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Circular RNA circLDLR facilitates cancer progression by altering the miR-30a-3p/SOAT1 axis in colorectal cancer

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26 **Abstract**

27 Colorectal cancer (CRC) is the third most common malignancy worldwide. Circular
28 RNAs (circRNAs) have been reported to play critical regulatory roles in
29 tumorigenesis, serving as tumor biomarkers and therapeutic targets. However, the
30 contributions of circRNAs to CRC tumorigenesis are unclear. In our study, high
31 expression of circLDLR was found in CRC tissues and cells and was closely
32 associated with the malignant progression and poor prognosis of CRC patients. We
33 demonstrated that circLDLR boosts growth and metastasis of CRC cells in vitro and
34 in vivo, and modulates cholesterol levels in vitro. Mechanistically, we showed that
35 circLDLR competitively binds to miR-30a-3p and prevents it from reducing the
36 SOAT1 level, facilitating the malignant progression of CRC. In sum, our findings
37 illustrate that circLDLR participates in CRC tumorigenesis and metastasis via the
38 miR-30a-3p/SOAT1 axis, serving as a potential biomarker and therapeutic target in
39 CRC.

40 **Keywords:** colorectal cancer, circLDLR, miR-30a-3p, SOAT1

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45 **Introduction**

46 Colorectal cancer (CRC) is one of the most common tumors and the leading cause of
47 cancer-related death all over the world [1]. In spite of great improvements in
48 therapeutic strategies, including colectomy, chemotherapy and immunotherapy, the
49 high frequencies of recurrence and metastasis make CRC a serious menace to human
50 health [2, 3]. CRC diagnosed at an advanced stage, particularly distant metastasis
51 patients, remain a low 5-year survival rate [4, 5]. Thus, discovering new biomarkers
52 for early diagnosis, precise metastasis prediction and prognosis is needed.

53 As a kind of abundant and ubiquitous noncoding RNAs, circular RNAs (circRNAs)
54 have single-stranded closed-loop structures [6]. Accompanied by the continuous
55 technical advance of the next-generation sequencing, circRNAs are potentiality for
56 serving as tumor biomarkers and curative targets in the clinic [7]. Recently,
57 literature have demonstrated that circRNAs partake in regulating miscellaneous tumor
58 biological processes, such as invasion, metastasis, proliferation, tumor angiogenesis,
59 drug resistance and cancer metabolism [8]. For example, circ-ERBIN is highly
60 expressed and facilitates the proliferation, migration and metastasis in CRC [9].
61 Knockdown of circHIPK3 effectively inhibits various biological functions in CRC
62 cells by sponging miR-7, such as proliferation, migration, and invasion [10]. Lei et al.
63 noted that circCUL2 activated autophagy in a miR-142-3p/ROCK2 axis-dependent
64 manner, and functioned as a tumor suppressor and regulator of resistance to cisplatin
65 [11]. Moreover, circ-PVT1 activates miR-106a-5p/HK2 signaling, regulating
66 biological processes, such as growth and metastasis, as well as glycolytic metabolism

in oral squamous cell carcinoma [12]. However, there is still no universally accepted explanation for how key differential circRNAs regulate CRC progression and metastasis.

In this work, we scouted the results of ribosomal RNA-depleted RNA-sequencing data for five CRC patients and focused on a circular RNA (circ_0006877) stemmed from the LDLR gene, labeled as circLDLR. And circLDLR was obviously boosted in both CRC tissues and CRC cell lines, and it was associated with a poor prognosis in CRC patients. Moreover, circLDLR was identified as a key regulator in CRC. In vitro and in vivo experiments displayed that it modulates CRC proliferation and metastasis. Our mechanistic study evidenced that circLDLR deeds as a blocker for miR-30a-3p to modulate the level of sterol O-acyltransferase 1 (SOAT1), further facilitating the tumorigenesis of CRC. Therefore, circLDLR has the potential to become promising therapeutic target for CRC.

Materials and methods

Human CRC tissue specimens

Five CRC tissue samples and paired adjacent normal tissue samples were obtained from patients who received surgery at the First Affiliated Hospital of Soochow University (Suzhou, China). We received approval from the Moral Principle Board of the First Affiliated Hospital of Soochow University before we collected the samples (2020084). Informed consent was signed by each CRC patient. Detailed clinicopathological characteristics of these patients are described in Supplementary Table S1.

89 **Cell lines and cell cultures**

90 The human HEK293T cells, normal colonic epithelial cell line NCM-460, and human
91 CRC cell lines (HCT116, HT29, RKO, SW620, HCT8, LoVo, SW480, and Caco-2)
92 were purchased from American Type Culture Collection (ATCC, USA). DMEM
93 (Eallbio, Beijing, China), containing 10% fetal bovine serum (FBS, Eallbio) and 1%
94 penicillin-streptomycin (Beyotime, Shanghai, China, #C0222), was used for all cells
95 maintain in a humidified incubator with 5% CO_2 at 37°C.

96 **Nucleic acid preparation and quantitative real-time polymerase chain reaction**
97 **(qRT-PCR)**

98 TRIzol reagent (Vazyme, Nanjing, China, #R401-01) was adopted to elicit total RNA
99 from tissues or cultured cells. We extracted the nuclear and cytoplasmic fractions with
100 Minute Cytoplasmic & Nuclear Extraction Kits for Cells (Invent Biotechnologies, Inc.,
101 Plymouth, MN, USA, #SC-003). Isolated RNA was used for reverse transcription
102 with MonScript RT Super Mix with dsDNase (Monad, Wuhan, China, #MR05201) in
103 the light of the manufacturer's manual. We performed the quantitative PCR with
104 SYBR green using the ChemoHS qPCR Mix kit (Monad, Wuhan, China, #MQ00401)
105 on a CFX96 Touch Real-Time-PCR system (Bio-Rad, CA, USA) in the light of the
106 manufacturer's manual. We performed expression analysis with specific primers for
107 each gene, which are shown in Table S2 in Supplementary materials.

108 **RNase R treatment**

109 We incubated total RNA from CRC cells with RNase R (Epicentre Technologies,
110 USA). The condition of incubation with RNase R was at a concentration of 3u /mg at

111 37°C for 30 min in accordance with the manufacturer's protocol. We detected the

112 stability of circLDLR and LDLR mRNA (mLDLR) using qRT-PCR.

113 **Actinomycin D assay**

114 RKO cells were forced on equally in 6-well plates (5×10^5 cells per well). We handled

115 cells with 2 μg/ml actinomycin D (MCE, HY-17559) for several specific times (0 h, 4

116 h, 8 h, 12 h or 24 h). Then, we reaped the cells and used them to analyze the mRNA

117 contents of the linear and circular forms of the LDLR gene using qRT-PCR. Then, we

118 normalized the expression of mRNA to the values measured in the 0 h group.

119 **Fluorescence in situ hybridization (FISH)**

120 Cy3-labeled circLDLR probes (Geneseed, Guangzhou, China) and FAM-labeled

121 miR-30a-3p probes (GenePharma, Shanghai, China) were used for the detection of the

122 colocalization of circLDLR and miR-30a-3p in CRC cells. We marked cell nuclei

123 using 4,6-diamidino-2-phenylindole (DAPI, #C1002). The Fluorescent In Situ

124 Hybridization Kit (RiboBio, Guangzhou, China, #C10910) were utilized to discover

125 the signals of the probes in the light of the manufacturer's instructions. Briefly, cells

126 (1×10^5) were keeped in 15 mm cell culture dishes with glass-bottom. The next day, we

127 used 4% paraformaldehyde to fix the cells at room temperature for 10 min,

128 permeabilized the cells in Triton X-100 (0.5%) for 5 min at 4°C. Then we rinsed them

129 in PBS. All the reagents were RNase-free. After incubating the cells for 30 min at

130 37°C in prehybridization buffer, we hybridized them with the probes in the

131 hybridization buffer (1:50) overnight. Next, the cells were washed in different

132 washing buffers in order, and the nuclei were stained with DAPI following the

133 manufacturer's protocol. We acquired all images on a confocal laser scanning
134 microscope (Olympus FLUOVIEW FV1000).

135 **Cell viability**

136 To evaluate the proliferation of CRC cells, Cell Counting Kit-8 (CCK-8, NCM,
137 Suzhou, China, #C6005) was applied. In the CCK-8 experiment, we cultured
138 transfected CRC cells into a well of 96-well plate at a concentration of 5000 cells. At
139 the same time every day, we added ten microliters of CCK-8 solution into each well ,
140 and the absorbance value was quantified at 450 nm as a reference.

141 **5-Ethynyl-2′-deoxyuridine (EdU) incorporation assay**

142 To perform the EdU experiment, we used the BeyoClick™ EdU Cell Proliferation Kit
143 with Alexa Fluor 555 (Beyotime, #C0075S) in the light of the manufacturer's protocol.
144 In Brief, we seeded cells (1×10^5) in 15 mm glass-bottom cell culture dishes. The next
145 day, we incubated the cells with 10 μM EdU working solution and cultured them at
146 37°C with 5% CO_2 for 2 h. After fixed in paraformaldehyde (4%), the cells were
147 permeabilized in 0.3% Triton X-100 and washed them in 3% BSA. Finally, we
148 incubated the cells with Click Additive Solution and Hoechst 33342 in the light of the
149 manufacturer's manual. Using a confocal laser scanning microscope (Olympus
150 FLUOVIEW FV1000), we obtained all images. Finally, we calculated the percentage
151 of EdU incorporation (DNA Synthesis) to evaluate cell proliferation.

152 **Transwell migration and invasion assays**

153 To carry out the migration assay, we resuspended cells (4×10^5 cells) in medium
154 without FBS and added them to the upper chamber in a 24-well plate with the pore of

155 8 µm (BD Biosciences, NJ, USA, #353097). To perform the invasion assay, we coated
156 the upper chambers with 100 µl of diluted Matrigel (200 µg/ml, Corning, Shanghai,
157 China, #356234) for 2 h. Then we filled the bottom chamber with 800 µl of cell
158 culture medium supplemented with 20% FBS as the attractant. After incubating the
159 cells for 24 h, we fixed the cells with 4% paraformaldehyde for 15 min, which were
160 remained on the bottom surface of the upper chamber. Then we stained these cells for
161 15 min with crystal violet (Beyotime, #C0121). Finally, we imaged the cells on the
162 lower side of the chamber membrane and counted them under an inverted microscope.

163 **Analysis of cellular cholesterol levels**

164 The low-density lipoprotein cholesterol (LDL-C) and total cholesterol (T-CHO) kits
165 (Nanjing Jiancheng Bioengineering Institution, Nanjing, China, #A111-1-1,
166 #A113-1-1) were used to measure the concents of T-CHO and LDL-C in CRC cells.

167 **Cell transfection and infection**

168 Human CRC cell lines were cultured in a 6-well plate at 37°C in a humidified 5%
169 CO_2 atmosphere overnight. CircLDLR-specific siRNA (siRNA-1, -2, -3, -4 and -5),
170 miRNA mimics and miRNA inhibitors (GenePharma) were transfected with
171 Lipofectamine 2000 (Invitrogen, USA) in the light of the manufacturer's protocol.
172 Lentiviruses carrying a circLDLR overexpression vector or short hairpin RNA
173 (shRNA) containing the sequence of circLDLR siRNA-2 was obtained from
174 Geneseed (Guangzhou, China). We used an empty backbone vector as a control.
175 When CRC cells grew to 30% confluence, lentiviral particles (MOI: 20) were used to
176 infect them. We verified the effectiveness of overexpression or interference by

177 fluorescence microscopy and qRT-PCR after 72 h.

178 **RNA Immunoprecipitation (RIP) assays**

179 CRC cells (3×10^7) were cumulated and lysed using RIP lysis. The lysis buffer
180 contained 2.5 mM $MgCl_2$, 60 U/ml Superase-In (Ambion, #AM2694), 20 mM Tris,
181 500 mM NaCl, 2% SDS, 1 mM DTT (Sigma, #43816), and protease inhibitors
182 (Biotool, #B14001). Then, we subjected the lysates to sonication, and incubated the
183 supernatants with an anti-AGO2 antibody (Proteintech, Wuhan, China, #10686-1-AP)
184 or IgG overnight at 4°C. Then, we added Protein A/G beads (MedChemExpress,
185 Monmouth Junction, NJ, USA, #HY-K0202) for incubation at 4°C for a further 3 h.
186 After washing the protein with washing buffer (PBS, 0.5% Triton X-100, pH 7.4), we
187 then purified the immunoprecipitated RNAs using TRIzol and assessed by qRT-PCR
188 analysis.

189 **RNA pull-down assay**

190 Biotinylated circLDLR were designed and synthesized (GenePharma, Shanghai,
191 China). We harvested approximately 3×10^7 circLDLR-overexpressing CRC cells, then
192 lysed and sonicated them for further experiments. We incubated the biotinylated
193 circLDLR probe with C-1 magnetic beads (Invitrogen) and cultured them at room
194 temperature for 1 h, generating probe-coated beads. Then, we incubated cell lysates
195 with the circLDLR probe at 4°C overnight, using oligo probe as control. After
196 washing beads with wash buffer, we eluted and extracted the RNA transcripts bound
197 to the beads with TRIzol for analysis.

198 **Luciferase reporter assay**

199 We seeded HEK293T cells (3×10^5) in 6-well plates, and cotransfected them with a
200 mixture of miRNA mimics and luciferase reporter plasmid (1 μg) using
201 Lipofectamine 2000 transfection reagent. 48 h later, we washed the cells with PBS
202 and lysed them in Promega Passive Lysis Buffer. Then, we measured the luciferase
203 activities by the Dual Luciferase Reporter Assay System (Promega, Madison, USA,
204 #E1910) following the manufacturer's instructions. Finally, we normalized the
205 luciferase values and calculated relative luciferase activity .

206 **Western blot analysis**

207 Our team drew proteins with RIPA lysis buffer (Beyotime, #P0013B) adding protease
208 inhibitors (Beyotime, #P1045). Utilizing a BCA protein assay kit (Beyotime, #P0010),
209 we determined the concentrations of proteins. Then, total proteins (30 μg) were
210 separated by electrophoresis using the 10% ExpressCast PAGE Kit (NCM, Suzhou,
211 China, #P2012) and transferred to PVDF membranes (GE Healthcare Life Science,
212 Germany). We used 5% BSA (Fcmacs, Nanjing, China,#FMS-WB021) to block the
213 membranes with for about 1 h, then incubated them with primary antibodies at 4°C
214 overnight. We used the primary antibodies anti-GAPDH (Abclonal, Wuhan, China,
215 #AC035) and anti-SOAT1 (CST, Beverly, Ma, USA, #35695S) in the light of the
216 manufacturer's manuals. After the membranes marking using a secondary antibody
217 for 1 h, we obtained images utilizing Imaging Systems of Bio-Rad ChemiDoc^{TM} MP.

218 **Animal experiments**

219 In vivo experiments were authorized by the Institutional Animal Care and Use
220 Committee of Soochow University (Suzhou, China; SUDA20210918A02). Animal

221 care and all experimental procedures were in the light of institutional ethical
222 guidelines for animal experiments. Stable circLDLR-overexpressing or
223 circLDLR-knockdown CRC cells and corresponding control cells were harvested and
224 suspended in PBS. Each BALB/c nude mouse (six weeks old, female) was implanted
225 subcutaneously with 5×10^6 cells in the right flank. The mice were monitored every
226 other day to measure tumor weight and tumor volume. About 3 weeks after injection,
227 we sacrificed the mice, then dissected and weighed the tumors. To bulid a metastasis
228 model, 7-week-old BALB/c nude mice (female) were administered stable
229 circLDLR-overexpressing or circLDLR-knockdown CRC cells (2×10^6 cells per
230 mouse) via tail intravenous injection. After forty days, the lungs were surgically
231 removed. Then, we fixed the lungs in 4% paraformaldehyde, then stained them with
232 hematoxylin and eosin (HE). Lung metastatic foci were counted by two experienced
233 pathologists.

234 **Hematoxylin and eosin (HE) staining and immunohistochemistry (IHC) analysis**

235 Paraffin sections (5-μm thick) from mouse tumor or lung tissues were used for HE
236 and IHC analyses. HE staining was conducted following the manufacturer's
237 instructions (Beyotime, #C0105). IHC analysis was conducted as described
238 previously [13, 14]. Sections were processed and stained with an anti-Ki-67 antibody
239 (BOSTER, California, USA, #BM4381, 1:50), anti-CD31 antibody (Abcam,
240 Cambridge, MA, USA, #ab32457, 1:1500) or anti-SOAT1 antibody (CST, Beverly,
241 Ma, USA, #35695S, 1:50).
242

Statistical analysis

GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA) and SPSS version 26.0 (IBM Corp., Armonk, NY, USA) were adopted for statistical analysis. Overall survival comparisons were conducted by the log-rank (Mantel–Cox) test for Kaplan–Meier plots. The relationship between circLDLR and patient characteristics was detected using the chi-squared test. Data are presented as the mean ± standard deviation (SD). Intergroup differences were analyzed by Student's t test or one-way ANOVA. P values of < 0.05 were considered statistically significant.

Results

CircLDLR is upregulated in CRC tissues and positively associated with a poor prognosis in CRC patients.

We first performed RNA-seq analysis of ribosomal RNA-depleted total RNA from five clinic CRC tissue samples and the normal paired adjacent tissue samples. Then, we obtained the constructed circRNA profiling database, and we found that the detected circRNAs' length was mostly less than 1000 nucleotides (Fig. 1a). In total, differentially expressed 411 circRNAs ($P < 0.05$ and fold change > 2.0) were identified in the CRC tissues relative to the adjacent normal tissues (Fig. 1b). Among these circRNAs, 184 were significantly elevated, and 277 were lessed (Fig. 1b, c, Supplementary Fig. S1). Next, we put attention to the upregulated circRNA hsa_circ_0006877, which termed circLDLR in the remainder of the article and is assumed to be derived from the low-density lipoprotein receptor (LDLR) gene. Although circLDLR did not have the highest fold change value and P value among

265 the 184 upregulated circRNAs in the circRNA profiling, compared with other

266 up-regulated circRNAs, the expression of circLDLR in 5 pairs of tissues has a better

267 consistency. The expression of circLDLR was re-examined in 80 human CRC and 15

268 normal tissue specimens. As Fig. 1d displayed, the expression of circLDLR was

269 obviously higher in CRC tissues than that in the adjacent tissues. Moreover, we

270 observed that the circLDLR level of most CRC cell lines tested (HCT116, SW480,

271 SW620, RKO, HCT8, HT29, LoVo and Caco-2) was higher than that of the colonic

272 epithelial cell line NCM-460 (Fig. 1e).

273 Next, we investigated the relationships between clinicopathological characteristics

274 and circLDLR expression in CRC patients. Correlation analysis manifested the

275 expression of circLDLR was markedly related to the TNM stage of

276 clinicopathological parameter (Supplementary Table S3). Besides, CRC patients who

277 had higher circLDLR expression had poorer overall survival (OS) (Fig. 1g). Overall,

278 our data show that circLDLR is abnormally expressed in CRC tissues and cell lines,

279 has a positive relation to the poor prognosis of CRC patients.

280 **Characterization of circLDLR**

281 CircLDLR, a predicted length of 295 nt, arises from exons 13 and 14 of the LDLR

282 gene and is located at chromosome 19p13.2 (Fig. 2a). Its precise genomic location is

283 chr19:11,230,768-11,231,198 (GRCh38/hg38) (Fig. 2a). Subsequently, we used

284 qRT-PCR to amplified the back-spliced junction of circLDLR with divergent

285 primers, then verified them via Sanger sequencing (Fig. 2a). Furthermore, we

286 detected circLDLR expression in cDNA and genomic DNA (gDNA) of RKO cells

287 using PCR with divergent primers or convergent primers and an agarose gel
288 electrophoresis assay. Our consequences suggested that circLDLR was amplified from
289 cDNA but not from gDNA by using divergent primers (Fig. 2b). A qRT-PCR assay
290 with oligo (dT)18 primers showed that circLDLR had no poly-A tail (Fig. 2c). To
291 investigate the stability of circLDLR, total RNA of RKO cells was treated with or
292 without RNase R. As shown in Fig. 2d, circLDLR could resist digestion by RNase R,
293 while linear LDLR mRNA (mLDLR) could be degraded by RNase R. Additionally,
294 circLDLR showed a longer half-life than mLDLR in RKO cells after we added
295 actinomycin D to them, which serves as an inhibitor of transcription (Fig. 2e).
296 Subsequently, nuclear and cytoplasmic fractionation followed by qRT-PCR or FISH
297 indicated that circLDLR was predominately positioned in the cytoplasm (Fig. 2f, g).
298 In conclusion, circLDLR was substantiated to be a stable circular RNA that was
299 principally positioned in the cytoplasm.

300 **CircLDLR facilitates CRC malignant behaviour and increases cholesterol levels**
301 **in vitro.**

302 Trying to identify the specific function of circLDLR in our study, gain- and
303 loss-of-function assays were executed. First, five short interfering RNAs (siRNAs)
304 which were devised to target the back-splice site of circLDLR (si-LDLR-1,
305 si-LDLR-2, si-LDLR-3, si-LDLR-4 and si-LDLR-5) were synthesized (Fig. 3a). Two
306 of them (si-LDLR-2 and si-LDLR-4) specifically downregulated the expression of
307 circLDLR in RKO and HCT116 cells without influencing the LDLR mRNA (mLDLR)
308 level (Fig. 3a). To explore the influence of circLDLR on CRC cell proliferation,

309 CCK-8 and EdU assays were performed. We found knocking down circLDLR
310 expression suppressed the rates of proliferation in CRC cells (Fig. 3b, c). The roles of
311 circLDLR in modulating the CRC cell behaviour of migration and invasion was
312 further exploded via Transwell assays. Our findings confirmed that the migration and
313 invasion of CRC cells were significantly suppressed after transfection with
314 si-LDLR-2 and si-LDLR-4 (Fig. 3d). Since LDLR is an key regulator of cholesterol
315 homeostasis [15], we tried to discover whether circLDLR affects cholesterol
316 metabolism of CRC cells. We observed that circLDLR knockdown markedly reduced
317 the total cholesterol (T-CHO) and low-density lipoprotein cholesterol (LDL-C)
318 expression levels of in CRC cells (Fig. 3e).
319 Furthermore, we ectopically expressed circLDLR to identify its biological function
320 using a circLDLR-overexpression plasmid. As Fig. 4a shows, the content of
321 circLDLR was significantly upregulated in SW480 and HT29 cells after transfection
322 with circLDLR-overexpression plasmids. As expected, overexpression of circLDLR
323 (circLDLR-OE) significantly facilitated the growth of SW480 and HT29 cells (Fig.
324 4b-c), which also boosted the migrative and invasive behaviour of these cells (Fig. 4d).
325 Moreover, circLDLR overexpression led to the elevated contents of T-CHO and
326 LDL-C in SW480 and HT29 cells (Fig. 4e). Overall, our consequents signified that
327 circLDLR boosted cell proliferation and metastasis in CRC cells, and increased the
328 contents of T-CHO and LDL-C.
329 **CircLDLR deeds as a miRNA sponge for miR-30a-3p.**
330 Given that circLDLR was predominantly positioned in the cytoplasm, which lacked

331 the ability to encode a protein (analyzed by circRNADb,
332 http://202.195.183.4:8000/circrnadb/circRNADb.php) (Fig. 2f, g, Supplementary
333 Fig.S2), we surmised that it might deed as a miRNA sponge. Therefore, an RIP using
334 an anti-AGO2 antibody was performed. The findings suggested that circLDLR was
335 specifically enriched in SW480 and HT29 cells by the AGO2-specific antibody after
336 transfection with circLDLR-overexpression plasmids (Fig. 5a). Next, three public
337 databases (miRanda, TargetScan and RNAhybrid) were combined to search for
338 candidate target miRNAs of circLDLR. With these bioinformatic approaches, 109
339 candidate miRNAs potentially interacting with circLDLR were identified, as shown in
340 Fig. 5b and Supplementary Table S4. Among these miRNAs, eleven potential target
341 miRNAs, which were previously reported to be negatively associated with tumor
342 progression, were selected for further analysis (Supplementary Table S5). Then, stable
343 circLDLR-knockdown (sh-circLDLR) RKO and HCT116 cells and stable
344 circLDLR-overexpressing SW480 and HT-29 cell lines were established
345 (Supplementary Fig. S3) and exploited to disclose the expression of the eleven
346 potential target miRNAs (Supplementary Fig. S4). As Fig. 5c shows, only the
347 expression miR-30a-3p has the negative correlation with the circLDLR level in these
348 four CRC cell lines, suggesting that circLDLR might interact with miR-30a-3p.
349 Furthermore, the data of RNA pull-down assay evidenced that both circLDLR and
350 miR-30a-3p were specifically enriched by the circLDLR probe compared with a
351 negative control oligo probe in stable circLDLR-overexpressing SW480 and HT29
352 cells (Fig. 5d). We further confirmed that miR-30a-3p had a minimal modulatory role

353 in circLDLR production in CRC cells (Fig. 5e). Moreover, FISH analysis indicated
354 miR-30a-3p colocalized with circLDLR in the CRC cell cytoplasm (Fig. 5f). To
355 further address whether circLDLR functions by sponging miR-30a-3p, we performed
356 a series of rescue experiments. An EdU assay indicated that circLDLR
357 knockdown-induced suppressive effects on cell proliferation were reversed by
358 treatment with miR-30a-3p inhibitors, while the promotive effects of circLDLR
359 overexpression was abolished by treatment with miR-30a-3p mimics (Fig. 5g). In
360 addition, the reduced cell migration and invasion of RKO arised from circLDLR
361 knockdown was effectively abolished by knockdown of miR-30a-3p (Fig. 5h).
362 Consistently, miR-30a-3p overexpression reversed the promotive consequences of
363 circLDLR overexpression on the migrative and invasive behaviour of SW480 cells
364 (Fig. 5h). Moreover, the introduction of a miR-30a-3p inhibitor abolished the
365 suppressive influences of circLDLR deletion on the T-CHO and LDL-C expression
366 (Fig. 5i). The decreased contents of T-CHO and LDL-C induced via circLDLR
367 overexpression were reversed by treatment with miR-30a-3p mimics (Fig. 6i). Taken
368 together, these data indicate that circLDLR facilitates CRC tumorigenesis and also
369 increases the levels of T-CHO and LDL-C by sponging miR-30a-3p.

370 **SOAT1 is a downstream target gene of miR-30a-3p.**

371 CircLDLR is assumed to be derived from the low-density lipoprotein receptor (LDLR)
372 gene, a key gene associated with cholesterol metabolism. Moreover, previous
373 researches have indicated that cholesterol metabolism exerts crucial roles in cancer
374 progression and metastasis [16, 17]. More importantly, we found that circLDLR not

375 only facilitates tumorigenesis in CRC, but also increases the levels of T-CHO and
376 LDL-Cby sponging miR-30a-3p. Hence, we inferred that the circLDLR/miR-30a-3p
377 axis might regulate cholesterol metabolism-related genes. According to TargetScan
378 (http://www.targetscan.org/vert_72/), we screened out two key cholesterol
379 metabolism-associated genes (SOAT1 and HMGCR) as the predicted downstream
380 regulatory genes of miR-30a-3p. qRT-PCR results indicated that miR-30a-3p mimics
381 could obviously decrease the expression of SOAT1, while miR-30a-3p inhibitors
382 markedly increased the level of SOAT1 in both RKO cells and SW480 cells (Fig. 6a).
383 However, the expression of miR-30a-3p had a smaller influence on the expression of
384 HMGCR (Supplementary Fig. S5a, b). The models of hybridization between the
385 SOAT1 3'UTR and miR-30a-3p are illustrated in Fig. S5c. A luciferase reporter assay
386 showed that miR-30a-3p overexpression decreased the activity of the luciferase
387 reporter containing the wild-type SOAT1 3'UTR (Fig. 6b). Moreover, overexpression
388 of miR-30a-3p markedly decreased the SOAT1 protein level of RKO cells, and
389 downregulation of miR-30a-3p produced the opposite results in SW480 cells (Fig. 6c).
390 These results propound that SOAT1 is a direct target gene of miR-30-3p. Next, we
391 explored whether circLDLR exerts a regulatory effect on SOAT1 expression via
392 miR-30a-3p. Western blot data indicated that silencing of circLDLR obviously
393 reduced SOAT1 expression in RKO and HCT116 cells, while overexpression of
394 circLDLR increased that in SW480 and HT29 cells (Fig. 6d). Furthermore, the
395 reduced SOAT1 expression caused by circLDLR knockdown was significantly
396 inverted by treatment with miR-30a-3p inhibitors in RKO cells (Fig. 6e). Moreover,

397 overexpression of miR-30a-3p abolished the promotion of SOAT1 protein expression

398 by circLDLR overexpression in SW480 cells (Fig. 6e). Collectively, these data

399 propose that SOAT1 is a downstream target of circLDLR/miR-30a-3p.

400 **The circLDLR/miR-30a-3p/SOAT1 axis modulates malignant behaviour and**

401 **increases cholesterol levels in CRC.**

402 To further explore the biological role of SOAT1, we examined whether SOAT1

403 participates in circLDLR-mediated CRC progression. EdU and Transwell assays were

404 performed and revealed that knocking down SOAT1 inhibited cell growth, migration

405 and invasion, which were enhanced in HT29 cells and SW480 cells after treatment

406 with a miR-30a-3p inhibitor (Fig. 6f, g, Supplementary Fig. S6a, b). Moreover,

407 SOAT1 downregulation significantly reversed the promotive effect of miR-30a-3p

408 inhibitors on T-CHO and LDL-C contents in CRC cells (Fig. 6h). Consistently,

409 knockdown of SOAT1 inverted the enhancement of proliferation, migration and

410 invasion induced by circLDLR overexpression (Fig. 6i, j, Supplementary Fig. S6c, d),

411 and reversed the promotive consequence of circLDLR overexpression on T-CHO and

412 LDL-C contents in CRC cells (Fig. 6k). Our findings indicated that SOAT1

413 suppression could obviously restrain circLDLR-mediated tumorigenesis and the

414 increase of cholesterol levels.

415 **CircLDLR benefits tumor growth and metastasis of CRC in vivo**

416 Our team further explored whether circLDLR contributes to CRC expansion in vivo,

417 so we constructed xenograft mouse models. Stable circLDLR-knockdown HCT116

418 cells (sh-circLDLR) or stable circLDLR-overexpressing HT29 cells (circLDLR-OE)

419 were infused into the subcutaneous of right hind flank of nude mice. The results
420 showed that circLDLR knockdown inhibited, while circLDLR overexpression
421 promoted, tumor growth in vivo, as evidenced by tumor imaging and results for tumor
422 volume and tumor weight (Fig. 7a-f). IHC staining showed that Ki-67, CD31 and
423 SOAT1 levels were significantly positively correlative with circLDLR contents in
424 xenograft tumor tissues (Supplementary Fig. S7). Conducting a tail vein injection
425 model, we then analyzed the action of circLDLR on CRC metastasis in vivo. The
426 findings pointed that circLDLR knockdown suppressed the metastasis of CRC cells to
427 the lungs (Fig. 7g-i). CircLDLR overexpression had the opposite effect (Fig. 7j-l).
428 Our findings suggest that circLDLR enhances CRC tumor expansion and metastasis
429 in vivo.

430 **Discussion**

431 Currently, numerous circular RNAs have been identified and are considered tumor
432 regulators in multiple cancers, including CRC [8]. For example, it has been reported
433 that circPPP1R12A enhances the proliferation ability, as well as migration and
434 invasive behaviours of colon cancer via Hippo-YAP signaling [18]. Silencing
435 circDENND4C could block the miR-760/GLUT1 axis, which obviously suppresses
436 cell expansion and migration, and glycolysis as well in CRC [19]. In our study,
437 circRNA profiling of CRC tissues was performed by RNA-seq analysis of ribosomal
438 RNA-depleted total RNA. Among the differential circRNAs, we focused on the
439 upregulated circRNA circLDLR, which was positively related to the OS and TNM
440 stage of CRC patients. Importantly, loss- and gain-of-function experiments signified

441 that circLDLR facilitated the abilities of proliferation, migration, and invasion in CRC
442 cells in vitro and accelerated CRC tumorigenesis and metastasis in vivo. These results
443 revealed that circLDLR is a novel oncogenic circRNA in CRC.

444 In this study, we further probed into the roles of circLDLR, which is derived from the
445 LDLR gene, a key gene associated with cholesterol homeostasis. Cholesterol is an
446 indispensable lipid component of various cell types and exerts critical effects on cell
447 signaling. The cholesterol accumulation is a well-known feature of tumors, and
448 picking out cholesterol metabolism has been explored as a novel therapeutic scheme
449 for cancer treatment [20]. There are literatures that LDLR is the patriarch of the
450 LDLR family, orchestrating cholesterol homeostasis [15]. Interestingly, exosomal
451 circLDLR has been revealed to be associated with the production of estradiol in
452 polycystic ovary syndrome [21]. We found that circLDLR increased the contents of
453 T-CHO and LDL-C in CRC cells. However, we only detected the contents of T-CHO
454 and LDL-C while did not elaborate on the mechanism of circLDLR in cholesterol
455 metabolism in several parts of our study. We focused on the change of cholesterol
456 levels in CRC cells and tried to provide an insight into the possibility of circLDLR in
457 cholesterol metabolism. Collectively, our outcomes imply that circLDLR exerts a
458 significant role in modulating cholesterol levels, which may be a key regulator of
459 cholesterol metabolism in CRC.

460 CircRNAs have been demonstrated to play critical effects on CRC via various
461 mechanisms, such as miRNA sponges [22]. As a sponge for miR-200c-3p, knockdown
462 of Hsa_circ_001783 markedly inhibits the ability of proliferation and the behavior

463 invasion in breast cancer cells [23]. Circ-RanGAP1 sponges miR-877-3p to raise
464 VEGFA production and boosts gastric cancer invasion and metastasis [24]. Herein,
465 circLDLR was confirmed to be predominantly positioned in the cytoplasm of CRC
466 cells, representing that circLDLR might deed as a miRNA sponge. Our results showed
467 that among all the potential miRNAs bound by circLDLR, miR-30a-3p, which is
468 downregulated in CRC tissues[25], interacted with circLDLR in CRC cells. Moreover,
469 we demonstrated that circLDLR exerted its function as a ceRNA (competing
470 endogenous RNA) through competitive binding to miR-30a-3p. It has been reported
471 that circRNAs mediate their functions via other mechanisms, such as translation to
472 produce functional peptides and interaction with RNA-binding proteins [22]. We used
473 a detailed database named circRNADb, which contains human circRNAs with
474 protein-coding annotations [26], to investigate whether circLDLR can be translated
475 into a functional protein. Our results indicated circLDLR lacking a protein-coding
476 sequence (Supplementary Fig. S2). However, we could not exclude the possibility that
477 circLDLR exerts its function via other mechanisms.
478 SOAT1, also known as cholesterol acyltransferase 1 (ACAT1), is a key player in
479 cellular cholesterol homeostasis [20]. It has been informed that SOAT1 is widely
480 expressed in different types of cells, highly expressed in various tumors as well [27].
481 More importantly, nevanimibe HCl, a novel SOAT1 inhibitor, was used in a phase 1
482 study of adrenocortical carcinoma [28]. In the current study, our findings showed that
483 the direct target gene of miR-30a-3p is SOAT1. CircLDLR could control SOAT1
484 production by restraining miR-30a-3p. Moreover, SOAT1 suppression could

485 significantly inhibit circLDLR-mediated tumorigenesis and the elevated contents of
486 T-CHO and LDL-C in CRC cells. Therefore, the circLDLR/miR-30a-3p axis
487 modulates CRC tumorigenesis and cholesterol levels via SOAT1.

488 In conclusion, we first demonstrated the clinical significance of circLDLR and
489 revealed that circLDLR promoted CRC cell tumorigenesis and increased cholesterol
490 levels via miR-30a-3p/SOAT1 signaling (Fig. 8). Based on our consequences, we trust
491 that circLDLR may serve as a encouraging curative gene and prognostic predictor in
492 CRC.

493 **Abbreviations**

494 CRC: Colorectal cancer; SOAT1: Sterol O-acyltransferase 1; CircRNAs: Circular
495 RNAs; RIP: RNA immunoprecipitation; FISH: Fluorescence in situ hybridization;
496 LDLR: Low-density lipoprotein receptor; OS: Overall survival; mLDLR: LDLR
497 mRNA; CeRNA: Competing endogenous RNA.

498 **Ethics approval and consent to participate**

499 This study was approved by the First Affiliated Hospital of Soochow University
500 (Suzhou, China; 2020084).

501 **Consent for publication**

502 Not applicable.

503 **Competing interests**

504 The authors declare that they have no competing interests.

505 **Availability of data and materials**

506 For all data requests, please contact the corresponding author.

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517 **Authors' contributions**

518 The authors checked and approved the final manuscript. XGZ, GBZ and TGS
519 designed all experiments, YJC and YQC collected clinical samples, RQW and JYW
520 performed all experiments. QHX and LQS performed the data analysis. The
521 manuscript was wrote by RQW and revised by XLD, TGS and WCC.

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615

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Figure legends

Fig. 1 CircLDLR is elevated in CRC tissues and positively related with a poor prognosis in patients with CRC. a The length distribution of exonic circRNAs. **b**, **c** Schematic illustration of the differentially expressed circRNAs in CRC tissues. **d** The fold change in circLDLR expression between CRC tissues and normal adjacent tissues was analyzed by qRT-PCR. **e** Relative expression of circLDLR in CRC cell lines compared to that in the NCM-460 cell line. **f** Kaplan-Meier analysis of the overall survival of CRC patients stratified into high and low circLDLR expression groups. *$P < 0.05$; ***$P < 0.001$; NS, no significance.

Fig. 2 circLDLR characterization in colorectal cancer. a Schematic diagram of circLDLR shows that it is generated by the circlization of LDLR exons 13 and 14. CircLDLR was scouted by qRT-PCR, which sequence was confirmed via Sanger sequencing. Red arrows used to indicate the special splicing junction of circLDLR. **b** CircLDLR expression in RKO cells detected by qRT-PCR followed by agarose gel electrophoresis showing that divergent primers amplified circLDLR in cDNA but not genomic DNA (gDNA). GAPDH served as a negative control. **c** After reverse transcription using random hexamer or oligo (dT)18 primers, the relative expression of circLDLR and mLDLR was analyzed by qRT-PCR. **d** Relative RNA contents were detected by qRT-PCR, then normalized to the value analyzed in the mock group. **E** Relative expression of circLDLR and mLDLR was detected by qRT-PCR after we treated them using actinomycin D at the several time points. **f** The abundance of circLDLR and mLDLR in cytoplasmic and nuclear parts of RKO cells was evaluated

639 by qRT-PCR. We applied U6 and GAPDH as positive controls for the cytoplasmic

640 and nuclear fractions, respectively. **g** The localization of circLDLR in RKO cells was

641 scouted by FISH. Nuclei were stained with DAPI (blue), and circLDLR probes were

642 labeled with Cy3 (red). Scale bar, 20 µm. CircLDLR, the circular RNA derived from

643 exons 13 and 14 of the LDLR gene; Data are presented as the mean±SD of three

644 independent experiments. **P < 0.01; ***P < 0.001.

645 **Fig. 3 CircLDLR suppression inhibits CRC malignant behaviour and increases**

646 **cholesterol levels in vitro. a** The circLDLR and mLDLR expression was assessed in

647 RKO and HCT116 cells transfected with five independent siRNAs targeting

648 circLDLR by qRT-PCR. **b** Cell proliferation was scouted at the indicated time points

649 by CCK-8 assays evaluating HCT116 cells and RKO cells stimulated with si-NC or

650 si-circLDLR. **c** EdU analysis of the proliferative ability of HCT116 cells and RKO

651 cells treated with si-NC or si-circLDLR. Representative images are shown. Scale bar,

652 200 µm. Statistical analysis of the EdU-positive cell percentage in transfected GC

653 cells is shown in the bar graph. **d** The cell migration and invasion of CRC cells were

654 examined by Transwell assays after cells were transfected with si-circLDLR or si-NC.

655 Representative images are shown. Scale bar, 200 µm. Statistical analysis of the

656 migrated and invaded cell numbers is shown in the bar graph. **e** The production of

657 T-CHO and LDL-C was assessed in CRC cells transfected with si-NC or si-circLDLR.

658 Data are presented as the mean±SD of three independent experiments. *P < 0.05; **P

659 < 0.01; ***P < 0.001.

660 **Fig. 4 CircLDLR overexpression facilitates CRC malignant behaviour and**

increases cholesterol levels in vitro. a The expression of circLDLR in RKO and HCT116 cells transfected with a circLDLR-overexpression vector (circLDLR-OE) or the control vector (Vector) was assessed by qRT-PCR. **b** Cell proliferation was scouted at the indicated time points by CCK-8 assays evaluating RKO cells and HCT116 cells transfected with circLDLR-OE or Vector. **c** EdU analysis of the proliferative ability of RKO cells and HCT116 cells transfected with circLDLR-OE or Vector. Representative images are shown. Scale bar, 200 µm. Statistical analysis of the EdU-positive cell percentage in transfected CRC cells is shown in the bar graph. **d** The cell migration and invasion of CRC cells were examined by Transwell assays after cells were transfected with circLDLR-OE or Vector. Representative images are shown. Scale bar, 200 µm. Statistical analysis of the migrated and invaded cell numbers is shown in the bar graph. **e** The production of T-CHO and LDL-C in CRC cells transfected with circLDLR-OE or Vector were appraised. Data are presented as the mean±SD of three independent experiments. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Fig. 5 CircLDLR acts as a miRNA sponge for miR-30a-3p. a RIP assays were carried out using an AGO2-specific antibody and SW480 or HT29 cells, and the richness of circLDLR was scouted by qRT-PCR. **b** Schematic illustration showing the 109 overlapping miRNAs with potential binding to circLDLR predicted by miRanda, RNAhybrid and TargetScan. **c** Schematic illustration showing that miR-30a-3p was verified to be one of the 11 predicted miRNAs associated with tumor progression among the 109 overlapping miRNAs in different CRC cell lines. **d** Lysates prepared from circLDLR-OE SW480 and HT29 cells were incubated with biotinylated probes

683 against circLDLR, and then an RNA pull-down assay was performed. qRT-PCR was
684 carried out to prove the contents of circLDLR and miR-30a-3p. **e** The production of
685 circLDLR in different CRC cell lines transfected with miR-30a-3p mimics or mimic
686 NC were evaluated by qRT-PCR. **f** The circLDLR and miR-30a-3p colocalization in
687 RKO cells was detected by RNA FISH. Nuclei were stained with DAPI (blue).
688 CircLDLR probes were labeled with Cy3 (red), and miR-30a-3p probes were labeled
689 with FAM (green). Scale bar, 20 µm. **g** EdU analysis of the proliferative ability of
690 RKO cells transfected with sh-circLDLR or cotransfected with sh-circLDLR and
691 miR-30a-3p inhibitors. EdU analysis of the proliferative ability of SW480 cells
692 treated with circLDLR-OE or co-transfected with circLDLR-OE and miR-30a-3p
693 mimics. Representative images are shown. Scale bar, 200 µm. Statistical analysis of
694 the EdU-positive cell percentage in transfected RKO and SW480 cells is displayed in
695 the bar graph. **h** The cell migration and invasion of RKO cells transfected with
696 sh-circLDLR or cotransfected with sh-circLDLR and miR-30a-3p inhibitors were
697 examined. The cell migration and invasion of SW480 cells transfected with
698 circLDLR-OE or co-stimulated with circLDLR-OE and miR-30a-3p mimics were
699 examined. Representative images are shown. Scale bar, 200 µm. Statistical analysis of
700 the migrated and invaded cell numbers is shown in the bar graph. **i** The T-CHO and
701 LDL-C contents in RKO cells transfected with sh-circLDLR or cotransfected with
702 sh-circLDLR and miR-30a-3p inhibitors were assessed. The T-CHO and LDL-C
703 contents in SW480 cells treated with circLDLR-OE or cotransfected with
704 circLDLR-OE and miR-30a-3p mimics were assessed. Data are presented as the

mean±SD of three independent experiments. **$P < 0.01$; ***$P < 0.001$; NS, no significance.

Fig. 6 SOAT1 is a downstream target of miR-30a-3p. a RKO and SW480 cells were transfected with miR-30a-3p mimics or inhibitors. SOAT1 expression was scouted by qRT-PCR. **b** Relative activities of luciferase were measured in HEK293T cells after transfection with SOAT1-Mut or SOAT1-WT and miR-30a-3p mimics or mimic NC. **c** Overexpression of miR-30a-3p restrained the protein production of SOAT1. Suppression of miR-30a-3p raised the expression of SOAT1 protein. **d** Knockdown of circLDLR (sh-circLDLR) inhibited the protein expression of SOAT1. Overexpression of circLDLR (circLDLR-OE) increased the protein expression of SOAT1. **e** Knockdown of miR-30a-3p reversed the sh-circLDLR-induced downregulation of SOAT1 expression in RKO cells. Overexpression of miR-30a-3p reversed the circLDLR-OE-induced upregulation of SOAT1 expression in SW480 cells. GAPDH deeded as a loading control. **f** EdU analysis of the cell proliferation ability in SW480 and HT29 transfected with miR-30a-3p inhibitors or cotransfected with si-SOAT1 and miR-30a-3p inhibitors. **g** Cell migration and invasion in SW480 and HT29 transfected with miR-30a-3p inhibitors or cotransfected with si-SOAT1 and miR-30a-3p inhibitors were examined. **h** The contents of T-CHO and LDL-C in SW480 and HT29 cells transfected with miR-30a-3p inhibitors or cotransfected with si-SOAT1 and miR-30a-3p inhibitors were assessed. **i** EdU analysis of the cell proliferation ability in SW480 and HT29 transfected with circLDLR-OE or cotransfected with si-SOAT1 and circLDLR-OE. **j** Cell behaviors of migration and

727 invasion in HT29 and SW480 cells transfected with circLDLR-OE or cotransfected

728 with si-SOAT1 and circLDLR-OE were examined. **k** The contents of T-CHO and

729 LDL-C in SW480 and HT29 cells transfected with circLDLR-OE or cotransfected

730 with si-SOAT1 and circLDLR-OE were assessed. Data are presented as the mean±SD

731 of three independent experiments. *P < 0.05; **P < 0.01; ***P < 0.001; NS, no

732 significance.

733 **Fig. 7 CircLDLR knockdown restrains CRC tumor growth and metastasis in**

734 **vivo. a** Representative images of subcutaneous xenograft tumors from sh-circLDLR

735 group and the sh-NC group (n=5). **b**, **c** In comparison with the sh-NC group, the

736 sh-circLDLR group had tumors with observably decreased volume (**b**) and weight (**c**).

737 **d** Representative images of subcutaneous xenograft tumors from the circLDLR-OE

738 group and the Vector group (n=5). **e**, **f** In comparison with the Vector group, the

739 circLDLR-OE group had tumors with observably increased volume (**e**) and weight (**f**).

740 **g** Representative images of mouse lungs six weeks after transplantation. **h, i** Images

741 of HE staining are shown (**h**), and the tumor area was measured (**i**). **j** Representative

742 images of mouse lungs six weeks after transplantation. **k, l** Images of HE staining are

743 shown (**k**), and the tumor area was measured (**l**). Data are presented as the mean±SD

744 of three independent experiments. *P < 0.05; **P < 0.01; ***P < 0.001.

745 **Fig. 8 Schematic diagram showing the regulatory mechanisms of the**

746 **circLDLR/miR-30a-3p/SOAT1 axis in CRC.**

6.7-Wang

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