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Review Article

Multifaceted regulation and functions of replication factor C family in human cancers

Yanling Li*, Sijie Gan*, Lin Ren*, Long Yuan, Junlan Liu, Wei Wang, Xiaoyu Wang, Yi Zhang, Jun Jiang, Fan Zhang, Xiaowei Qi

*Breast Disease Center, Southwest Hospital, Third Military Medical University, Chongqing 400038, China. *Equal contributors.*

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Abstract: Replication factor C (RFC) family is a complex comprised of the RFC1, RFC2, RFC3, RFC4, and RFC5 subunits, which acts as a primer recognition factor for DNA polymerase. It is reported that RFC, biologically active in various malignant tumors, may play an important role in the proliferation, progression, invasion, and metastasis of cancer cells. It could act as an oncogene or tumor suppressor gene based on the cellular and histological characteristics of the tumor. In this review, we summarized the updated researches on the structure, physiological function, and expression pattern of RFC in a variety of tumors, the underlying mechanisms on carcinogenesis, and the potentials of RFC family members in the diagnosis and prognosis prediction.

Keywords: Replication factor C, expression, function, human cancer

Overview of the replication factor C (RFC) family

Replication factor C (RFC; activator 1), which was first purified from the extracts of human cervical cancer HeLa cells, is an essential host factor for the *in vitro* replication of simian virus 40 (SV40) DNA [1, 2]. RFC is a structure-specific DNA-binding protein that acts as a primer recognition factor for DNA polymerase [3]. RFC plays an important role in *in vivo* processes, including DNA replication and repair, cell proliferation, regulation of cell cycle checkpoints, and cell growth under stress.

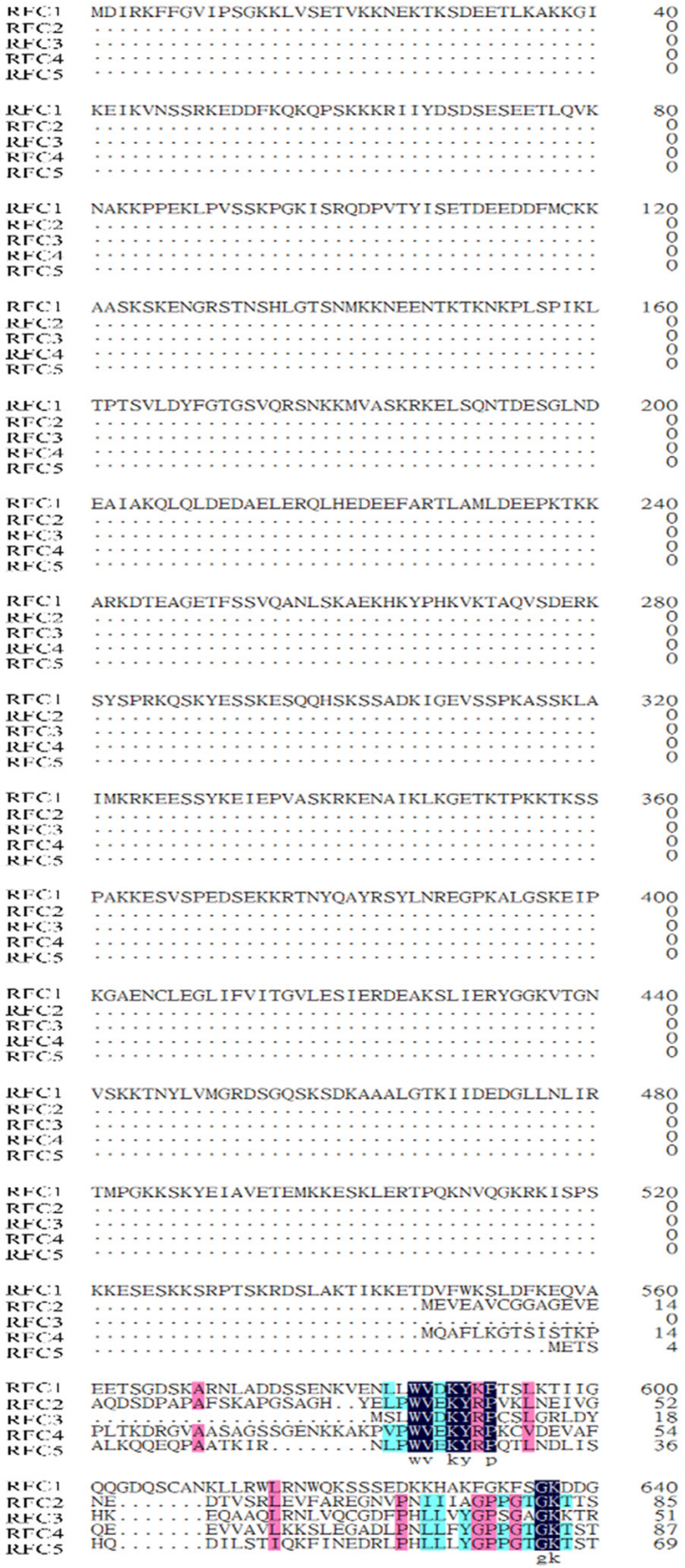
RFC subunits, structure, and localization

RFC is a five-subunit complex comprised of the RFC1 (140 kDa), RFC2 (40 kDa), RFC3 (38 kDa), RFC4 (37 kDa), and RFC5 (36 kDa) subunits [4], which can be found in eukaryotes, including yeast, mice, *Drosophila*, calf thymus, humans, rice, and *Arabidopsis* [5-17]. It is reported that the genes for p140 (*RFC1*), p40 (*RFC2*), p38 (*RFC3*), p37 (*RFC4*), and p36 (*RFC5*) are located within the human chromosomal segments 4p13-p14, 7q11.23, 13q12.3-q13, 3q27, and 12q24.2-q24.3, respectively [1, 5].

The five subunits (RFC1-5) of the human RFC complex share several highly conserved amino acid sequences known as RFC boxes [18], indicated in **Figure 1**. The large RFC subunit, RFC1, contains eight RFC boxes (I-VIII), whereas the four small subunits contain seven RFC boxes (II-VIII). RFC box I is a 90-amino acid-long region; RFC box II is highly conserved in each RFC subunit; RFC box III contains the most highly conserved region, namely the phosphate-binding loop; RFC box V is the second most conserved box; and RFC box VI is different between the large RFC subunit (VIa) and small RFC subunits (VIb) [19]. The RFC is first formed by a core complex consisting of p36, p37, and p40, which then interacts with RFC1 via the bridging action of the p38 subunit [19]. The middle portion of RFC1 has a region homologous to bacterial DNA ligases, and the more carboxyl portion contains several domains homologous to RFC2-5 [20].

Physiological functions of RFC

Systematic analysis of the STRING [21] database indicated that RFC family members are mainly involved in telomere maintenance, nuclear DNA replication, mismatch repair, and



nucleotide excision repair, as shown in **Table 1**. RFC activity depends on the binding of the five subunits. RFC can load proliferating cell nuclear antigen (PCNA) and DNA polymerase onto the primer-bound DNA template in the presence of adenosine triphosphate (ATP) to form the DNA-RFC-PCNA-DNA polymerase complex, which then elongates along the DNA template via the action of human single-stranded DNA-binding protein (hSSB) in the presence of deoxynucleotides (dNTPs). In addition, RFC can bind to cell cycle checkpoint proteins to initiate signal transduction downstream of DNA damage checkpoints and thereby participate in the mismatch repair and excision repair of damaged DNA [22, 23].

Further studies on RFC have demonstrated that each subunit functions differently. RFC1 contains the main DNA-binding region and directly interacts with PCNA. It is associated with Hutchinson-Gilford progeria syndrome (HGPS) [24] and can promote cell survival following DNA damage via the retinoblastoma (Rb) pathway [25]. Moreover, *RFC1* overexpression can prevent cell death induced by histone H3K56 hyperacetylation [26, 27]. Therefore, RFC1 is generally considered as a direct functional replacement of RFC in DNA replication and repair [28]. RFC2 is responsible for loading PCNA onto the chromatin during DNA replication. It is associated with DNA replication and repair and cell cycle checkpoint signaling and involved in the PCNA-related mismatches and damage repair me-

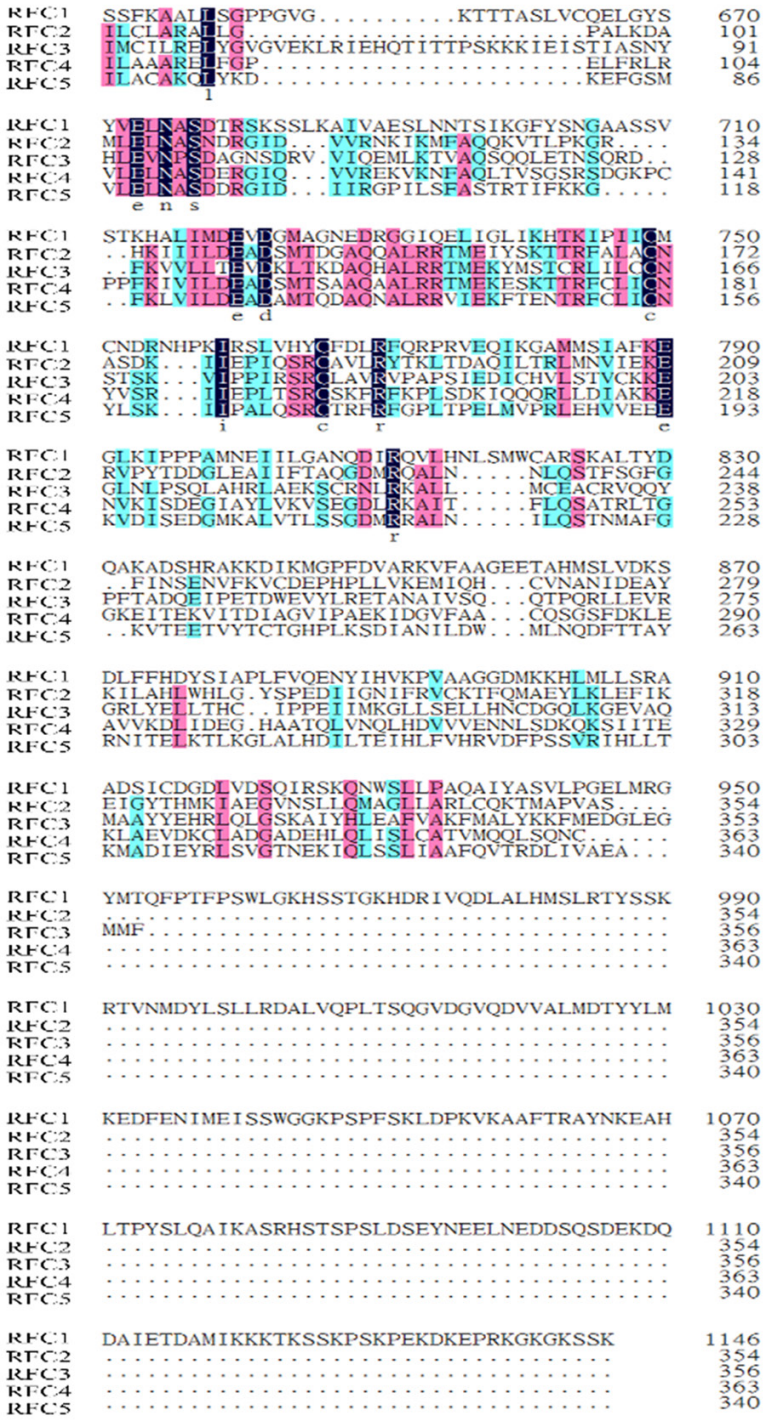


Figure 1. Protein sequence alignment of the five human RFC family members (DNAman). Different colors indicate the different levels of homology of the five proteins. Black denotes the highest level of homology, and pink, blue and yellow denote the decreasing levels of homology.

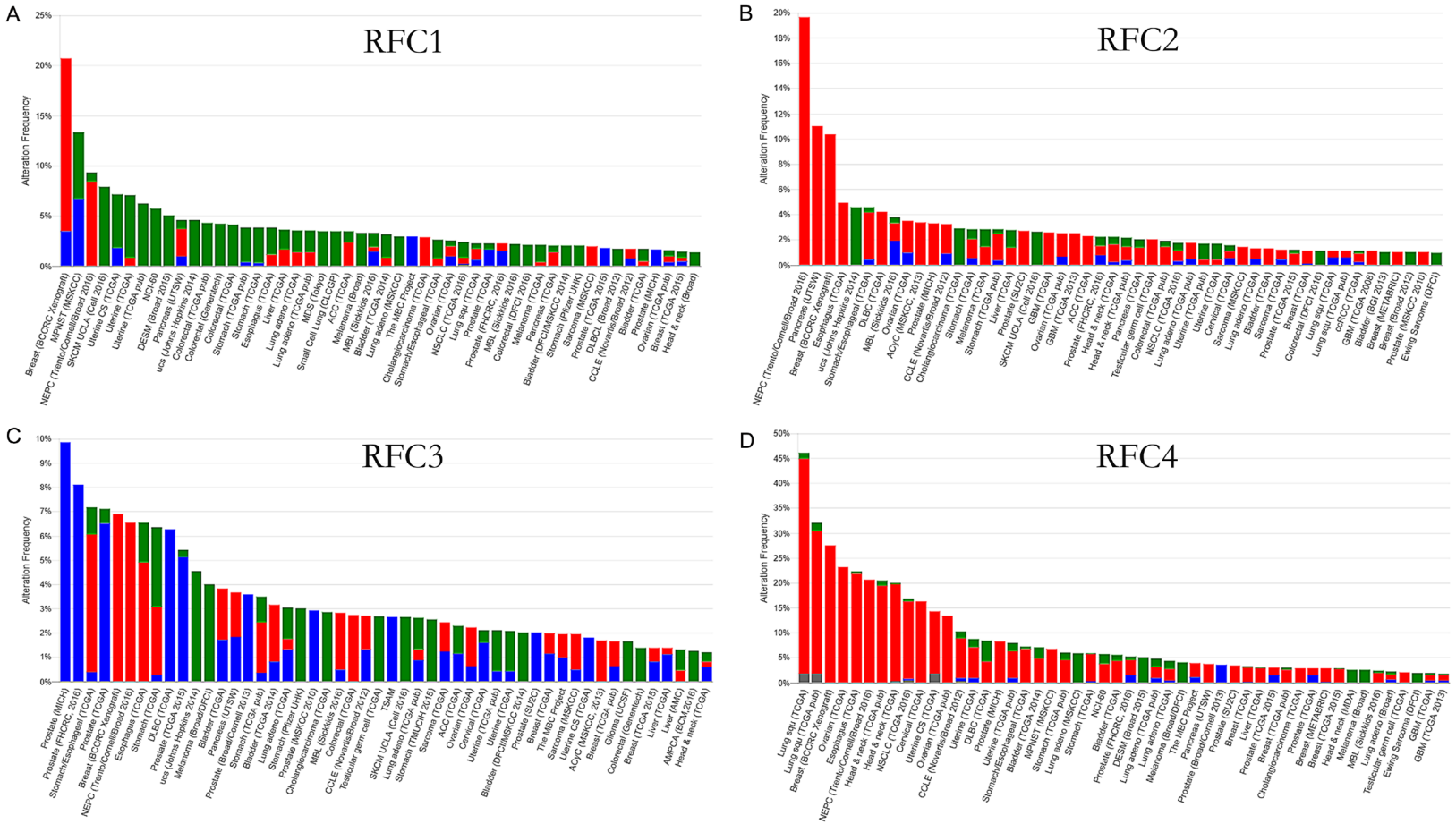
chanisms following DNA damage. Therefore, downregulation *of RFC2* could result in incorrect chromosome segregation in newborns [29]. RFC4 plays an important role in DNA damage checkpoint pathways [30] and can enhance the antitumor activity of DNA-damaging chemotherapeutic agents [31]. RFC5 is necessary to open the PCNA clamp during DNA replication.

It is reported that the functions of RFC can be mediated with other human proteins. RFC2-5 can bind to human Rad17 to form the Rad17-RFC complex. This complex is structurally similar to the RFC clamp loader, but is more compact and has deeper grooves. Moreover, it not only has DNA-binding and ATPase activities, but can also load the PCNA-like Rad9-Hus-Rad1 complex onto DNA to initiate DNA damage checkpoint signal transduction [26, 30, 32]. The chromosome transmission fidelity factor 18 (Ctf18)-RFC complex plays a key role in establishing sister chromatid cohesion, and acts through DNA damage bypass and post-replication repair at the replication fork to prevent triplet repeat instability, chromosome fragility, and cell cycle delays in the S and G2/M phases while promoting genomic stability [33]. Ctf18p-RFC can promote sister chromatid pairing and form the cohesion establishment factor Ctf7p/Eco1p *in vitro*. RFC5 binds to Ctf18 to form the Ctf18-RFC5 complex. This complex can inhibit and stimulate DNA synthesis, change the mode of DNA synthesis, and regulate sister chromatid pairing during the S phase of the cell cycle [28, 34]. In addition, RFC can also interact with other protein to exert its functions. For example, *RFC2* and *RFC3* can interact with the oncogene c-*MYC* to induce cell division and proliferation [35].

Table 1. Functional enrichments and network of replication factor C family members

Biological Process (GO)				
Pathway ID	Pathway description	Observed gene count	Matching proteins in your network	False discovery rate
GO.0006297	Nucleotide-excision repair, DNA gap filling	4	RFC1, RFC3, RFC4, RFC5	1.22E-08
GO.0042276	Error-prone translesion synthesis	4	RFC1, RFC3, RFC4, RFC5	1.22E-08
GO.0070987	Error-free translesion synthesis	4	RFC1, RFC3, RFC4, RFC5	1.22E-08
GO.0032201	Telomere maintenance via semi-conservative replication	4	RFC1, RFC3, RFC4, RFC5	1.41E-08
GO.0000722	Telomere maintenance via recombination	4	RFC1, RFC3, RFC4, RFC5	1.99E-08
GO.0033260	Nuclear DNA replication	4	RFC1, RFC3, RFC4, RFC5	1.99E-08
GO.0006271	DNA strand elongation involved in DNA replication	4	RFC1, RFC3, RFC4, RFC5	3.77E-08
GO.0042769	DNA damage response, detection of DNA damage	4	RFC1, RFC3, RFC4, RFC5	3.98E-08
GO.0006283	Transcription-coupled nucleotide-excision repair	4	RFC1, RFC3, RFC4, RFC5	1.18E-07
GO.0006284	Base-excision repair	4	RFC1, RFC3, RFC4, RFC5	1.22E-07
GO.0000278	Mitotic cell cycle	4	RFC1, RFC3, RFC4, RFC5	0.00442
Molecular Function (GO)				
Pathway ID	Pathway description	Observed gene count	Matching proteins in your network	False discovery rate
GO.0003689	DNA clamp loader activity	2	RFC1, RFC3	0.000295
Cellular Component (GO)				
Pathway ID	Pathway description	Observed gene count	Matching proteins in your network	False discovery rate
GO.0005663	DNA replication factor C complex	4	RFC1, RFC3, RFC4, RFC5	5.61E-12
GO.0005657	Replication fork	4	RFC1, RFC3, RFC4, RFC5	9.98E-08
GO.0005694	Chromosome	4	RFC1, RFC3, RFC4, RFC5	0.00254
KEGG Pathways				
Pathway ID	Pathway description	Observed gene count	Matching proteins in your network	False discovery rate
3430	Mismatch repair	5	RFC1, RFC2, RFC3, RFC4, RFC5	3.24E-13
3030	DNA replication	5	RFC1, RFC2, RFC3, RFC4, RFC5	1.56E-12
3420	Nucleotide excision repair	5	RFC1, RFC2, RFC3, RFC4, RFC5	4.39E-12

GO: Gene Ontology, KEGG: Kyoto Encyclopedia of Genes and Genomes.


A
RFC1
Alteration Frequency
B
RFC2
Alteration Frequency
C
RFC3
Alteration Frequency
D
RFC4
Alteration Frequency

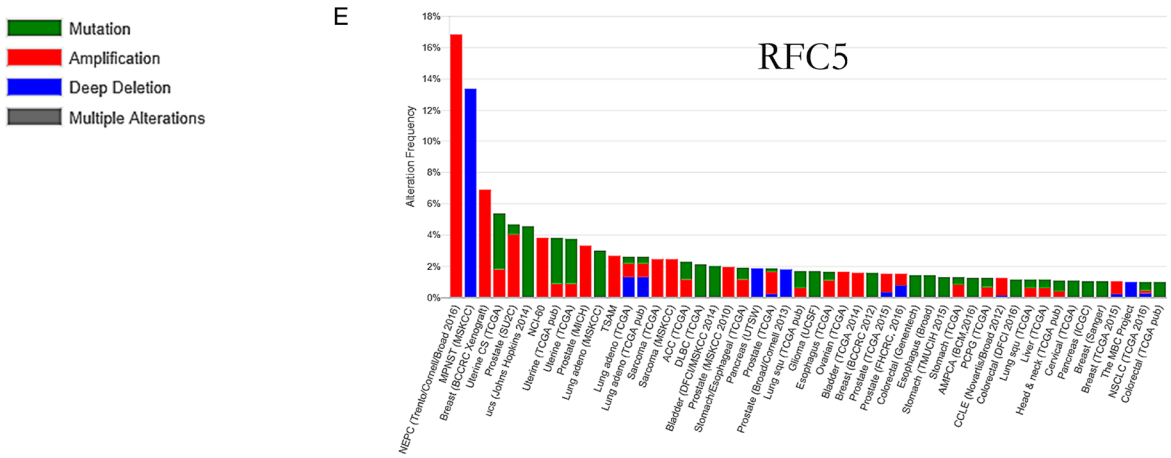


Figure 2. Mutation and copy number alterations of RFC family members across different human cancers (cBioPortal).

Expression and function of RFC subunits in human cancers

RFC is biologically active in various malignant tumors and plays an important role in the proliferation, progression, invasion, and metastasis of cancer cells. It may act as an oncogene or tumor suppressor gene based on the cellular and histological characteristics of the tumor and therefore it is regarded as a potential prognostic factor for malignant tumors. The mutation and copy number alterations of RFC family members in different human cancers are acquired from cBioPortal [36, 37] and shown in **Figure 2**, and the expression and function of RFC family members in human cancers are summarized in **Table 2**.

RFC1

RFC1 is involved in DNA synthesis, DNA repair, and the cell cycle. Unlike the other small RFC subunits, the relationship between the large RFC subunit (RFC1) and cancer has seldom been reported. Fung et al. used complementary DNA (cDNA) microarray hybridization (Atlas cDNA microarray) to determine differential gene expression between malignant and non-malignant nasopharyngeal epithelial cells and found significantly higher RFC1 expression in malignant nasopharyngeal epithelial cells than in non-malignant ones. Moggs et al. found that E2 (17β-estradiol) can inhibit the proliferation of estrogen receptor (ER)-negative MDA-MB-231 breast cancer cells into which ERalpha had been reintroduced by inhibiting RFC1 expression [39].

RFC2

RFC2 is the only RFC subunit that can independently unload PCNA and inhibit DNA polymerase activity, and its expression is elevated in some cancer tissues and cells [40]. Xiong et al. reported significantly higher RFC2 expression in nasopharyngeal cancer tissues (64.53%) than in normal tissues, and RFC2 may serve as a putative molecular marker of nasopharyngeal carcinoma [41]. Cui et al. also found significantly elevated RFC2 protein expression in choriocarcinoma tissues than in normal tissues [42, 43]. In addition, RFC2 can also act as a prognostic indicator for cancer patients. For example, it is reported that RFC2 could predict the progression and metastasis in ER-positive, ER-negative, or triple-negative breast cancer [40].

RFC3

RFC3 is the dominant gene in the 13q13 amplicon, and it is believed that *RFC3* acts as an oncogene or anti-oncogene in different cancers based on the cellular and histological characteristics. *RFC3* expression is significantly higher in certain cancer tissues or cells, such as esophageal adenocarcinoma, liver cancer, and ovarian cancer, than in normal tissues. Shen et al. found that *RFC3* was highly expressed in more than 70.0% of ovarian cancers, 28.1% of invasive cancer cells, 17.6% of marginal cancer cells, 11.1% of cystadenoma cells, and 5.0% of normal ovarian cells [44]. Hatfield et al. reported that *RFC3* was highly expressed in patients with acute myeloid leukemia (AML) with long-term cell proliferation [45]. Therefore, RFC3 could be a potential biomarker for early diagnosis of cancer.

As for the biological functions of RFC3, it is reported that *RFC3* plays a key role in the proliferation and survival of cancer cells. Shen et al. found that *RFC3* was significantly elevated in ovarian cancer OVCAR-3 cells, and *RFC3* downregulation could lead to S-phase arrest and induce apoptosis in OVCAR-3 cells [46]. In addition, Yao et al. reported that the knockdown of *RFC3* could suppress the proliferation and viability of hepatocellular carcinoma (HCC) cell and arrest the cell cycle at the S phase by upregulating tumor suppressor genes involved in G1-S phase transition [47]. Therefore, RFC3 has an important role in the growth and development of cancer.

Apart from survival, *RFC3* is also involved in the invasion and metastasis of cancer cells, considered as a promising indicator for prognosis of cancer patients. Lockwood et al. found that high *RFC3* expression in esophageal adenocarcinoma may be an indicator of poor prognosis, and it is a candidate oncogene in esophageal adenocarcinoma [48]. In addition, the mean survival was shortened from 92.9 months in ovarian cancer patients with normal *RFC3* expression to 7.7 months in patients with *RFC3* overexpression [44]. He et al.'s study showed that inhibition of *RFC3* expression can attenuate metastasis and progression mediated by epithelial-mesenchymal transition (EMT) in tri-

Table 2. Expression and function of replication factor C family members in human cancers

RFC members	Cancer type	Roles in human cancers	Reference
RFC1	Breast cancer	Repressed by E2 in ERα-negative breast cancer cells in which ERα has been re-expressed.	Moggs et al., 2005
	Nasopharyngeal carcinoma	Overexpressed.	Fung et al., 2000
RFC2	Breast cancer	Amplified. Severed as a molecular marker.	Gupte, 2015
	Choriocarcinoma	Increased expression.	Cui et al., 2004; Cui et al., 2003
	Nasopharyngeal carcinoma	Overexpressed. Severed as a putative molecular marker.	Xiong et al., 2011
RFC3	Acute myeloid leukemia	Overexpressed.	Hatfield et al., 2014
	Breast cancer	Downregulated by hsa_circ_0011946.	Zhou et al., 2018
	Colorectal cancer	Mutation and loss-expression promoted cancer progression.	Kim et al., 2010
	Cervical cancer cells	Upregulated by SIX homeobox 1.	Liu et al., 2014
	Esophageal adenocarcinoma	Amplified and high expression predicted poor prognosis. Knockdown inhibited proliferation and anchorage independent growth.	Lockwood et al., 2012
	Gastric cancer	Mutation and loss-expression promoted cancer progression.	Kim et al., 2010
	Hepatocellular carcinoma	Upregulated, knockdown suppressed cell proliferation and viability and arrested the cell cycle at the S phase.	Yao et al., 2015
	Ovarian carcinoma	Overexpression indicated shortened survival. Knockdown suppressed cell growth and proliferation.	Shen et al., 2014; Shen et al., 2015
	Triple-negative breast cancer	Downregulated attenuated proliferation, migration and invasion via epithelial-mesenchymal transition signal pathways. Overexpression associated with poor prognosis.	He et al., 2017
RFC4	Breast cancer	Amplification indicated reduced overall survival.	Fatima et al., 2017
	Cervical cancer	Overexpressed. Upregulated by SIX homeobox 1. High expression predicted poor prognosis.	Jung et al., 2009; Narayan et al., 2007; Niu et al., 2017; Zhai et al., 2007
	Colon cancer	Overexpressed.	Jung et al., 2009
	Gastric cancer	Overexpressed.	Jung et al., 2009
	Head and neck squamous cell carcinoma	Highly expressed in HPV+ samples.	Slebos et al., 2006
	Hepatocellular carcinoma	Over-expressed. Involve in cell cycle arrest and apoptosis.	Skawran et al., 2008
	Lung cancer	Overexpressed. Regulated by Protein Kinase Cι.	Jung et al., 2009; Erdogan et al., 2009
	Prostate cancer	Overexpressed.	Jung et al., 2009; LaTulippe et al., 2002; Barfeld et al., 2014
	Skin cancer	Overexpressed.	Jung et al., 2009
RFC5	Cervical cancer cells	Upregulated by SIX homeobox 1.	Liu et al., 2014
	Diffuse large B-cell lymphoma	Co-expression with DNA (cytosine-5)-methyltransferase 1 and downregulated upon its silencing.	Loo et al., 2017
	Glioma	Activated by forkhead box M1.	Peng et al., 2017
	Head and neck squamous cell carcinoma	Overexpressed in HPV+ samples.	Martinez et al., 2007
	Prostate cancer	Overexpressed in advanced prostate tumor cells than in normal prostate cancer and early prostate tumor cells.	Barfeld et al., 2014

ple-negative breast cancer; *RFC3* knockdown can significantly reduce cancer cell proliferation, invasion, and metastasis, while *RFC3* overexpression can promote cancer cell progression, invasion, and metastasis *in vitro*; therefore, *RFC3* may be an independent prognostic factor and therapeutic target in triple-negative breast cancer [49]. Recently, Zhou et al. figured out that the downregulation of hsa_circ_0011946 could significantly inhibit the expression of *RFC3* and suppress the migration and invasion of the breast cancer cell line MCF-7 by targeting *RFC3* [50]. In addition to *RFC3* amplification, *RFC3* gene mutations and loss of expression have also been identified in certain cancer tissues. Kim et al. found that *RFC3* expression was lost in 51% of stomach cancer tissues and 65% of colorectal cancer tissues, suggesting that *RFC3* may act as an anti-oncogene in these cancers [51]. All these results indicate that *RFC3* plays an important role in the progression of cancer.

RFC3 also interacts with other factors to participate in the proliferation of cancer cell *in vivo*. Maeng et al. found that RFC3 can interact with retinoid X receptor α (RXRα) and participate in *cis*-retinoic acid-mediated suppression of retinoic acid-sensitive breast cancer cell growth [52]. RFC3 is regulated by other factors in some cancer tissues. For example, Liu et al. found that the upregulated SIX homeobox 1 (*SIX1*) expression in cervical cancer tissues resulted in significant upregulation of several DNA replication initiation-related genes, including *RFC3*, *RFC4*, and *RFC5* (clamp loader) [53]. Chae et al. suggested that E2F and cyclic AMP response element-binding protein (CREB) could regulate *RFC3* expression in the KG-1 AML cell line [54].

RFC4

RFC4 was highly expressed in the tissues or cells of cancers, such as liver cancer, non-small cell lung cancer (NSCLC), prostate cancer, colon cancer, two brain cancers (neuroblastoma and glioblastoma), cervical cancer, and leukemia [31, 55-63]. Therefore, RFC4 may be a new cancer treatment target. Bachtiary et al. found higher *RFC4* expression in grade III than in grade II cervical cancer [60]. Niu et al. found significantly higher *RFC4* expression in cervical squamous cell carcinoma than in high-grade squamous intraepithelial lesions [57]. In addition, Slebos et al. found upregulated *RFC4* expression in head and neck squamous cell carcinoma, and that the expression level of *RFC4* was 3.4-fold higher in human papillomavirus (HPV)-positive tumors than normal tissue [61]. Moreover, *RFC4* expression was associated with cervical cancer progression and prognosis, and it was also a predictor of poorer overall survival in breast cancer [57, 64]. These findings suggest that *RFC4* may be a potential prognostic biomarker and therapeutic target.

Other factors can regulate *RFC4* expression in cancer. Results from Garnett et al. revealed that *RFC4* expression was regulated by *RB1* in various cancer cell lines with *RB1* mutations [65]. Cao et al. showed that microRNA-504 overexpression in smooth muscle cells can significantly upregulate *RFC4* expression [66]. Furthermore, protein kinase Cι (PKCι) regulates *RFC4* expression in multiple lung adenocarcinoma cell lines [62], and 13q deletion in HCC and dedifferentiated HCC significantly upregulates the *RFC4* expression [67].

RFC5

In eukaryotes, RFC5 is involved in repairing mismatches, DNA double helix damage, nucleotide excision, and regulating the cell cycle [68, 69]. It is reported that *RFC5* is significantly upregulated in cancer tissues or cells, and its expression is elevated with the cancer progression. Martinez et al. reported significant *RFC5* upregulation in HPV-positive squamous cell carcinoma of the head and neck tissues than in normal oral mucosal tissues and in HPV-negative oropharyngeal squamous cell carcinoma tissues [70]. Stefan et al. also found higher *RFC5* expression in prostate cancer tissues than in normal prostate tissues [63]. Liu et al. found that *RFC5* is relatively highly expressed in the multidrug-resistant leukemia cell line HL-60R and can inhibit cell differentiation induced by all-*trans* retinoic acid (ATRA) [68]. Some studies have shown that *RFC5* expression is associated with cancer prognosis. Varghese et al. demonstrated that *RFC5* overexpression in tumor tissues prior to isolated hepatic perfusion is significantly associated with poor prognosis [71]. Moreover, other factors regulate *RFC5* expression in cancer cells. *SIX1* overexpression in cervical cancer C33A cells can upregulate *RFC5* expression [53]. *RFC5* expression, highly correlated with DNA (cytosine-5)-methyltransferase 1 (*DNMT1*) dys-

regulation in diffuse large B-cell lymphoma (DLBCL) HT cells, is downregulated following shDNMT1 treatment in HT cells [72]. Recently, Peng et al. reported that forkhead box M1 could transcriptionally activate *RFC5* expression to promote temozolomide resistance in human glioma cells by interaction with the RFC5 promoter [73].

Summary and prospect

In summary, each RFC subunit is biologically active in various malignant tumors and may act as an oncogene or anti-oncogene depending on the cellular and histological features of the tumor. RFC expression is significantly higher in most malignant tumors than in normal tissues, so it can serve as a predictor of cancer prognosis. However, a series of RFC-related issues, including the potentials of RFC as a new cancer biomarker and treatment target, the different biological activities of each RFC subunit in different cancer tissues, the biological functions of RFC1, RFC2, and RFC5 in cancer and the factors and signaling pathways that regulate RFC subunits *in vivo,* still require further researches.

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Disclosure of conflict of interest

None.

Address correspondence to: Drs. Xiaowei Qi, Fan Zhang and Jun Jiang, Breast Disease Center, Southwest Hospital, Third Military Medical University, Gaotanyan Street 29, Chongqing 400038, China. Tel: 86-23-68754160; Fax: 86-23-68754160; E-mail: qxw9908@foxmail.com (XWQ); zhangfan316@163.com (FZ); jcbd@medmail.com.cn (JJ)

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