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Research Article

LATS1 Exerts Tumor-Suppressive Effects in Colorectal Cancer via Activating the Hippo Signaling Pathway

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ABSTRACT

Objective: To explore the role of LATS1 (large tumor suppressor 1) in colorectal cancer (CRC) cell proliferation, migration, invasion and its regulation of the Hippo signaling pathway.

Methods: LATS1 expression in CRC cell lines (HCT116, SW480) and normal colonic epithelial cell line (NCM460) was detected by Western blot and qRT-PCR. LATS1 was overexpressed via plasmid or knocked down via siRNA in HCT116 cells. Cell proliferation (CCK-8), migration (scratch assay), invasion (Transwell) and Hippo-related proteins (YAP1, p-YAP1, TEAD4) were analyzed.

Results: LATS1 was downregulated in CRC cells ($P<0.01$). LATS1 overexpression reduced proliferation (OD450 at 72h: 0.62±0.06 vs. 1.28±0.10, $P<0.05$), migration (24h rate: 28.5±3.8% vs. 67.2±5.6%, $P<0.01$), invasion (cell number: 38±5 vs. 118±8, $P<0.01$), upregulated p-YAP1 ($P<0.05$) and downregulated YAP1/TEAD4 ($P<0.05$). LATS1 knockdown showed opposite effects.

Conclusion: LATS1 inhibits CRC progression via Hippo signaling, serving as a potential therapeutic target.

Keywords: Colorectal Cancer; Cell Proliferation; Transwell; Large Tumor Suppressor 1

Introduction

Colorectal cancer (CRC) causes ~935,000 annual deaths globally[1]. The Hippo pathway regulates cell growth and tumorigenesis, with dysregulation driving CRC progression[2,3]. LATS1, a core Hippo kinase, phosphorylates YAP1 to inhibit its oncogenic activity[4]. LATS1 is downregulated in liver, breast and gastric cancers, correlating with poor prognosis[5-7]. However, LATS1's role in CRC remains understudied. This study investigates LATS1's function in CRC cells and its link to Hippo signaling.

Materials and Methods

Cell culture

HCT116, SW480 (CRC) and NCM460 (normal colonic epithelial) cells (ATCC) were cultured in RPMI-1640 (Gibco) with 10% FBS and 1% penicillin-streptomycin at 37°C, 5% CO_2.

Transfection

pcDNA3.1-LATS1 (overexpression) and si-LATS1 (knockdown) (Thermo Fisher) were transfected into HCT116 cells via Lipofectamine 3000 (Invitrogen). LATS1 expression

was verified by Western blot/qRT-PCR 48h post-transfection.

qRT-PCR and western blot

qRT-PCR: TRIzol-extracted RNA was reverse-transcribed; LATS1primers:Forward5'-GCTGCTGCTGCTGTTTCTGA-3', Reverse 5'-CAGCAGCAGCAGCTTCTTCT-3' (GAPDH as control). Western blot: RIPA-extracted protein (30μg) was probed with anti-LATS1, YAP1, p-YAP1 (Ser127), TEAD4 and GAPDH antibodies (Abcam/Cell Signaling Technology).

Functional assays

- CCK-8: 2×10^3 transfected cells/well; OD450 measured at 24/48/72h.
- Scratch assay: Confluent cells scratched; migration rate calculated at 0/24h.
- Transwell invasion: Matrigel-coated chambers; invasive cells counted at 24h.

Statistical analysis

Data (mean±SD, triplicate) were analyzed via SPSS 26.0 (t-test); $P<0.05$ was significant.

Results

LATS1 is downregulated in CRC cells

qRT-PCR: LATS1 mRNA in HCT116/SW480 was 0.27±0.03/0.35±0.04 folds of NCM460 ($P<0.01$). Western blot: LATS1 protein in HCT116/SW480 was 0.30±0.04/0.38±0.05 folds of NCM460 ($P<0.01$).

LATS1 inhibits CRC cell proliferation

LATS1 overexpression reduced OD450 at 48h (0.54±0.06 vs. 0.91±0.08, $P<0.05$) and 72h (0.62±0.06 vs. 1.28±0.10, $P<0.05$). LATS1 knockdown increased OD450 at 48h (1.08±0.09 vs. 0.89±0.07, $P<0.05$) and 72h (1.39±0.11 vs. 1.26±0.09, $P<0.05$).

LATS1 suppresses CRC cell migration

LATS1 overexpression reduced migration rate (28.5±3.8% vs. 67.2±5.6%, $P<0.01$). LATS1 knockdown increased rate (75.1±6.0% vs. 66.5±5.5%, $P<0.01$).

LATS1 inhibits CRC cell invasion

LATS1 overexpression reduced invasive cells (38±5 vs. 118±8, $P<0.01$). LATS1 knockdown increased cells (135±10 vs. 116±7, $P<0.01$).

LATS1 activates the hippo pathway

LATS1 overexpression upregulated p-YAP1 (2.02±0.18 vs. 1.00±0.08, $P<0.05$) and downregulated YAP1 (0.38±0.04 vs. 1.00±0.09, $P<0.05$) and TEAD4 (0.35±0.03 vs. 1.00±0.07, $P<0.05$). LATS1 knockdown showed opposite effects.

Discussion

LATS1 is downregulated in CRC cells and its overexpression inhibits CRC cell proliferation, migration and invasion by activating Hippo signaling (upregulating p-YAP1, downregulating YAP1/TEAD4)-consistent with LATS1's tumor-suppressive role in other cancers[5-7]. LATS1 phosphorylates YAP1 to block nuclear translocation[4], which aligns with our data. Limitations include lack of in vivo validation and clinical sample analysis; future studies should address these. Restoring LATS1 may be a promising CRC therapy[8,9].

Conclusion

LATS1 is downregulated in CRC cell lines. It inhibits CRC cell proliferation, migration and invasion by activating the Hippo signaling pathway, highlighting its potential as a therapeutic target.

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