresses tumor growth *in vivo*. Collectively, the researchers demonstrate that the circ_0038985/miR-3614-5p/RFC5 axis serves a critical role in the progression of CRC, and RFC5 may promote CRC progression via modulation of the VEGFA/VEGFR2/ERK signaling pathway.

In acute myeloid leukemia (AML), bioinformatics analysis showed that high RFC5 expression served as an independent prognostic factor for the poor OS of patients with AML. Additionally, elevated RFC5 mRNA levels were positively associated with plasma cell and M2 macrophage infiltration, implicating TIME remodeling in RFC5-driven leukemic progression (63). Zhang *et al* (64) demonstrated that basic transcription factor 3 directly binds to the RFC5 promoter and upregulates RFC5 expression in PCa cells.

5. Role of the RFC family in different signaling pathways

The RFC family members mainly participate in DNA associated regulation. Here, the molecular mechanism associated with the RFC family in cancers are discussed (Fig. 4).

It has been demonstrated that Forkhead box O1 (FOXO1), a nuclear transcription factor, is able to directly activate RFC2 expression in a transcriptional process by binding to the promoter of RFC2. Knockdown of the FOXO1/RFC2 gene regulatory network increases caspase-3 and poly(ADP-ribose) polymerase (PARP) in temozolomide resistance a glioma cell line (65). In CRC cells, RFC2 activates the MET/PI3K/AKT/mTOR pathway, and RFC2 knockdown decreases the levels of phosphorylated (p-)PI3K, p-AKT, p-mTOR and p-70S6K in both HCT116 and SW480 cell lines (7). In CRC chemo-resistant cells, knockdown of RFC3 inhibited the expression of β-catenin and glutathione peroxidase 4 (GPX4). Immunostaining assays further demonstrated that the loss of RFC3 diminished the nuclear localization of β-catenin in these cells and rescue experiments also supported these results. These findings indicate that RFC3 knockdown disrupts the Wnt/β-catenin/GPX4 axis (9).

In GC, transcriptional coactivator YAP1 binds to the transcriptional factor TEAD and induces the expression of RFC3. RFC3 silencing increased the expression of Bax and decreased the expression of Bcl-2 (5). In addition, RFC3 knockdown also reduces X-linked inhibitor of apoptosis protein expression (5). Overexpression of RFC3 increased Wnt expression, the p-GSK3β(Ser9)/GSK3β ratio, and β-catenin protein levels. Since β-catenin has a critical function in EMT, this results in downregulated E-cadherin and upregulated N-cadherin. These results suggest that RFC3 may trigger the Wnt/β-catenin signaling pathway and promote LUAD migration and invasion through EMT (42).

Upon canonical Notch signaling activation, the Notch1 intracellular domain (NICD1) undergoes nuclear translocation and binds to the transcription factor recombination signal binding protein for immunoglobulin kJ, initiating transcription of downstream targets such as hairy and enhancer of split (HES) 1, HES5 and hes related family bHLH transcription factor with YRPW motif 1. These transcriptional repressors suppress differentiation-promoting genes, maintaining progenitor cell states. Under pathological conditions, RFC4 directly interacts with NICD1 via high-affinity binding. This interaction competitively abrogates CDK8-induced phosphorylation and F-box and WD repeat domain containing 7-induced ubiquitination-dependent degradation of NICD1.

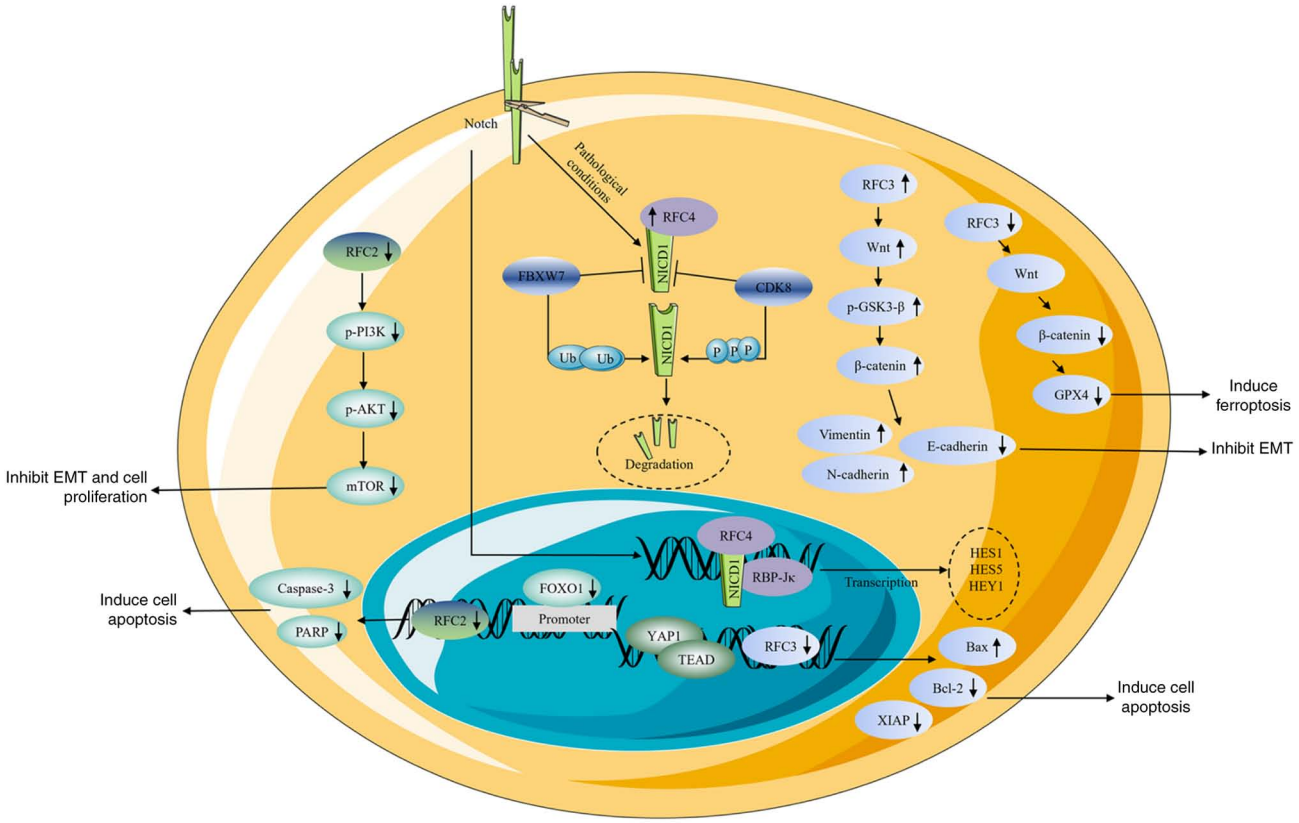

Figure 4. Roles of RFC subunits in different signaling pathways. RFC2 participates in the FOXO1 and PI3K/AKT signal pathways. RFC3 participates in the YAP1/TEAD1 and Wnt/β-catenin signal pathways. RFC4 participates in Notch1 signaling pathway. ↑, increase; ↓, decrease; RFC, replication factor C; FOXO1, Forkhead box protein O1; YAP1, yes-associated protein 1; TEAD, TEA domain family member 1; p-, phosphorylated; PARP, poly(ADP-ribose) polymerase; EMT, epithelial-mesenchymal transition GSK3β, glycogen synthase kinase-3 β; GPX4, glutathione peroxidase 4.

A feedforward loop between elevated RFC4 and NICD1 levels drives sustained overactivation of Notch signaling, promoting NSCLC tumorigenesis and metastasis (10). In ESCC cells, overexpression of RFC4 increases cyclin D1 and Rad51 levels, whereas p53 and p21 levels are notably decreased. Conversely, RFC4 knockdown has the opposite effect (11). However, the precise nature of the regulation of the p53 signaling pathway by RFC4 remains somewhat unclear.

6. Function and regulation of RLCs in humans

Rad17-RFC complex. RAD17 interacts with the small subunits RFC2-5 and forms a sophisticated complex, which is composed of two effective layers: i) The lower part is an open and slightly twisted C-shaped ring formed by the N-terminal Rossmann fold domains and central helical bundle domains of RAD17, RFC2, RFC3, RFC4 and RFC5; and ii) the upper ring, which forms a collar over the central cavity, is offset from the central of the lower C-shaped ring, lying predominantly over RFC3, RFC4 and RFC5 (66).

The Rad17-RFC complex functions as DNA damage sensor (67). When DNA damage occurs, it recruits the 9-1-1 (RAD9-RAD1-HUS1 checkpoint clamp component) complex in an ATP-dependent manner to the damage site and initiates the phosphorylation of ATM serine/threonine kinase and ataxia telangiectasia and Rad3 related (ATR) (68). Additionally, it loads the 9-1-1 complex at the double stranded DNA/single stranded DNA junctions of DNA damage sites in an replication protein-dependent manner and promotes the activation of ATR and checkpoint kinase 1 (CHK1) (12). Wang *et al* (69) demonstrated that RAD17 knockout HCT116 cells are unable to form colonies, and the protein level of $Chk1^{phospho\text{-}Ser\ 345}$ is also downregulated. These results indicate that the RAD17 complex is required for ATR-mediated phosphorylation of Chk1 (69). The Rad17-RFC complex and 9-1-1 complex also bind with DNA topoisomerase II binding protein 1 which participates in the activation of ATR (12). Moreover, the Rad17-RFC complex is involved in ATP hydrolysis, but the precise role of this process remains unclear.

CTF18-RFC. The multifunctional factor CTF18 exhibits two distinct binding modalities within the cellular context: i) CTF18 stably associates with DNA replication and sister chromatid cohesion 1 (DCC1) and CTF8, and the three proteins form a heptameric complex with RFC2-5; and ii) CTF18 can also combine with RFC2-5 to form a pentamer. The heptameric CTF18-DCC1-CTF8-RLC complex (CTF18-RLC) has emerged as a central regulator of DNA metabolism, orchestrating pivotal processes such as PCNA loading at replication forks, establishment of sister chromatid cohesion and activation of the DNA replication checkpoint (12).

In human cells, CTF18-RLC interacts with Pol ε by binding to the CTF18-DCC1-CTF8 (CTF18-1-8) module's core component DCC1 and loads PCNA; this combination is more efficient compared with the pentamer. Meanwhile, Terret *et al* (70) further underscore the critical role of

CTF18-RLC in sister chromatid cohesion and maintenance of processive DNA replication fork. The authors studies using DCC1-knockout hTERT-RPE1 cells revealed severe defects in these pathways, highlighting the indispensable nature of the intact heptameric complex for genomic stability (70). Mounting evidence demonstrates that patients with CRC and high DCC1 expression have a lower survival rate compared with the lower-expression group. It has also been demonstrated that HCT116 cells with DCC1 knockdown grow more slowly and exhibit lower invasiveness compared with the control group. The low protein expression levels of cyclin D1 and E-cadherin in the DCC1 knockdown group also support these phenotypic changes.

Furthermore, DCC1 knockdown induces the proteolysis of CTF18, whereas CTF18 knockdown does not affect cell invasion. This differential effect establishes DCC1 as the dominant functional component within the CTF18-1-8 module for promoting CRC progression. It may be a promising molecular target for therapeutic intervention in CRC (71).

ATAD5-RLC. Once DNA synthesis has ceased, PCNA must be unloaded, a process primarily mediated by the ATAD5-RLC complex (12). The C-terminal region of ATAD5 contains both an ATPase domain and an RFC2-5 binding motif, which are essential for efficient PCNA unloading. Experimental evidence demonstrates that ATAD5 depletion leads to S phase arrest, impaired PCNA unloading and markedly reduced DNA replication rates (72). The N-terminal domain of ATAD5 facilitates interactions with multiple protein partners involved in regulating various aspects of DNA metabolism (72). With the depletion of ATAD5, spontaneous HR increases and the DSB-induced HR decreases (73).

In U2OS cells, the ATAD5 knockdown group showed higher sensitivity to olaparib compared with the control group. This result was caused by trapping of PARP1 on chromatin (30). This observation was further validated in both HeLa and 293T cell lines, where ATAD5 depletion resulted in the accumulation of replication factors on chromatin in a PCNA-dependent manner (74). These findings collectively suggest that ATAD5 serves a crucial role in regulating interactions between proteins and chromatin during DNA replication and repair processes.

7. Exploration of RFC family molecular functions and regulation pathways using bioinformation tools

Using bioinformatics tools, the potential molecular functions involved in interactions and regulatory pathways of the RFC family have been explored. First, a co-expression network among RFC family members was constructing using the STRING database (75) and their potential connections with other genes were investigated (Fig. 5). Additionally, Gene Ontology analysis was performed on the RFC family (Fig. 6A) to identify their biological processes, molecular functions and cellular components. Kyoto Encyclopedia of Genes and Genomes pathway analysis was performed to identify molecular pathways in which RFC family members were involved (Fig. 6B). In summary, RFC family members primarily participate in DNA damage and repair. Since DNA damage acts as an initiator of innate immunity (76), future investigations should focus on the connection between RFC family members and immune regulation.

8. Clinical relevance of the RFC family

In recent years, research on biomarkers has drawn increasing attention due to its ability to improve diagnostic accuracy, guide individualized treatment and evaluate long-term prognosis. Moreover, biomarkers also assist doctors in assessing the potential effectiveness of treatments and prognosis (77). The rise of bioinformatics methods contributes to identification of new biomarkers using tumor data platforms. In CRC, sarcoma, HCC and LGG, patients with high RFC2 expression had worse OS (3,7,78,79). Similarly, increased expression of RFC3 predicts worsened OS in HNSCC, BC and LC (38,41,42). Higher RFC4 expression is associated with worse prognosis in ESCC and HCC (3,48), whereas it is associated with improved OS in patients with CC (57,80). For patients with CRC and CC, higher RFC5 expression is associated with a worse OS (62,81). These results provide new insights for cancer research; however, to a certain extent, they reflect the association between clinical prognosis and potential biomarker expression level. Further experimental validation and larger databases are needed to draw more definitive conclusions in the future.

Numerous patients have benefited from multiple treatments, including chemotherapy, radiotherapy and immunotherapy; however, the benefits remain limited. Chemoresistance and radioresistance are the main causes of treatment failure; thus, combination therapies may overcome the limitations of therapeutic outcomes. Oshima *et al* (35) proposed that RFC2 inhibition could be a potential therapeutic strategy for CRPC resistant to PARP inhibitor (PARPi) by inhibiting the NER pathway. In glioma, knockdown of RFC2 suppressed temozolomide resistance (65,82). Wu *et al* (9) demonstrated that depletion of RFC3 enhances the sensitivity of CRC cells to oxaliplatin by inducing ferroptosis. In BC, RFC3 knockdown enhances tamoxifen sensitivity by inducing S-phase arrest (39). RFC4 deficiency enhances radiosensitivity by promoting DNA damage in ESCC, BC and LARC (11,50,56). Nelarabine, in combination with other chemotherapies, is able to reduce RFC4 gene expression (83). In addition, RFC5 knockdown enhances radiation sensitivity by impaired homologous recombination repair activity (58). The high RFC4 expression indicates a stronger therapeutic response to immunotherapy in LUAD (54). Notably, most of these studies are based on model organisms; therefore, more clinical trials are needed in the future.

Due to the poor selectivity and off-target effects, traditional treatments have notable clinical limitations. Thus, the specific target therapy focusing on the molecular targets has become a potential alternative. Previously, research by Alaa *et al* (83) and colleagues demonstrated that vorinostat and trichostatin A act as RFC4 inhibitors using molecular docking and molecular dynamics simulation.

Moreover, the potential application of RLCs in clinical treatment has also drawn more attention. ATAD5-depleted cells show high sensitivity to antitumor drugs including methyl methanesulphonate, camptothecin, mitomycin C and PARPi (30). Rohde *et al* (84) discovered a new compound

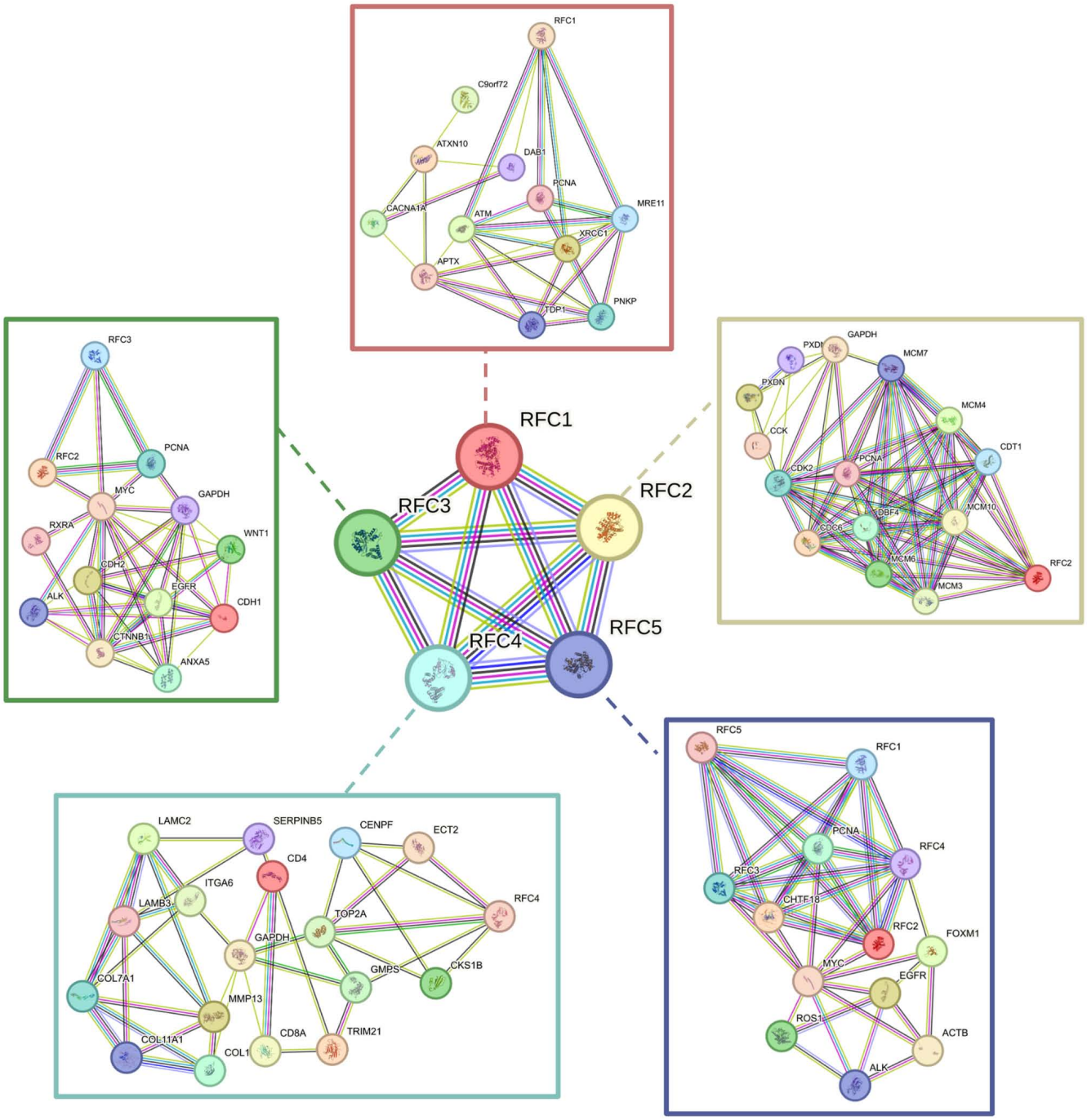

Figure 5. Protein-protein interaction network of RFC family members relevant genes. RFC, replication factor C.

ML367 which inhibits ATAD5 stabilization. ML367 could block DNA repair pathways including RPA32-phosphorylation and CHK1-phosphorylation in response to UV irradiation. It serves as a sensitizer of PARPi to enhance the antitumor effects synergistically. For inhibitors intended for clinical use, further experimental validation is essential. In ESCC, negative elongation factor complex member A (NELFA) mRNA promotes cell apoptosis, partially by inhibiting the interaction between Rad17 and the Rad17-RFC2-5 complex. Furthermore, higher NELFA expression is associated with worse OS. As a key regulator of the Rad17-RFC2-5 complex, NELFA holds promise as a novel therapeutic target in cancer (85).

9. Conclusions and future perspectives

The RFC family members serve critical roles in tumorigenesis and cancer progression. Specifically, individual RFC subunits serve as crucial regulators of malignant phenotypes including aberrant cell proliferation, EMT and tumor metastasis. Clinically, elevated expression levels of RFC members are associated with poor OS across multiple malignancies, establishing them as potent diagnostic and prognostic biomarkers. Although current research emphasizes the effects of RFC family member on particular signaling pathways, there are relatively few studies regarding RFC1 and RFC5. In 2019, the (AAAGGG)n motif

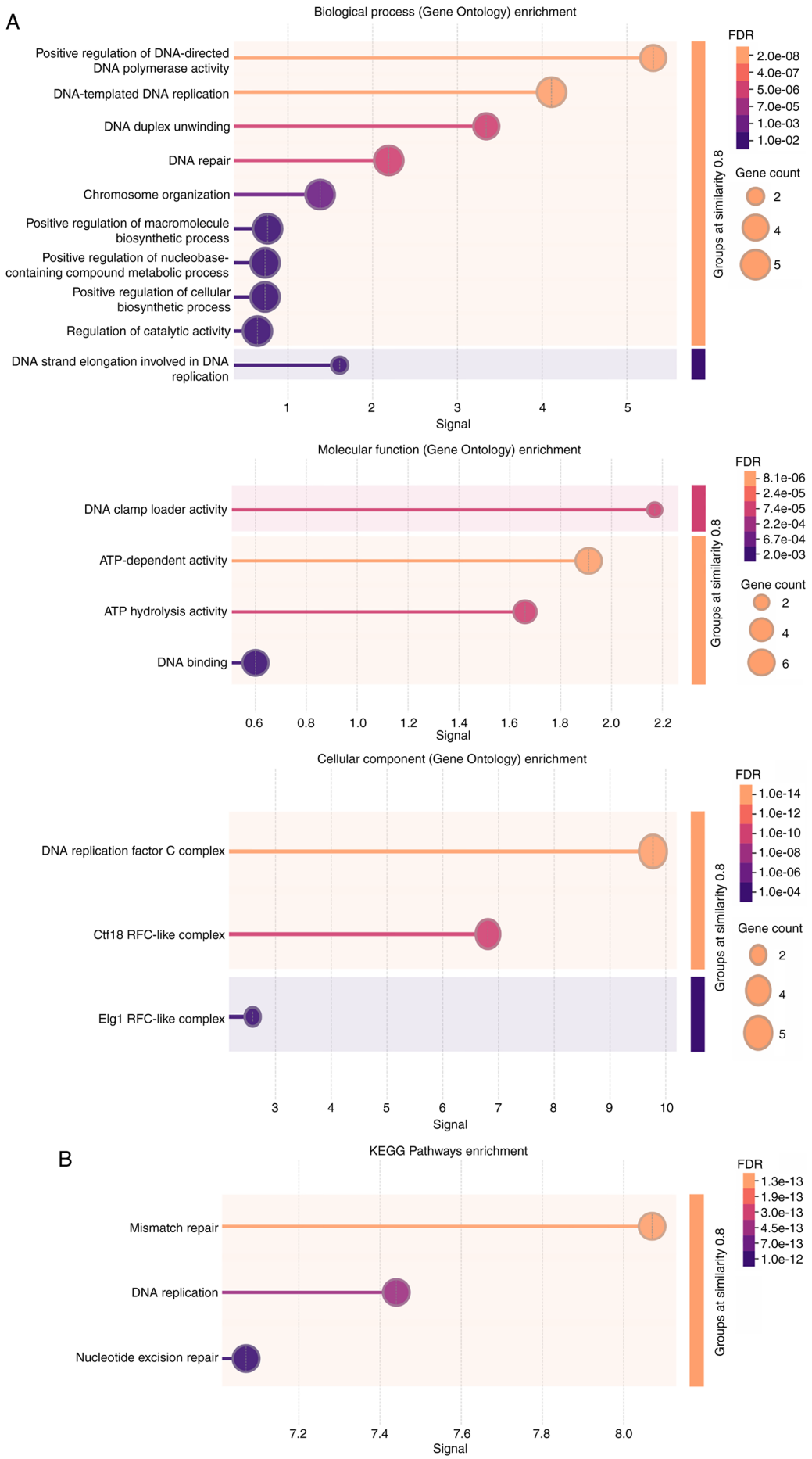

Figure 6. Enrichment analysis based on (A) GO and (B) KEGG pathway analysis. GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table II. Expression and function of replication factor C family members in human cancers.

RFC family members	Cancer type	Roles in human cancers
RFC1	Nasopharyngeal carcinoma	Overexpressed
	Breast cancer	Repressed by E2 in ERα-negative breast cancer cells in which ERα has been re-expressed.
	Colorectal cancer	Targeted by microRNA-26a-5p.
RFC2	Lower-grade glioma	RFC2 overexpression correlates with immune checkpoint genes. An independent predictor of adverse prognosis. An anti-tumor factor.
	Gastric cancer	RFC2 ubiquitination enhances cell invasion and migration.
	Hepatocellular carcinoma	Severed as a novel biomarker for the prognosis. RFC2 silencing inhibits proliferation and migration.
	Colorectal cancer	Upregulated RFC2 expression correlates with poor clinical outcomes. RFC2 promotes aerobic glycolysis and MET/PI3K/AKT/mTOR pathway.
	Castration-resistant prostate cancer	Overexpressed. RFC2 downregulation inhibits cell proliferation, induces apoptosis and aggravates DNA damage. Elevated RFC2 protein expression is associated with unfavorable prognosis
	Ewing's sarcoma	Overexpressed. High expression predicted poor OS and EFS.
RFC3	Head and neck squamous cell carcinoma	High expression predicts poor clinicopathological features and associates with oncogenic signaling pathways, such as MYC/MYCN, HIPPO, and mTOR.
	ER positive breast cancer	High expression predicts poor prognosis, downregulated RFC3 induces S phase arrest and attenuated cell.
	Lung adenocarcinoma	High expression predicts poor prognosis, overexpressed RFC3 facilitates cell cycle progression from G_1 to S phase, RFC3 promoted EMT through the Wnt/β-catenin signaling pathway.
	Hepatocellular carcinoma	RFC3 silencing induces cell cycle arrest at S phase.
	Gastric cancer	The YAP1/TEAD pathway transcriptionally activated RFC3, driving tumor progression.
	Colorectal cancer	KIF14 upregulation counteracts the suppressive effects of RFC3 depletion on aggressive phenotypes.
RFC4	Nasopharyngeal carcinoma	Overexpressed.RFC4 knockdown induces G_2/M cell cycle arrest and inhibits cellular proliferation. Overexpression of HOXA10 partially rescues the suppressive effects of RFC4 silencing.
	Esophageal squamous cell carcinoma	Overexpressed. high RFC4 expression predicts poor prognosis.
	Locally advanced rectal cancer	A radiation resistance factor. Served as an effective predictive biomarker of radiation sensitivity and a target for radio-sensitization.
	Colorectal cancer	Overexpressed, Downregulated RFC4 inhibits cell proliferation and induces S phase arrest.
	Hepatocellular carcinoma	RFC4 downregulation enhances the cytotoxic effects of doxorubicin and camptothecin.
	Lung adenocarcinoma	RFC4 exhibits significant co-expression with PKCι, and PKCι knockdown markedly suppresses RFC4 expression.
RFC5	Glioma	AEG-1 knockdown downregulates RFC5 expression. RFC5 serves as a critical mediator of DNA damage response. High levels of RFC5 is associated with poor prognosis.
	HPV negative squamous cell carcinoma of the head and neck	Overexpressed RFC5 enhances the tumor cells' capacity to withstand genotoxic stress.

Table II. Continued.

RFC family members	Cancer type	Roles in human cancers
	Lung cancer	RFC5 functions as an oncogene in lung cancer. Elevated RFC5 levels correlate with aggressive clinicopathological features.
	Colorectal cancer	RFC5 overexpression promotes CRC cell proliferation and metastasis. RFC5 may promote CRC progression via modulation of the VEGFA/VEGFR2/ERK signaling pathway.
	Acute myeloid leukemia	High RFC5 expression served as an independent prognostic factor for the poor OS. Elevated RFC5 mRNA levels correlated positively with plasma cell and M2 macrophage infiltration.

RFC, replication factor C; ER, estrogen receptor. PI3K, phosphoinositide 3-kinase. mTOR, mammalian target of rapamycin. OS, overall survival. EFS, event-free survival. YAP1, yes-associated protein 1. TEAD, TEA domain. KIF14, kinesin family member 14. HOXA10, HOXA10 homeobox A10. PKCι, protein kinase C-like. AEG-1, astrocyte elevated gene-1. CRC, colorectal cancer. VEGFA, vascular endothelial growth factor A. VEGFR2, Vascular endothelial growth factor receptor 2.

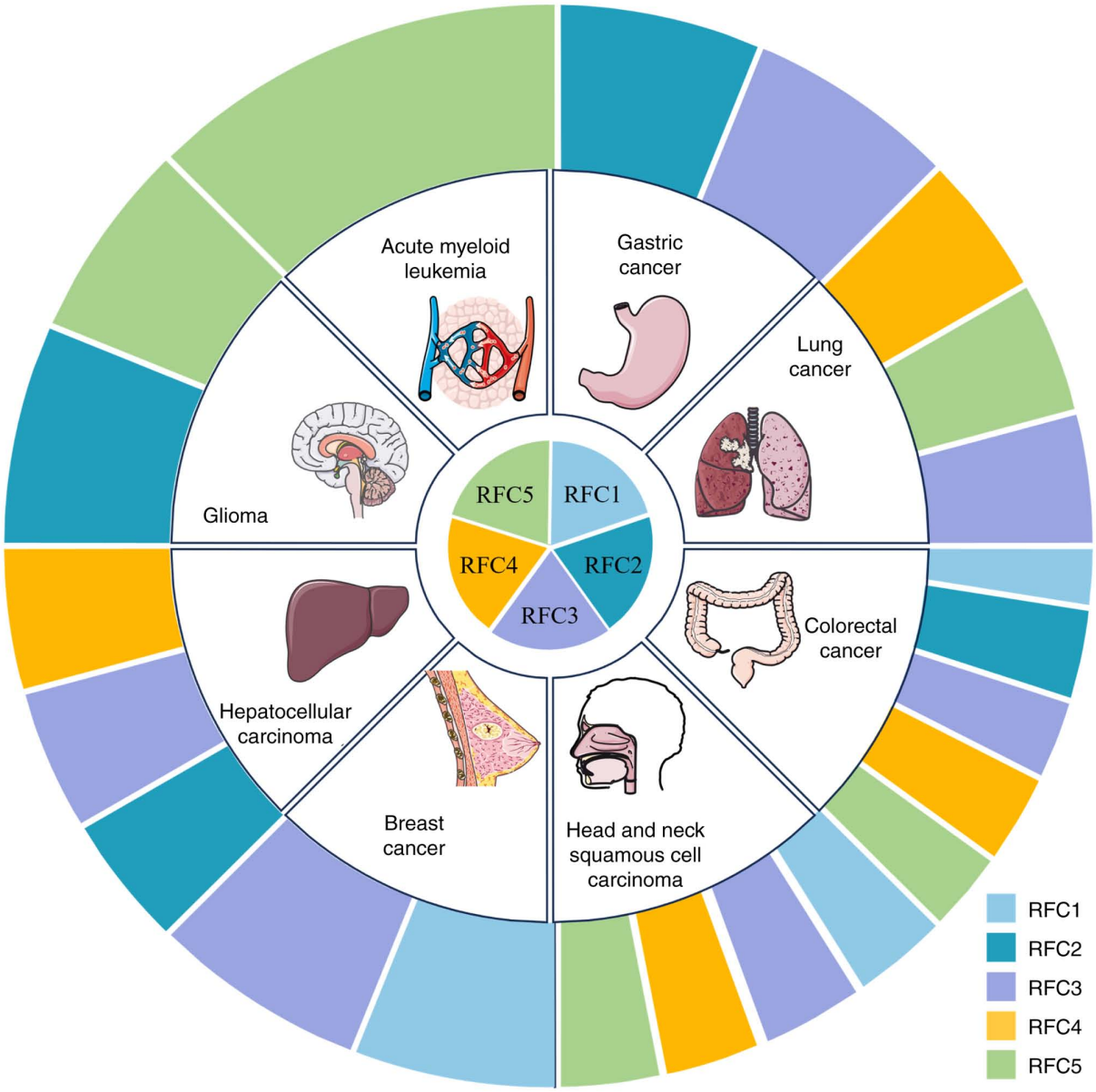

Figure 7. Map of RFC subunits and multiple tumors. RFC, replication factor C.

expansions of RFC1 were first shown to be a main cause late-onset ataxia (86). To date, the majority of research into RFC1 are concentrated on genopathy (29). Moreover, research on the regulatory mechanisms of RFC5 in cancers has not been sufficiently in-depth. This may be a new direction in cancer biology.

In the present review, the map of RFC family members which are associated with cancers is shown in Fig. 7 and the regulation mechanisms are shown in Table II. The present review had some limitations. Much of the analysis remains at basic experimental level, lacking forward-looking perspective. Additionally, there is insufficient discussion on the connection between RFC family members. With the rapid progression of understanding of RFC family members in human cancers, their dual potential as either oncogenes or tumor suppressors have been demonstrated. It was hypothesized that the contradictory effects observed in previous studies arise from variations in sample sources and tumor heterogeneity. Cancer cells and the TIME can exhibit molecular characteristic variations; these changes may further contribute to the distinct roles of specific factors across different tumors (87). Functional experiments often rely on immortalized cell lines and standardized animal models, which may overlook other potential influencing factors. Furthermore, some results derived from publicly available datasets could be affected by multiple confounding variables, including variations in sample composition, batch effects, differences in sequencing technologies, data processing pipelines and normalization methods (88).

While individual members of the RFC have been characterized across various cancer types, their underlying mechanisms require further investigation. Several critical questions emerge from the current research: First, do the family members have more notable oncogenic effects collectively compared with individually, potentially through synergistic interactions? Second, are there novel mechanisms being explored to elucidate tumorigenesis? Finally, from a clinical perspective, could the RFC family members serve as valuable diagnostic and prognostic biomarkers? Addressing these questions will require comprehensive studies to elucidate the complex roles of RFC proteins in cancer biology and their potential translational applications. Future research should focus on characterizing these molecular relationships and evaluating their clinical utility for improved cancer management.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of Hubei Province (grant no. 2022CFB808) and the Open Project of Minda Hospital Affiliated to Hubei University for Nationalities (grant no. OIR202302Q).

Availability of data and materials

Not applicable.

Authors' contributions

DL wrote the original draft. DL and BL prepared the figures. XJ reviewed and revised the manuscript. All authors reviewed the manuscript. Data authentication is not applicable. All authors 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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