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RAD51 novel target EIF4A1 promotes colorectal cancer cell proliferation and migration via the CYP51A1/cholesterol metabolic homeostasis pathway

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Abstract. Colorectal cancer (CRC) is a highly prevalent malignant tumor of the digestive tract worldwide. Although there is indirect evidence suggesting that Eukaryotic translation initiation factor 4A1 (EIF4A1) may be involved in the progression of CRC, its specific regulatory role in the proliferation and migration of CRC cells and the related molecular mechanisms remain unclear at present. This study found that knockdown of EIF4A1 significantly inhibited the proliferation and migration of CRC cells; knockdown of EIF4A1 significantly reduced the intracellular total cholesterol content and the protein expression level of CYP51A1 in CRC cells, and the recombinant protein of CYP51A1 could reverse the reduction effect of knockdown of EIF4A1 on the intracellular total cholesterol content and the inhibition effect on the proliferation and migration of CRC cells; knockdown of RAD51 significantly reduced the expression level of EIF4A1 in CRC cells and there was a RAD51 binding site in the EIF4A1 promoter region, that is, EIF4A1 could be transcribed and activated by RAD51. In summary, this study found that EIF4A1 could promote the proliferation and migration of CRC cells through the CYP51A1/cholesterol metabolic homeostasis pathway under the transcriptional activation effect of RAD51.

Keywords: Colorectal cancer, Eukaryotic translation initiation factor 4A1, Cytochrome P450 family 51 subfamily A member 1, Cholesterol metabolic homeostasis, RAD51 recombinase

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors of the digestive system in clinical practice. It originates from colorectal mucosal epithelial cells and develops from the malignant transformation of adenomatous polyps[1,2]. It ranks as the third most commonly diagnosed cancer and the second leading cause of cancer-related death worldwide, with approximately 1.8 million new cases and 900,000 deaths annually[3]. Although significant progress has been made in therapeutic approaches including surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy, the clinical efficacy of CRC treatment remains relatively limited due to the complexity of its pathogenic mechanisms [4-7]. Therefore, elucidating the molecular mechanisms underlying CRC and identifying its potential therapeutic targets are of great theoretical and practical significance.

Dysregulation of translation initiation is a key driver for the occurrence and progression of multiple malignancies including CRC[8]. As a crucial component of the translation initiation complex EIF4F, eukaryotic translation initiation factor 4A1 (EIF4A1) plays an essential role in tumor progression by controlling the selective translation of various oncogenes[9]. EIF4A1 is commonly overexpressed in a variety of malignant tumors and is positively correlated with poor patient prognosis[10]. High expression of EIF4A1 is associated with tumor growth and reduced overall survival in hepatocellular carcinoma, and EIF4A1-targeted inhibitors significantly suppress the growth of liver cancer cells[11]. EIF4A1 can be recruited by IGF2BP2 to drive G1/S phase transition in tumor cells, thereby promoting the proliferation of triple-negative breast cancer cells[12]. EIF4A1 also accelerates cell proliferation and tumor growth in prostate cancer by enhancing the translation of BRD2[13]. In addition, the long non-coding RNA MAPKAPK5-AS1 has been reported to promote CRC cell migration and invasion by recruiting EIF4A1 to enhance MK5 translation[14]. Bioinformatic analyses have shown that EIF4A1 is upregulated in CRC and is significantly associated with poor

prognosis of CRC patients[15,16].

Cholesterol is an essential component of cell membranes. The rapid proliferation of tumor cells typically leads to an increased demand for cholesterol synthesis[17,18]. High levels of cholesterol in turn promote CRC progression. For example, NUDT21 promotes cholesterol biosynthesis and thereby enhances CRC cell proliferation[19]; Clostridium symbiosum strengthens the stemness of CRC cells by elevating intracellular cholesterol synthesis[20]; lanosterol, an intermediate of cholesterol biosynthesis accumulated in CRC cells, suppresses $CD8^+$ T-cell activation to mediate immune evasion[21]. However, whether EIF4A1 regulates CRC cell proliferation and migration by modulating cholesterol metabolism remains unclear. Cytochrome P450 family 51 subfamily A member 1 (CYP51A1) is one of the key enzymes in the de novo cholesterol synthesis pathway[22]. CYP51A1 is significantly overexpressed in CRC, and its inhibition reduces the accumulation of cholesterol precursors and suppresses CRC progression[23]. Simvastatin and lovastatin have been shown to exert anti-CRC effects by targeting CYP51A1 [24]. Given the preliminary evidence supporting the regulatory role of CYP51A1 in CRC progression, together with dataset (GSE58111) analysis showing that CYP51A1 is among the most significantly downregulated differentially expressed genes under EIF4A1 knockdown, we therefore asked: can EIF4A1 regulate CRC cell proliferation and migration through the CYP51A1/cholesterol metabolic homeostasis pathway?

RAD51 recombinase (RAD51), a transcription factor, is one of the key factors maintaining genomic stability in eukaryotes. However, abnormally high expression of RAD51 is closely associated with malignant progression and therapeutic resistance in various tumor[25,26]. RAD51 is significantly overexpressed in CRC tissues and positively correlated with poor patient prognosis[27,28]. Genetic susceptibility studies have also revealed a positive association between RAD51 gene polymorphisms and the risk of CRC in human populations[29]. Bioinformatic analysis showed a significant positive correlation between RAD51 and EIF4A1 expression, and predicted potential binding sites of RAD51 in the EIF4A1 prom

oter region. It is therefore speculated that EIF4A1 might be transcriptionally activated by RAD51 and thereby participate in regulating the proliferation and migration of CRC cells. The present study demonstrated that EIF4A1, transcriptionally activated by RAD51, promotes cholesterol synthesis by upregulating CYP51A1 expression, thereby enhancing the proliferation and migration of CRC cells. These findings suggest that EIF4A1 represents a promising therapeutic target for CRC.

Materials and Methods

1. Bioinformatics Analysis

The differential expression of EIF4A1 across pan-cancer was analyzed using the SangerBox database (http://sangerbox.com/tool.html)；The correlation between EIF4A1 and RAD51 was evaluated via the CHIP-base database (https://rna.sysu.edu.cn/chipbase/)； The binding sites of RAD51 in the EIF4A1 promoter region were predicted with the GTRD database (https://gtrd20-06.biouml.org/)；The comparison groups were set as the EIF4A1 control group and the knockdown group, all genes were ranked based on the $\log^2$ FC of differentially expressed genes to generate a ranked gene list. The analysis parameters were set as follows: number of permutations=1000, permutation type="gene-set", enrichment statistic ="weighted", and the significance threshold was set at FDR<0.001. The direction and statistical significance of pathway enrichment were assessed by calculating the NES, P-value, and FDR. Finally, the enrichment score curve were generated using the built-in plotting function of GSEA.

2. Cell Culture and Treatment

RKO cells were cultured in DMEM supplemented with 10% FBS, and HCT-116 cells were maintained in McCoy’s 5A medium containing 10% FBS. Both cell lines were incubated at 37 °C in a 5% CO_2 humidified incubator. (RKO and HCT-116 cells were obtained from the Cell Bank of the Medical Experimental Research Center, Yan’an University) CRC cells at the logarithmic growth pha

se were seeded into cell culture plates and cultured for 24 h before transfection with siRNAs. EIF4A1-siRNA, RAD51-siRNA, and negative control siRNA (si-NC) were purchased from GenePharma Co., Ltd.The si-RNA sequences were as follows:si-*EIF4A1*: forward(5'-3'): GAGUAACUGGAAUGAGAUUTT, reverse (5'-3'): AAUCUCAUUCCAGUUACUCTT; si-*RAD51*: forward(5'-3'): CCCUUU ACAGAACAGACUATT，reverse(5'-3'): UAGUCUGUUCUGUAAAGGGCG; si-*NC*: forward(5'-3'): UUCUCCGAACGUGUCACGUTT, reverse(5'-3')： ACGUG ACACGUUCGGAGAATT.

3. CCK-8 Assay and Colony Formation Assay

CCK-8 Assay: CRC cells were seeded into 96-well plates at a density of 3×10^3 cells per well. After 24 h of incubation at 37 °C in a 5% CO_2 atmosphere, cells were transfected with corresponding siRNAs. At 0 h, 24 h, 48 h, and 72 h, 10 μL of CCK-8 solution was added to each well, followed by incubation at 37 °C for 2 h. The absorbance at 450 nm was measured using a microplate reader.Colony Formation Assay: Transfected CRC cells were seeded into 12-well plates at 1×10^3 cells per well and cultured for 7-10 days at 37 °C in a 5% CO_2 incubator. Cells were washed with PBS, fixed with 4% paraformaldehyde for 30 min, stained with 0.1% crystal violet for 30 min, then rinsed, air-dried, and photographed.

4. Transwell Assay

Transfected CRC cells (15×10^4) were seeded into the upper chamber containing medium supplemented with 1% FBS, while the lower chamber was filled with 800 μL medium containing 10% FBS. Cells were incubated for 48 h at 37 °C in a 5% CO_2 atmosphere. Subsequently, cells were fixed with 4% paraformaldehyde for 30 min, stained with 0.1% crystal violet for 30 min, and photographed.

5. ChIP

Cells were processed according to the manufacturer's instructions (ChIP Assay Kit, purchased from Boxin Biotechnology Co., Ltd., Guangzhou, Cat. No. Bes5001). A total of 2×10^7 CRC cells were collected and subjected to cross-linking,

nuclear isolation, sonication, washing, immunoprecipitation (IP), and elution. After reverse cross-linking of the enriched target protein–DNA complexes, qRT-PCR was performed to detect the binding sites between the target protein (RAD51) and DNA (EIF4A1 promoter). The primer sequences for the EIF4A1 promoter binding site were as follows: forward(5'-3'): ACGGAGCCACATGACCAAGG, reverse(5'-3'): CGCAGGCACCATTGGATAACTC; *β-actin*: forward(5'-3'): CCAACCGCGAGA AGATGA, reverse(5'-3'): CCAGAGGCGTACAGGGATAG.

6. Western blot

Total protein was extracted from transfected CRC cells, followed by BCA quantification, SDS-PAGE electrophoresis, membrane transfer, incubation with primary antibodies overnight at 4 °C, incubation with secondary antibodies at room temperature for 1.5 h, and subsequent chemiluminescent imaging. Primary antibodies used were as follows: MMP2, MMP9 and CYP51A1 antibodies were purchased from ProteinTech Group, Inc. (10373-2-AP, 10375-2-AP, 13431-1-AP); β-actin antibody was purchased from Servicebio (ZB15001-HRP-100); EIF4A1 antibody was purchased from Abcam (ab31217).

7. qRT-PCR

Total RNA was extracted from CRC cells, and the RNA was reverse-transcribed into cDNA, followed by quantitative real-time PCR detection. The primer sequences were as follows: *EIF4A1*: forward(5'-3'): TCATCAACACCCGGAGGAAG, reverse(5'-3'): TGCACATCAATGCCTCTGGC; *HMGCR*: forward(5'-3'): TTCTTGCCAACTACTTCGTG, reverse(5'-3')：CATAATCATCTTGACCCTCTG; *SQLE*: forward(5'-3'): ATAAGAAATGCGGGGATGTCAC, reverse(5'-3'): ATATCCGAGAAGGCAGCGAAC; *SREBF2*: forward(5'-3'): GCAGCAACGGGACCATTCT, reverse(5'-3'): CCCCATGACTAAGTCCTTCAACT; *LDLR*: forward(5'-3'): TGACTCAGACGAACAAGGCTG, reverse(5'-3'): ATCTAGGCAATCTCGGTCTCC; *ABCA1*: forward(5'-3'): TATAATGCGACAGGAGATAGG, reverse(5'-3'): TTGCCATTGACTGAAAGAAC; *CYP51A1*: forward(5'-3'): GAAACGCAGACAGTCTCAAGA, reverse(5'-3'): ACGCCCATCCTTGTATGTAGC, *β-actin*: forward(5'-3'): AAACTGGGACCAAACTAGCTG, reverse(5'-3'): AAACTGGGACCAA

ACTAGCTG.

8. Detection of Intracellular Total Cholesterol Content

Transfected CRC cells were extracted with cholesterol lysis buffer, lysed on ice for 10 min, centrifuged at 2000 g for 5 min, and the supernatant was collected. Working solution was added and incubated at 25℃ for 20 min, and the absorbance at 550 nm was measured. Meanwhile, BCA quantification was used for normalization. The enzymatic assay kit for total cholesterol content in tissue and cells was purchased from Applygen Technologies Inc. (E1015).

9. Bioinformatics Analysis

Using the EIF4A1 control group and knockdown group as comparative groups, all genes were ranked based on the log2 fold change (log2 FC) of differentially expressed genes to generate a ranked gene list. The analysis parameters were set as follows: number of permutations=1000, permutation type="gene-set", enrichment statistic="weighted", and the significance threshold was set at FDR<0.001. The direction and statistical significance of pathway enrichment were assessed by calculating the normalized enrichment score (NES), P-value, and false discovery rate (FDR). Finally, the enrichment score curve and gene distribution map were generated using the built-in plotting function of GSEA.

10. Statistical Analysis

Data analysis was performed using SPSS 26.0 software, and all data were presented as mean ± standard deviation (mean ± SD). Independent-samples t-test was used for comparison between two groups, and one-way ANOVA was used for comparison among multiple groups. A value of $P<0.05$ was considered statistically significant.

Results

1. EIF4A1 can promote the proliferation and migration of CRC cells

The differential expression of EIF4A1 across pan-cancer was analyzed using the SangerBox database, and the results showed that EIF4A1 was significantly hi

ghly expressed in CRC (Figure 1A). CRC cells were transfected with EIF4A1-siRNA to investigate the regulatory role of EIF4A1 in the proliferation and migration of CRC cells. The effects of EIF4A1 knockdown on CRC cell proliferation were examined by CCK-8 and colony formation assays, which revealed that the proliferative capacity of CRC cells in the EIF4A1-siRNA group was significantly lower than that in the control group (Figure 1B-E). Transwell assay results demonstrated that the migratory ability of CRC cells was markedly decreased in the EIF4A1-siRNA group compared with the control group (Figure 1F-G). Furthermore, Western blot was performed to detect the expression levels of migration marker proteins MMP9 and MMP2 in CRC cells of each treatment group. The results showed that the protein expression levels of MMP9 and MMP2 were significantly lower in CRC cells treated with EIF4A1-siRNA than in the control group (Figure 1H-I). These findings indicate that EIF4A1 significantly enhances the proliferation and migration of CRC cells, suggesting that EIF4A1 promotes CRC cell proliferation and migration.

2. EIF4A1 can promotes CRC cell proliferation and migration by regulating the homeostasis of cholesterol metabolism.

GSEA enrichment analysis results showed that EIF4A1 was significantly positively correlated with the cholesterol metabolism pathway (Figure 2A). To investigate whether EIF4A1 could regulate the proliferation and migration of CRC cells by modulating cholesterol metabolism homeostasis, we detected and analyzed the effects of EIF4A1 knockdown on the intracellular total cholesterol content and the relative mRNA expression levels of cholesterol metabolism-related genes in CRC cells. The results revealed that the intracellular total cholesterol content in CRC cells of the EIF4A1 knockdown group was significantly lower compared with the control group (Figure 2B-C). qRT-PCR assay results demonstrated that, compared with the control group, EIF4A1 knockdown significantly decreased the relative mRNA expression levels of cholesterol synthesis-related genes (SREBF2, HMGCR, SQLE) and cholesterol uptake-related gene (LDLR), while significantly increasing the relative mRNA expression level of the cholestero

l efflux-related gene (ABCA1) (Figure 2D-E). These findings indicate that EIF4A1 knockdown reduces intracellular total cholesterol content, promotes cholesterol synthesis and uptake, and inhibits cholesterol efflux in CRC cells, suggesting that EIF4A1 may promote the proliferation and migration of CRC cells by positively regulating cholesterol metabolism homeostasis.

3. EIF4A1 can promotes CRC cell proliferation and migration by regulating cholesterol metabolism via upregulating CYP51A1 expression.

Given the important regulatory role of CYP51A1 in cholesterol metabolism and CRC progression, together with the results from the dataset (GSE58111) analysis indicating that CYP51A1 is one of the significantly downregulated genes under EIF4A1 knockdown conditions. Could EIF4A1 participate in the regulation of cholesterol metabolism homeostasis by modulating the expression level of CYP51A1, thereby exerting a promotional effect on CRC proliferation and migration? The results of qRT-PCR and Western blot assays showed that EIF4A1 knockdown significantly decreased the relative mRNA and protein expression levels of CYP51A1 in CRC cells (Figure 3A-D). To further investigate the specific mechanism by which EIF4A1 regulates cholesterol metabolism homeostasis and thereby promotes CRC cell proliferation and migration via upregulating CYP51A1 expression, we treated CRC cells with exogenous CYP51A1 recombinant protein. As shown in Figure 3E-F, the intracellular total cholesterol content in CRC cells of the EIF4A1 siRNA group was significantly lower than that of the control group, while the intracellular total cholesterol content in CRC cells of the EIF4A1 siRNA+exogenous CYP51A1 recombinant protein group was significantly higher than that of the cells in the EIF4A1 siRNA group; that is, treatment with exogenous CYP51A1 recombinant protein could reverse the effect of EIF4A1 knockdown on reducing the intracellular cholesterol content of CRC cells. The results of CCK-8 and colony formation assays showed that the proliferative capacity of CRC cells in the EIF4A1 siRNA group was significantly lower than that of the control group, whereas the proliferative capacity of CRC cells in the EIF4A1 siRNA+exogenous CYP51A1 recombinant protein group

was significantly higher than that of the cells in the EIF4A1 siRNA group; tha t is, treatment with exogenous CYP51A1 recombinant protein could reverse the inhibitory effect of EIF4A1 knockdown on CRC cell proliferation (Figure 3G-J). Similarly, the results of Transwell assays indicated that treatment with exog enous CYP51A1 recombinant protein could reverse the inhibitory effect of EIF 4A1 knockdown on CRC cell migration (Figure 3K-L). The above research fin dings suggest that EIF4A1 can positively regulate cholesterol metabolism home ostasis by upregulating the expression level of CYP51A1, thereby playing a rol e in promoting the proliferation and migration of CRC cells.

4. EIF4A1 can promotes CRC cell proliferation and migration under the tr anscriptional activation of RAD51.

Bioinformatics analysis showed that RAD51 may be a transcription factor of E IF4A1, and the expression levels of RAD51 and EIF4A1 were significantly pos itively correlated in CRC (r=0.851, *P*=0) (Figure 4A). Given that evidence sug gests RAD51 may act as an oncogene to regulate the development and progres sion of CRC, we hypothesized that EIF4A1 may be involved in regulating CR C proliferation and migration under the transcriptional activation of RAD51. It was found that the relative mRNA and protein expression levels of EIF4A1 in CRC cells of the RAD51 siRNA group were significantly lower than those in the control group, indicating that RAD51 knockdown significantly reduced EIF 4A1 expression in CRC cells (Figure 4B-E). ChIP-qPCR results demonstrated t he presence of RAD51 binding sites in the promoter region of EIF4A1 (Figure 4F-G). These findings suggest that EIF4A1 promotes CRC proliferation and m igration under the transcriptional activation of RAD51. In summary, EIF4A1 pr omotes CRC proliferation and migration by positively regulating the CYP51A1/ cholesterol metabolism pathway under the transcriptional activation of RAD51 (Figure 5).

Discussion

CRC ranks among the most prevalent and lethal malignancies worldwide, posin

g a severe threat to human health[30,31]. Elucidating the molecular pathogenesis of CRC and identifying potential therapeutic targets is of great significance for targeted therapy of CRC. Studies have shown that EIF4A1 can cooperate with RBM4 to promote the translation of MK5, thereby enhancing migration and invasion of CRC cells[14]; miR-133a can inhibit CRC cell proliferation, migration and invasion by targeting EIF4A1[32]. Consistent with these reports, the present study found that EIF4A1 was significantly upregulated in CRC, and EIF4A1 knockdown effectively suppressed the proliferation and migration of CRC cells. These findings indicate that EIF4A1 functions as an oncogenic factor in regulating the initiation and progression of CRC. In addition, it has been reported that zotatifin, a specific inhibitor of EIF4A1, promotes apoptosis and reduces tumor invasiveness in cholangiocarcinoma cells, thereby improving the prognosis of patients with cholangiocarcinoma[33]; EIF4A1 inhibitors RBF197, RBF203 and RBF208 significantly reduce the viability of diffuse large B-cell lymphoma cells[34]. Compared with the non-specific cytotoxicity of conventional chemotherapeutic agents, EIF4A1 inhibitors can precisely target the dysregulated translation processes on which tumor growth depends, thus exerting prominent anti-tumor effects in various malignancies. Developing specific EIF4A1-targeted inhibitors for CRC holds important clinical translational value and provides a novel strategy for targeted therapy of CRC.

The results of the present study showed that, compared with the control group, the total cholesterol content in CRC cells of the EIF4A1 knockdown group was significantly decreased, and the relative mRNA expression levels of cholesterol synthesis-related genes (SREBF2, HMGCR, SQLE) were markedly downregulated, suggesting that EIF4A1 may increase intracellular total cholesterol content by promoting cholesterol biosynthesis, thereby enhancing the proliferative and migratory capacities of CRC cells. Consistent with this, studies have reported that circINSIG1 promotes CRC cell proliferation and migration by inducing cholesterol biosynthesis[35]; crosstalk exists between SREBP2 and dysregulated signaling pathways including PI3K/AKT/mTORC1 and TGF-β, which can drive col

orectal carcinogenesis[36]; upregulated HMGCR expression and elevated cholesterol levels are closely associated with poor prognosis in CRC patients[37]; SQLE is overexpressed in CRC and promotes CRC cell proliferation while inhibiting apoptosis[38]. On the other hand, the present study found that, compared with the control group, the expression of LDLR, a cholesterol uptake-related gene, was significantly downregulated, whereas the expression of ABCA1, a cholesterol efflux-related gene, was remarkably upregulated in CRC cells of the EIF4A1 knockdown group, which may represent another mechanism underlying the reduced intracellular total cholesterol content induced by EIF4A1 knockdown. In line with our findings, EFNB2/EPHB4 has been reported to promote CRC liver metastasis by enhancing LDLR-mediated cholesterol uptake[39]; ABCA1 facilitates cellular cholesterol efflux and thereby suppresses CRC cell growth[40]. Interestingly, other studies have suggested that high ABCA1 expression increases cholesterol efflux, enhances the fluidity of CRC cell membranes, and ultimately promotes CRC metastasis[41,42]. These findings indicate that the role of ABCA1 in regulating CRC progression may vary under different conditions.

CYP51A1 is a key enzyme in the cholesterol synthesis pathway. It not only regulates homeostasis of cholesterol metabolism but also controls cell death through non-cholesterol-dependent mechanisms, thereby participating in tumor progression[43]. For example, BHLHA15 can transcriptionally activate CYP51A1 to induce cholesterol synthesis and thus promote cervical cancer progression[44]; CYP51A1 suppresses pancreatic cancer progression by inhibiting pH-dependent alkaliptosis[45]. These findings suggest that CYP51A1 functions as an oncogenic driver in the progression of tumors such as cervical cancer and pancreatic cancer. Similarly, the present study is the first to verify the tumor-promoting role of CYP51A1 in CRC progression. Our results showed that EIF4A1 knockdown significantly reduced CYP51A1 expression in CRC cells, and recombinant CYP51A1 protein reversed the EIF4A1 knockdown-mediated reduction in intracellular cholesterol content and inhibition of CRC cell proliferation and migration. We demonstrate for the first time that EIF4A1 promotes CRC cell proliferation and

migration by upregulating CYP51A1 expression to positively maintain cholesterol metabolism homeostasis, and that the regulatory role of CYP51A1 in CRC cell proliferation and migration is achieved in a cholesterol-dependent manner. In addition, the present study found that RAD51 knockdown resulted in decreased expression of EIF4A1. ChIP-qPCR results indicated that potential RAD51-binding sites exist in the promoter region of EIF4A1, suggesting that RAD51 acts as a transcriptional activator of EIF4A1. This study reveals for the first time that EIF4A1 promotes CRC cell proliferation and migration under the transcriptional activation of RAD51. Consistent with this, studies have shown that RAD51 promotes mitosis of CRC stem cells[46]; VCP recruits RPA and RAD51 to DNA damage sites, enhancing homologous recombination repair and ultimately promoting radioresistance in CRC[47]. In summary, EIF4A1, under the transcriptional activation of RAD51, upregulates CYP51A1 expression to positively maintain cholesterol metabolism homeostasis, ultimately promoting CRC cell proliferation and migration. EIF4A1 represents a promising therapeutic target for CRC, and the completion of this study provides a novel perspective for investigating the pathogenesis and targeted therapy of CRC.

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Data Availability Statement

The data that support the findings of this study are openly available in public databases and bioinformatics platforms.

SangerBox: The operation steps are as follows: 1) Click "Pan-Cancer Analysis" - click "Gene Expression Differential Analysis" - in the "Please enter gene" dialog box, select "ENSG00000161960 (EIF4A1)" - for "Data Source," select "TCGA + GTEx" - for "Sample Source," select "All Samples" - for "Data Transformation," select "log2(x+0.001)" - for "Test Method," select "Non-parametric Test" - click "Submit Immediately."

ChIPBase: The operation steps are as follows: 1) Access the database homepage and select the "Co-Expression" co-expression analysis module; 2) From the "Select a project (study) of gene expression data" drop-down menu, select the "TCGA Pan-Cancer (PANCAN)" pan-cancer dataset; 3) In the "Search Terms" search box, simultaneously enter the target genes "EIF4A1" and "RAD51"; 4) Select the "Co-Expression statistics" module to view the co-expression statistical results; 5) In the "Diseases or Studies" option, filter for "Colorectal cancer" CRC-related data.

GTRD: The operation steps are as follows: 1) On the GTRD homepage, click the "Start" button and select "GTRD" on the left side; 2) Locate the "Advanced search" module, enter "EIF4A1" in the "Gene symbol or ID" search box under "Binding sites near the specifies gene," and enter "RAD51" in the "Transcription factor" search box; 3) In the "Data set" checkbox, select the dataset "macs2 peaks"; 4) In the "Transcription factor" checkbox under "Gene regulated by the specifies transcription factor," select "RAD51" and click "Run"; 5) Obtain the predicted binding sites between the transcription factor and the target gene.

Gene Set Enrichment Analysis (GSEA): The specific dataset analyzed was GSE58111, which is publicly available in the NCBI Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE58111).

Authors' contribution

LXS and MQG performed the experiments. HQY and SBT analysed and interp reted the data. MNC and HYB contributed to the conception and design of the study and participated in data interpretation. LXS wrote the original draft. LX S, MQG, HQY, SBT, MNC, HYB and FL revised the original draft. FL secure d funding. All authors read and approved the final manuscript. LXS and FL c

onfirm the authenticity of all the raw data.

Declarations

Ethical Approval and Accordance: Not applicable. This study did not involve human participants or animal models. All cell lines used were obtained from Experimental Research Center, Yan'an Medical College, Yan'an University, and all in vitro experiments were conducted in accordance with standard laboratory guidelines.

Consent to participate: Not applicable.

Consent to publish: Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Fig.1 Knockdown of EIF4A1 inhibits the proliferation and migration of CRC cells

Note: (A) Expression level analysis of EIF4A1 in pan-cancer; (B-C) Effect of EIF4A1 knockdown on the proliferative ability of RKO cells; (D-E) Effect of EIF4A1 knockdown on the proliferative ability of HCT116 cells; (F-G) Effect of EIF4A1 knockdown on the migratory ability of CRC cells; (H-I) Effect of EIF4A1 knockdown on the protein expression levels of MMP2 and MMP9 in CRC cells. **P*<0.05，***P*<0.01，****P*<0.001.

Fig.2 The effect of EIF4A1 knockdown on the cholesterol metabolism

Note: (A) EIF4A1 is positively correlated with the cholesterol metabolism pathway. (B-C) Effect of EIF4A1 knockdown on intracellular total cholesterol content in CRC cells. (D-E) Effect of EIF4A1 knockdown on the relative mRNA expression levels of cholesterol metabolism-related genes (SREBF2, HMGCR, SQLE, LDLR, ABCA1). **P*<0.05，***P*<0.01，****P*<0.001.

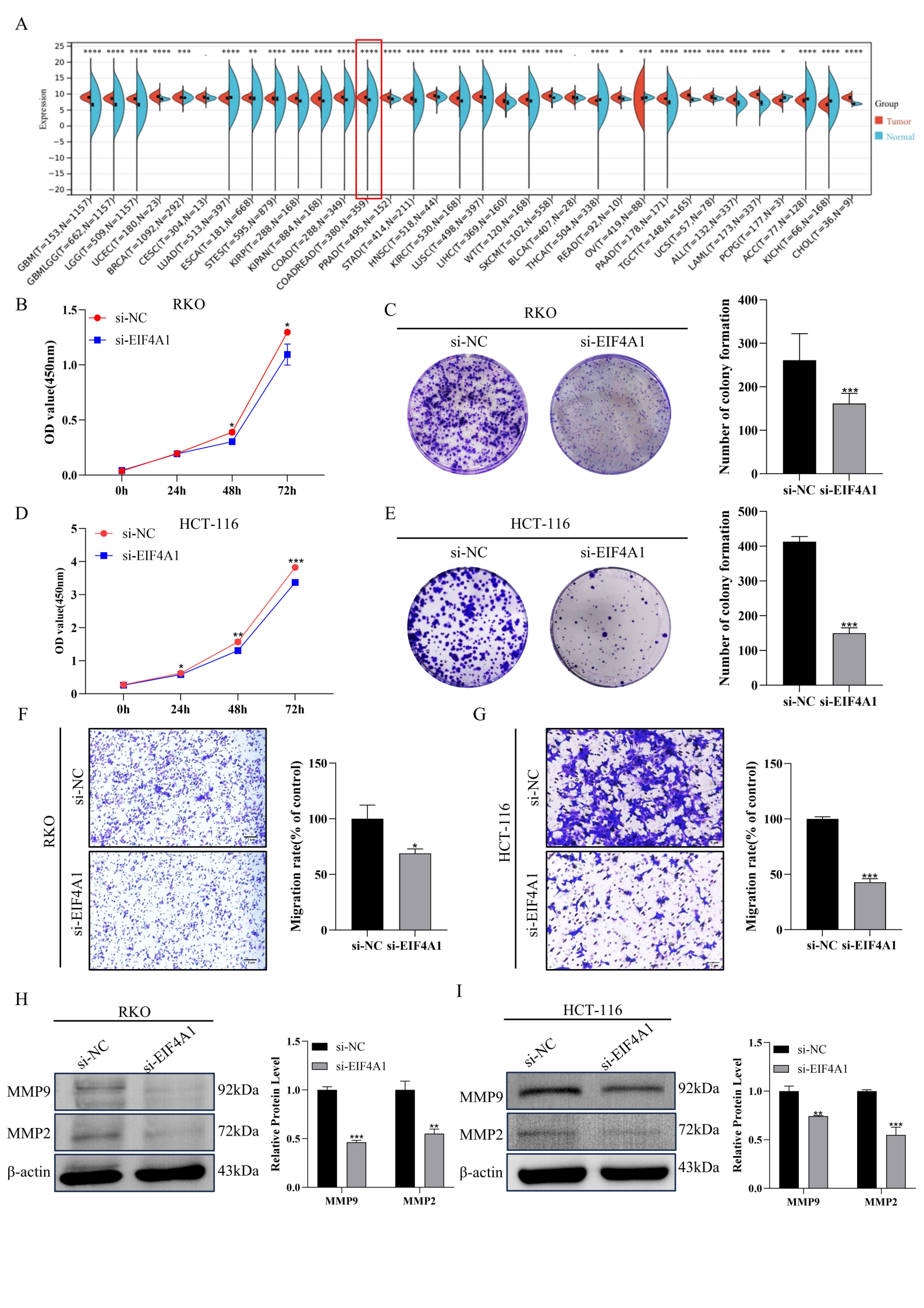
Fig.3 EIF4A1 regulates cholesterol metabolism by upregulating CYP51A1 expression, thus regulating the proliferation and migration of CRC cells

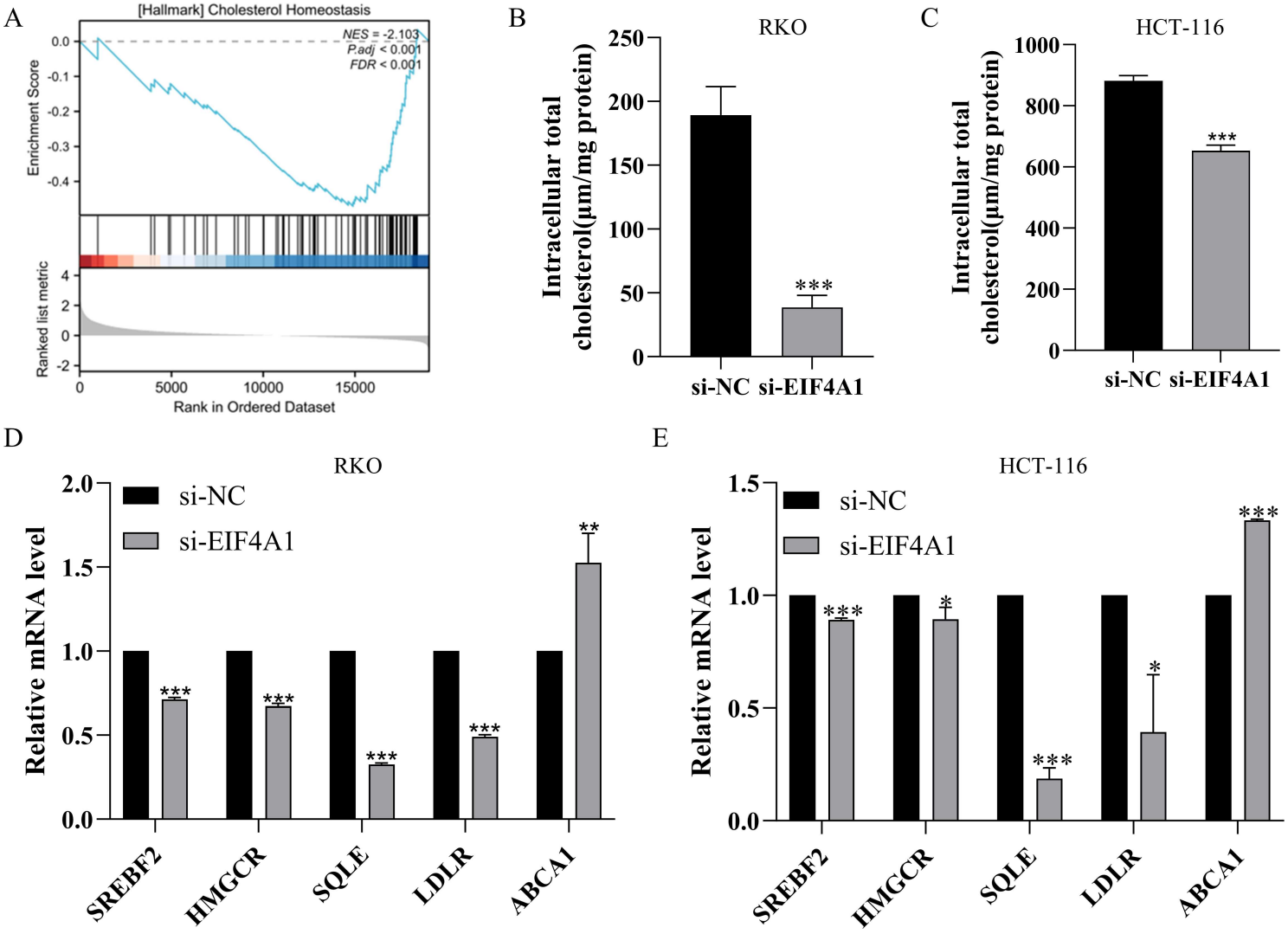
Note: (A-B) Effect of EIF4A1 knockdown on the relative mRNA expression level of CYP 51A1; (C-D) Effect of EIF4A1 knockdown on the protein expression level of CYP51A1. (E-F) Treatment with CYP51A1 recombinant protein (150 ng/ml) reverses the effect of EI F4A1 knockdown on intracellular total cholesterol content in CRC cells; (G-J) CYP51A1 r ecombinant protein treatment reverses the inhibitory effect of EIF4A1 knockdown on CRC cell proliferation; (K-L) CYP51A1 recombinant protein treatment reverses the inhibitory ef fect of EIF4A1 knockdown on CRC cell migration. *P<0.05，**P<0.01，***P<0.001.

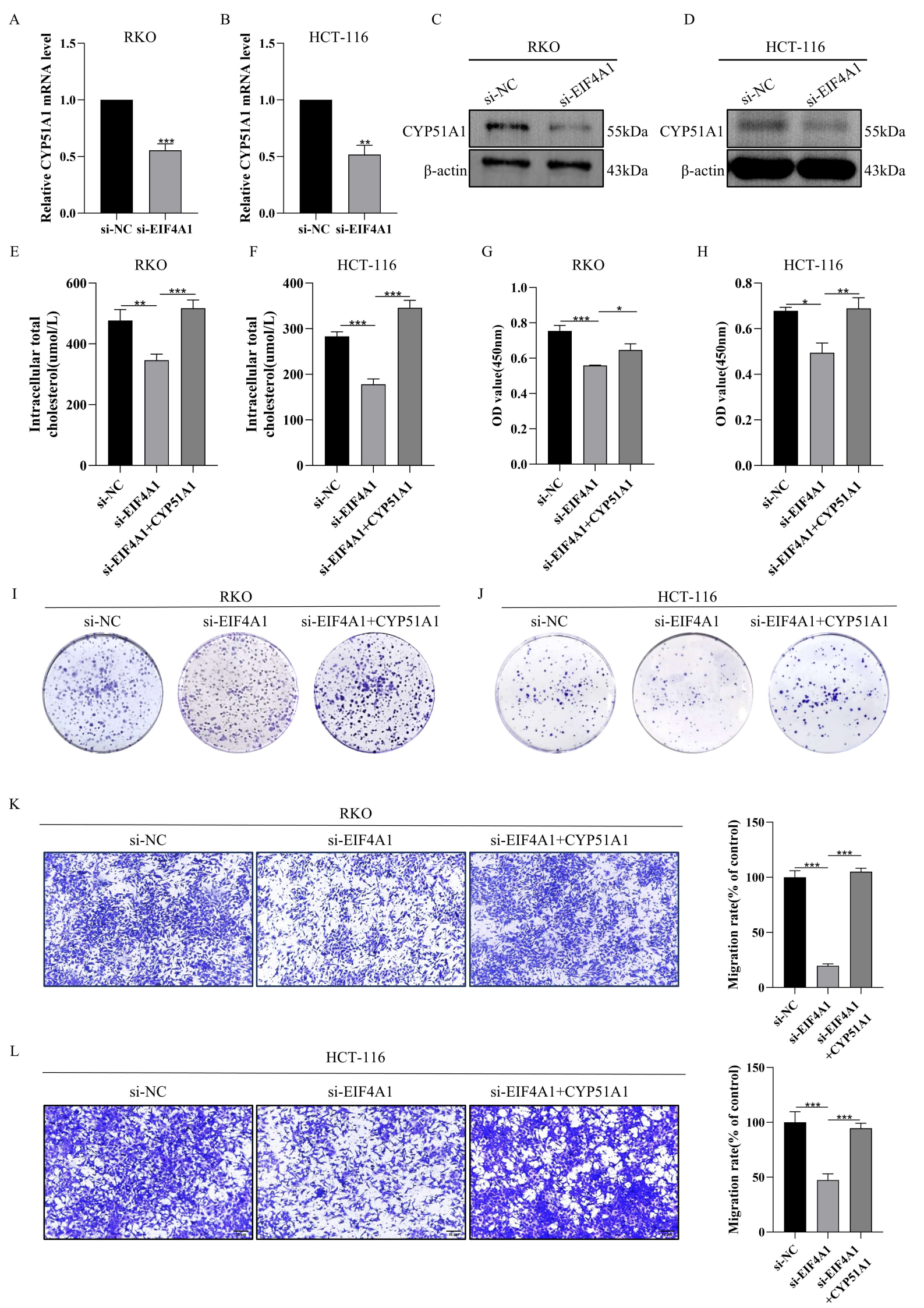
Fig.4 EIF4A1 can promotes the proliferation and migration of CRC cells under the transcr iptional activation of RAD51

Note: (A) Correlation analysis between EIF4A1 and RAD51; (B-C) Effect of RAD51 knoc kdown on the relative mRNA expression level of EIF4A1; (D-E) Effect of RAD51 knockd own on the protein expression level of EIF4A1; (F-G) ChIP-qPCR assay for the presence of RAD51 binding sites in the EIF4A1 promoter region. *P<0.05，**P<0.01，***P<0.001.

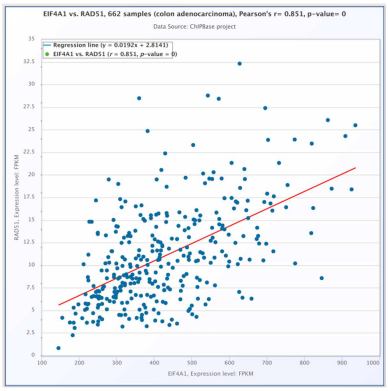
Fig.5 Schematic diagram of molecular mechanism of EIF4A1 regulating CRC cell prolifera tion and migration


A
Expression
Group
Tumor
Normal
GBM(T=153,N=1157)
GBMLGG(T=662,N=1157)
LGG(T=509,N=1157)
UCEC(T=180,N=23)
BRCA(T=1092,N=292)
CESC(T=304,N=13)
LUAD(T=513,N=397)
ESCA(T=181,N=668)
STES(T=595,N=879)
KIRP(T=288,N=168)
KIPAN(T=884,N=168)
COAD(T=288,N=168)
COADREAD(T=380,N=349)
PRAD(T=495,N=152)
STAD(T=414,N=211)
HNSC(T=518,N=44)
KIRC(T=530,N=168)
LUSC(T=498,N=397)
LIHC(T=369,N=160)
WT(T=120,N=168)
SKCM(T=102,N=558)
BLCA(T=407,N=28)
THCA(T=504,N=338)
READ(T=92,N=10)
OV(T=419,N=88)
PAAD(T=178,N=171)
TGCT(T=148,N=165)
UCS(T=57,N=78)
ALL(T=132,N=337)
LAML(T=173,N=337)
PCPG(T=177,N=3)
ACC(T=77,N=128)
KICH(T=66,N=168)
CHOL(T=36,N=9)
B
RKO
si-NC
si-EIF4A1
OD value(450nm)
0h
24h
48h
72h
C
RKO
si-NC
si-EIF4A1
Number of colony formation
D
HCT-116
E
HCT-116
F
RKO
G
HCT-116
Migration rate(% of control)
H
RKO
MMP9
MMP2
β-actin
92kDa
72kDa
43kDa
Relative Protein Level
I
HCT-116

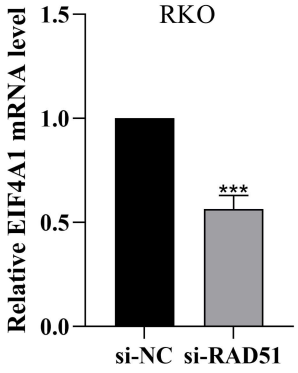

A
[Hallmark] Cholesterol Homeostasis
NES = -2.103
P.adj < 0.001
FDR < 0.001
Enrichment Score
Ranked list metric
Rank in Ordered Dataset
B
RKO
Intracellular total cholesterol(μm/mg protein)
si-NC
si-EIF4A1
C
HCT-116
Intracellular total cholesterol(μm/mg protein)
si-NC
si-EIF4A1
D
RKO
si-NC
si-EIF4A1
Relative mRNA level
SREBF2
HMGCR
SQLE
LDLR
ABCA1
E
HCT-116
si-NC
si-EIF4A1
Relative mRNA level
SREBF2
HMGCR
SQLE
LDLR
ABCA1


A
RKO
Relative CYP51A1 mRNA level
1.5
1.0
0.5
0.0
***
si-NC si-EIF4A1
B
HCT-116
Relative CYP51A1 mRNA level
1.5
1.0
0.5
0.0
**
si-NC si-EIF4A1
C
RKO
si-NC
si-EIF4A1
CYP51A1
55kDa
β-actin
43kDa
D
HCT-116
si-NC
si-EIF4A1
CYP51A1
55kDa
β-actin
43kDa
E
RKO
Intracellular total cholesterol(umol/L)
600
400
200
0
**
***
si-NC
si-EIF4A1
si-EIF4A1+CYP51A1
F
HCT-116
Intracellular total cholesterol(umol/L)
400
300
200
100
0
***
***
si-NC
si-EIF4A1
si-EIF4A1+CYP51A1
G
RKO
OD value(450nm)
1.0
0.8
0.6
0.4
0.2
0.0
***
*
si-NC
si-EIF4A1
si-EIF4A1+CYP51A1
H
HCT-116
OD value(450nm)
0.8
0.6
0.4
0.2
0.0
*
**
si-NC
si-EIF4A1
si-EIF4A1+CYP51A1
I
RKO
si-NC
si-EIF4A1
si-EIF4A1+CYP51A1
J
HCT-116
si-NC
si-EIF4A1
si-EIF4A1+CYP51A1
K
RKO
si-NC
si-EIF4A1
si-EIF4A1+CYP51A1
Migration rate(% of control)
150
100
50
0
***
***
si-NC
si-EIF4A1
si-EIF4A1 +CYP51A1
L
HCT-116
si-NC
si-EIF4A1
si-EIF4A1+CYP51A1
Migration rate(% of control)
150
100
50
0
***
***
si-NC
si-EIF4A1
si-EIF4A1 +CYP51A1

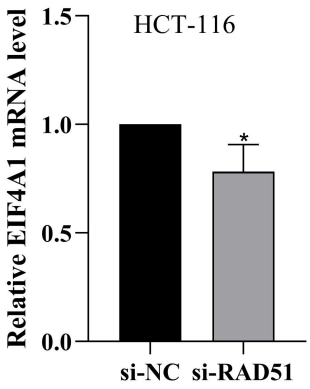
A


EIF4A1 vs. RAD51, 662 samples (colon adenocarcinoma), Pearson's r= 0.851, p-value= 0
Data Source: ChIPBase project
Regression line (y = 0.0192x + 2.8141)
EIF4A1 vs. RAD51 (r = 0.851, p-value = 0)
RAD51, Expression level: FPKM
EIF4A1, Expression level: FPKM

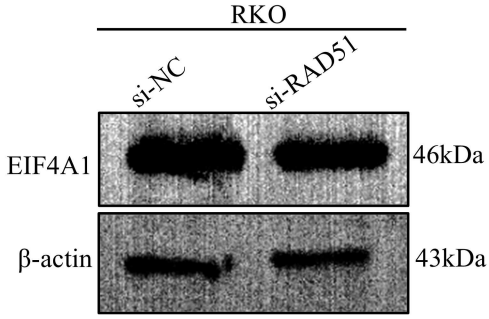
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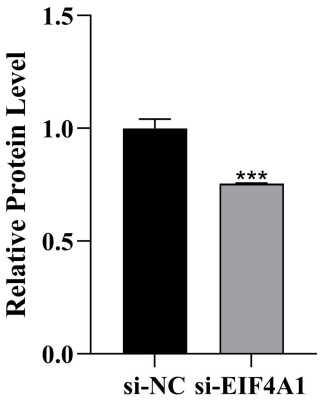

RKO
Relative EIF4A1 mRNA level
1.5
1.0
0.5
0.0
***
si-NC
si-RAD51

C

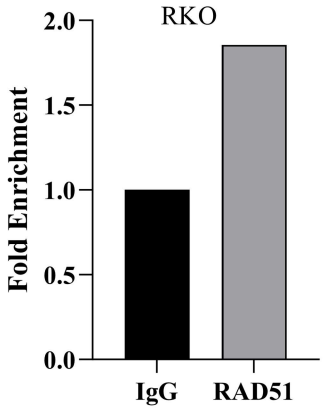

HCT-116
Relative EIF4A1 mRNA level
1.5
1.0
0.5
0.0
*
si-NC
si-RAD51

D

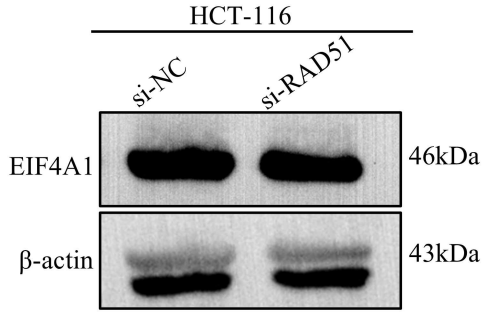

RKO
si-NC
si-RAD51
EIF4A1
46kDa
β-actin
43kDa

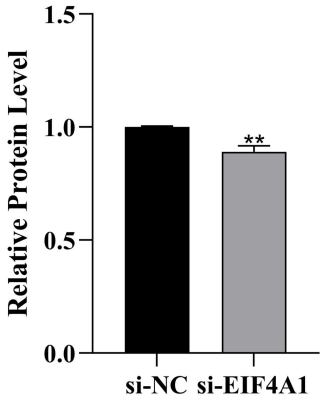

Relative Protein Level
1.5
1.0
0.5
0.0
***
si-NC
si-EIF4A1

F

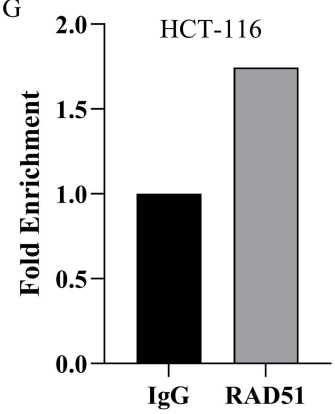

RKO
Fold Enrichment
2.0
1.5
1.0
0.5
0.0
IgG
RAD51

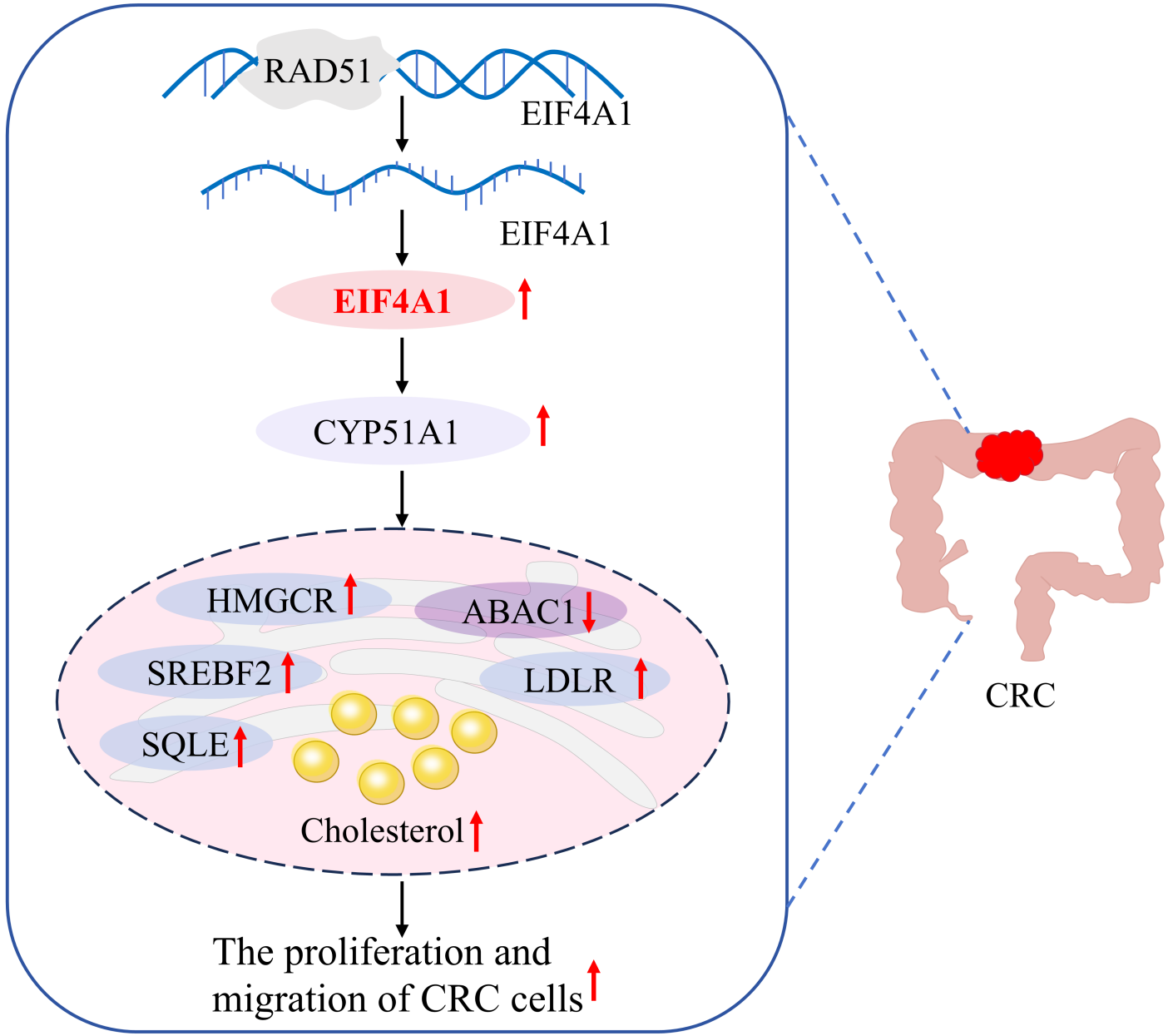
E


HCT-116
si-NC
si-RAD51
EIF4A1
46kDa
β-actin
43kDa


Relative Protein Level
1.5
1.0
0.5
0.0
**
si-NC
si-EIF4A1

G


HCT-116
Fold Enrichment
2.0
1.5
1.0
0.5
0.0
IgG
RAD51


RAD51
EIF4A1
EIF4A1
EIF4A1
CYP51A1
HMGCR
ABAC1
SREBF2
LDLR
SQLE
Cholesterol
The proliferation and
migration of CRC cells
CRC

Supplementary Files

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- Figure1HRKOWesternblot.xlsx
- Figure4DRKOWesternblot.xlsx
- Figure3DHCT116Westernblot.xlsx
- Figure3CRKOWesternblot.xlsx
- Figure4EHCT116Westernblot.xlsx
- Figure1IHCT116Westernblot.xlsx