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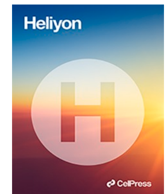

Research article

TL1A promotes metastasis and EMT process of colorectal cancer

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A R T I C L E I N F O

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A B S T R A C T

Background: Metastasis is the major problem of colorectal cancer (CRC) and is correlated with the high mortality. Tumor necrosis factor-like cytokine 1A (TL1A) is a novel regulatory factor for inflammatory diseases. This work aimed to investigate the role of TL1A in CRC metastasis.
Method: AOM/DSS-induced mouse model, xenograft tumor model and metastasis murine model were established to mimic the colitis-associated CRC and investigate CRC growth and metastasis *in vivo*. Colon tissues were assessed by hematoxylin/eosin (HE) staining and immunohistochemistry (IHC). CRC cell metastasis *in vivo* was observed using *in vivo* imaging system (IVIS). Cell viability and proliferation were examined using cell counting kit 8 (CCK-8) and EdU experiments. The expression of tumor growth factor β (TGFβ) and metastatic biomarkers were detected using western blotting experiment. The *in vitro* cell metastasis was measured by Transwell.
Results: Knockdown of TL1A notably suppressed the generation of colonic tumors in azoxymethane/dextran sodium sulfate (AOM/DSS) model, suppressed *in vivo* CRC cell growth, as well as lung and liver metastasis. The inflammation response and inflammatory cell infiltration in tumor sites were decreased by TL1A depletion. The *in vitro* CRC cell growth and metastasis was also suppressed by shTL1A, along with altered expression of epithelial mesenchymal transition (EMT) biomarkers. TL1A depletion suppressed the level of the TGF-β1 receptor (TβRI) and phosphorylation of Smad3 in CRC cells. Stimulation with TGF-β recovered the CRC cell migration and invasion that suppressed by shTL1A.
Conclusion: Our work implicated TL1A as a promoter of CRC generation and metastasis and defines TGF-β/Smad3 signaling as mediator of TL1A-regualated CRC cell metastasis.

1. Introduction

Colorectal cancer (CRC) ranks the top three most common cancer and presents the high cancer-related death rate worldwide [1,2]. Despite of the advances on targeted therapy and immunotherapy have made a great change in clinical therapy for CRC in recent years, the local and systemic recurrence of CRC remain a great obstacle in clinical practice [3,4]. It is worth to be noted that liver and lung metastasis of CRC are frequently occurred and correlated to over 50 % of CRC-related death [5,6]. Therefore, further exploration on molecular mechanisms of CRC metastasis is imperative for development of effective therapies against CRC.

It is well-known that the presence of epithelial-mesenchymal transition (EMT) phenotype is closely correlated with high metastatic potential of solid cancers including CRC [7]. During the process of EMT, cancer cells present suppressed features of epithelial cells (especially E-cadherin) and enhanced mesenchymal features (such as N-cadherin, Vimentin, and Snail) [8], hence exhibit higher potential to migrate and invade to blood vessels and metastatic foci [9]. The activation of EMT is dynamically controlled by various

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regulators from the tumor microenvironment (such as the inflammatory factors interleukin-6 (IL-6), IL-1β, and TGF-β) and intracellular signals [10,11].

Tumor necrosis factor (TNF)-like cytokine 1A (TL1A) is a member of the TNF superfamily and is a type 2 transmembrane protein that mainly self-assembles into stable trimers [12]. TL1A is constitutively expressed in endothelial cell and is upregulated in response to tumor necrosis factor-α (TNF-α) stimulation [13]. Studies have widely indicted the function of TL1A in immune and inflammation-related diseases, and soluble TL1A (sTL1A) that produced by TNF-α-converting enzyme (TACE) cleavage or alternative splicing [14,15] could be detected in serum from patients with inflammatory autoimmune diseases such as ankylosing spondylitis and rheumatoid arthritis [16]. As an important mediator of inflammation, TL1A has recently drawn great attention in cancer research area [17–19]. Noteworthy, high level of TL1A expression was found in the intestinal specimens of patients with ulcerative colitis and Crohn's disease [20,21]. However, the functions of TL1A in CRC is unclear.

In this work, we established *in vitro* and *in vivo* models and aimed to investigate the relative expression and biological function of TL1A in CRC progression and metastasis, as well as determine the correlated molecular mechanisms.

2. Materials and methods

2.1. Cell lines and transfection

CRC cell lines SW480, LoVo, SW620, RKO, and HCT116, luciferase labeled HCT116, and normal colorectal epithelial cell line FHC were bought from Wuhan Procell (China) and cultured in DMEM medium (Gibco, USA) that contains 10 % FBS (Gibco, USA) in a 37 °C incubator that filled with 5 % CO_2. The shTL1A and negative control (shNC) were bought from GenePharma (China) and transfected with Lipofectamine 2000 (Invitrogen, USA) according to producer's protocol.

2.2. Animals

All experimental procedures were reviewed and approved by the second hospital of Hebei medical university (approval No. ACUC-19-122) and were carried out in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals.

2.3. AOM/DSS-induced CRC model

All experiments were approved by the Animal Care and Use Committee of the second hospital of Hebei medical university. Male C57BL/6 mice that aged 6–8 weeks were bought from the Vital River Laboratory (Beijing, China). Mice were kept in a specific pathogen free condition. Mice were divided into sham, model, and model plus treatment group, and each group contained 10 mice. We choose 10 mice for each group to rule out the failed establishment of AOM/DSS-induced CRC and accidental death of mice, and five mice of each group were included in result analysis. The AOM/DSS-induced mouse model was established to mimic the colitis-associated CRC. In brief, Mice were divided into three groups: control group, AOM/DSS group, and shTL1A group. To induce CRC, mice were intraperitoneally injected with AOM (10 mg/kg body weight; Sigma, USA) for once and then fed with standard diet for one week. After that, mice were fed with 2.5 % DSS (Sigma, USA) in drinking water for one week, followed by fed with normal diet for another two weeks [22]. This DSS feeding cycle was repeated for 3 times. The mice were then randomly divided into AOM/DSS group and shTL1A group. Mice in shTL1A group received intraperitoneal injection with shTL1A every 2 days for 3 weeks. Mice in control and AOM/DSS group were treated with negative control shRNAs. After the treatment for 3 weeks, mice were sacrificed, and the colons were collected for subsequent study. The colon tissues were photographed. After that, colons were cut into pieces, fixed in 10 % formalin, dehydrated, and made into 5 μm thick paraffin-embedded samples. The samples were analyzed with hematoxylin and eosin (HE) and immunohistochemical (IHC) experiment.

2.4. In vivo xenograft and metastatic mouse model

BALB/C nude mice that aged 6-week-old were bought from Vital River Laboratory (Beijing, China) and subjected to xenograft mouse model and metastatic mouse model. In the xenograft mode, $5x10^6$ HCT116 cells suspended in saline was subcutaneously inoculated into the fat pad of each mouse. The length and width of tumors were measured every 5 days for 30 days and tumor volume was calculated. For treatment, shTLA1 was subcutaneously injected around the tumor site every 3 days from day 5 after tumor inoculation. The mice were then sacrificed, and tumors were collected to measure the weight and levels of proteins.

The metastatic mouse model was established by injection of $1x10^6$ luciferase labeled HCT116 cells (100 μl saline) through tail vein. Every week, the mice were observed under an IVIS Imaging System after intraperitoneal injections of D-luciferin (150 mg/kg body weight). The shTL1A was administrated through intraperitoneal injection every 3 days, and mice were sacrificed 9 weeks after treatment.

2.5. Enzyme-linked immune sorbent assay (ELISA)

The levels of inflammatory cytokines, including IL-1β, IL-6, and TGF-β1, in colon tissues or culture medium were measured using commercial assay kits (elabscience, USA) according to manufacturer's introduction.

2.6. IHC analysis

Tissues samples were deparaffinized in xylene and rehydrated in a series of alcohol, followed by antigen retrieval using citrate buffer. The tissues were then incubated in 3 % H_2O_2 to block endogenous peroxidase and hatched with primary antibody overnight at 4 °C. After that, sections were incubated with HRP-labeled polymer and 3,3-diaminobenzidine chromogen solution (SolarBio, China). The nuclei were counterstained with hematoxylin (SolarBio, China).

2.7. Cell viability and proliferation

Cell viability and proliferation were detected using cell counting kit 8 (CCK-8) and EdU assay. For CCK-8 assay, cells were seeded into 96-well plate and incubated for 24 h. CCK-8 reagent was added into culture medium for 2 h, and the optical density was measured at 450 nm using microplate reader (Thermo, USA). EdU assay was performed using EdU assay kit (Thermo, USA) in line with manufacturer's introduction.

2.8. Transwell assay

CRC cells (2×10^5/well) were suspended in 200 μl serum-free medium and placed on the upper chamber of a 24-well Transwell chamber (Corning, USA). The medium in the bottom chamber was supplied with DMEM containing 10 % FBS. After incubation for 48 h, the migrated cells on the underside of the chambers were fixed and stained with 0.2 % crystal violet in methanol. Images were taken with a microscope (Leica, Germany) and counted.

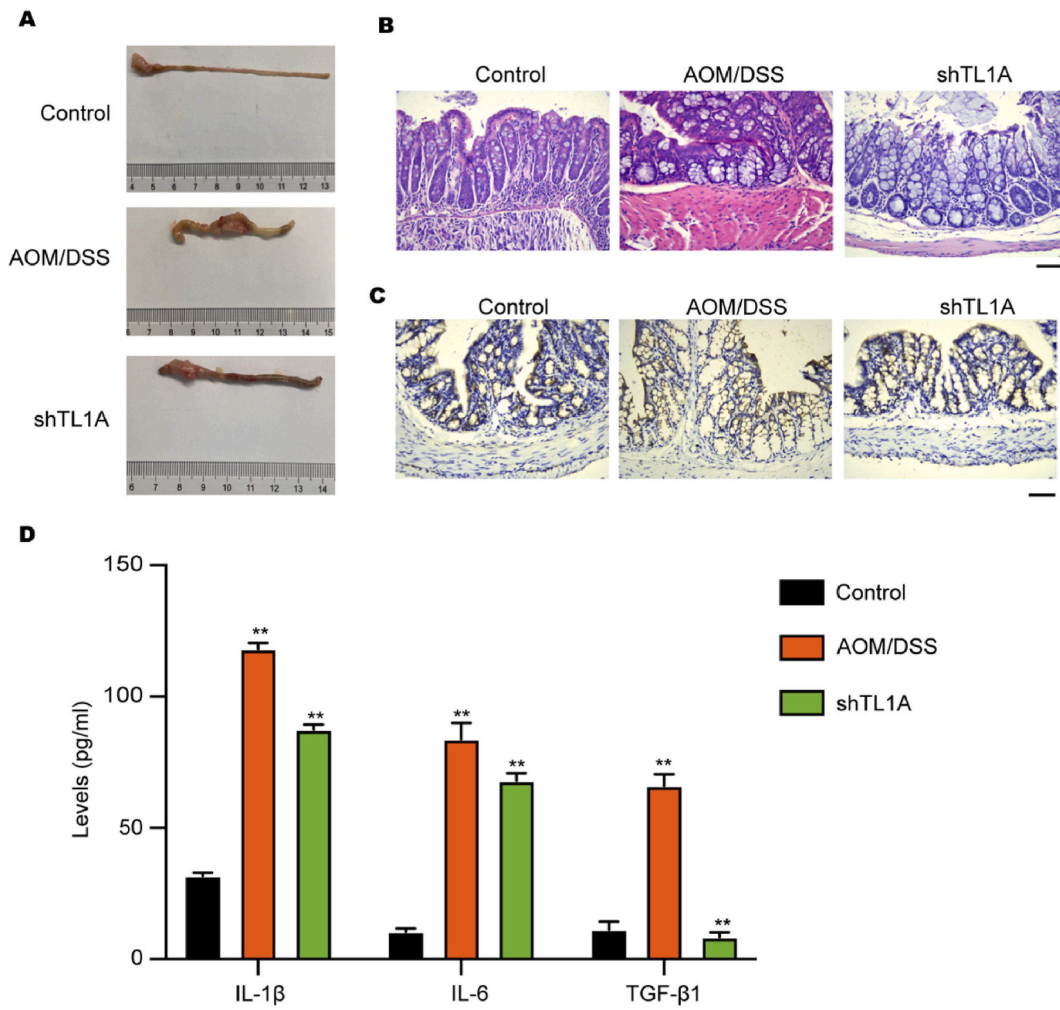

Fig. 1. TL1A regulates the AOM/DSS-induced CRC progression *in vivo*. An AOM/DSS murine model was established and treated with shTL1A. (A) The length and tumor sites in colon tissues were shown. (B) He analysis of the colon tissues. (C) IHC analysis of Ki67 in colon tissues. (D) The levels of IL-1β, IL-6, and TGF-β were measured by ELISA experiment. **$p < 0.01$.

2.9. Western blotting assay

The cells were lysed using RIPA lysis buffer (Invitrogen, USA) and protein concentration was measured with BCA assay kit (Beyotime, China). After separation in SDS-PAGE and blotting to PVDF membranes (Millipore, USA), the blots were incubated with primary antibody against E-Cadherin, Vimentin, TL1A, Smad3, phosphorylated smad3, TβR1 and β-actin (Abcam, USA) overnight at 4 °C. Next day, the blots were probed with HRP-conjugated secondary antibody and were detected using enhanced chemiluminescence (ECL; Millipore, USA).

2.9.1. qPCR assay

Total RNA was extracted from cells with TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions. The cDNA was synthesized using the PrimeScript RT Master Mix (TAKARA, Japan) and subjected to qPCR using SYBR Green Premix (TAKARA, Japan). The expression of TL1A was calculated according to the $2^{-\Delta\Delta Ct}$ method and normalized to GAPDH expression.

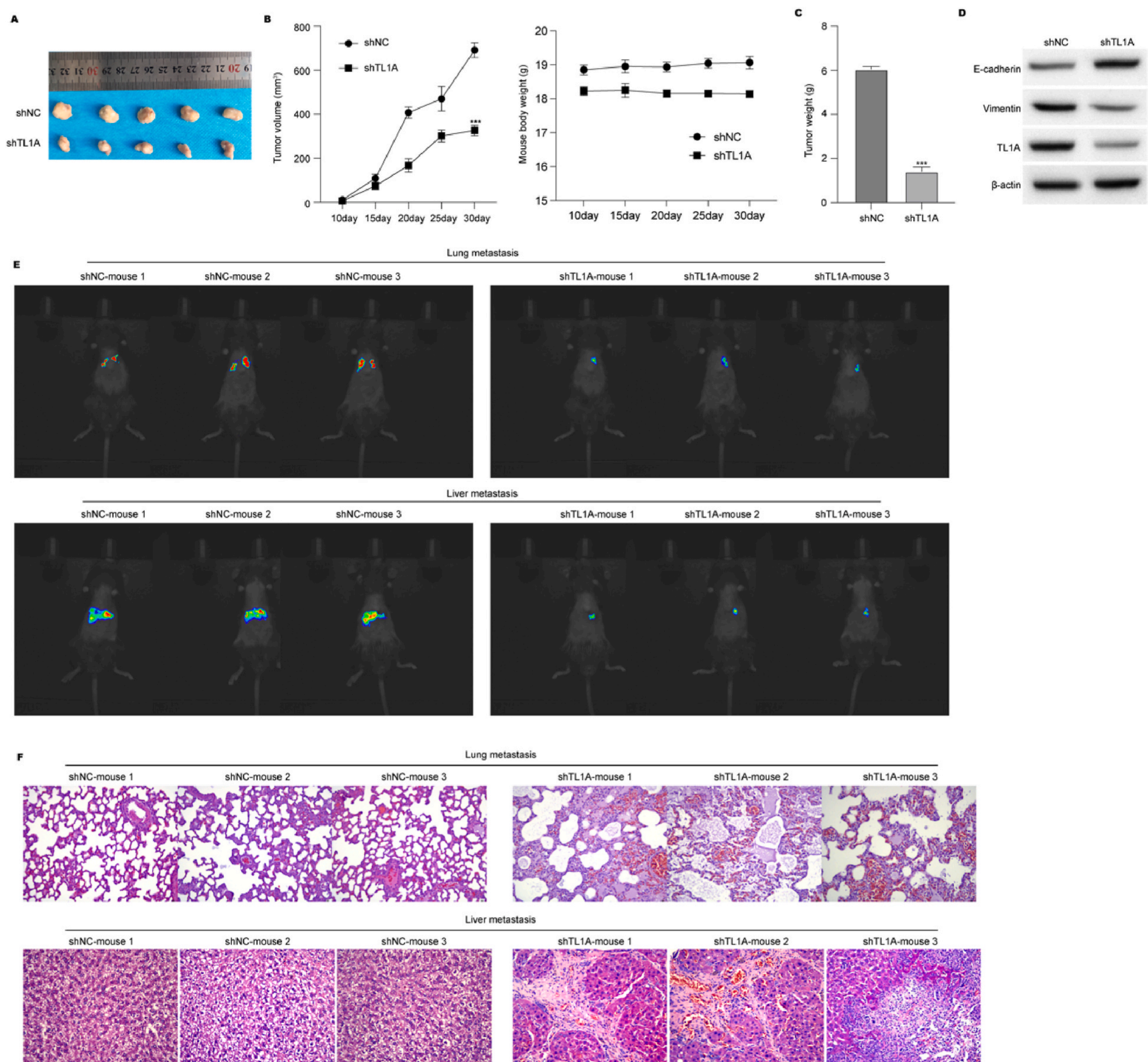

Fig. 2. TL1A regulates the growth and metastasis of CRC in mouse models. (A–D) A xenograft tumor model was established using HCT116 cells. Then (A) tumor size and mouse body weight, (B) tumor growth cure, (C) tumor weight was recorded. (D) The expression of E-cadherin, Vimentin, and TL1A was measured by western blotting assay. (E–F) Metastatic murine model was established using tail vein injection of luciferase-labeled HCT116 cells. (A) The lung and liver metastasis of HCT116 cells was detected using IVIS system. (F) The metastatic sites on lung and liver tissues were examined using HE analysis. ***P < 0.001 vs shNC.

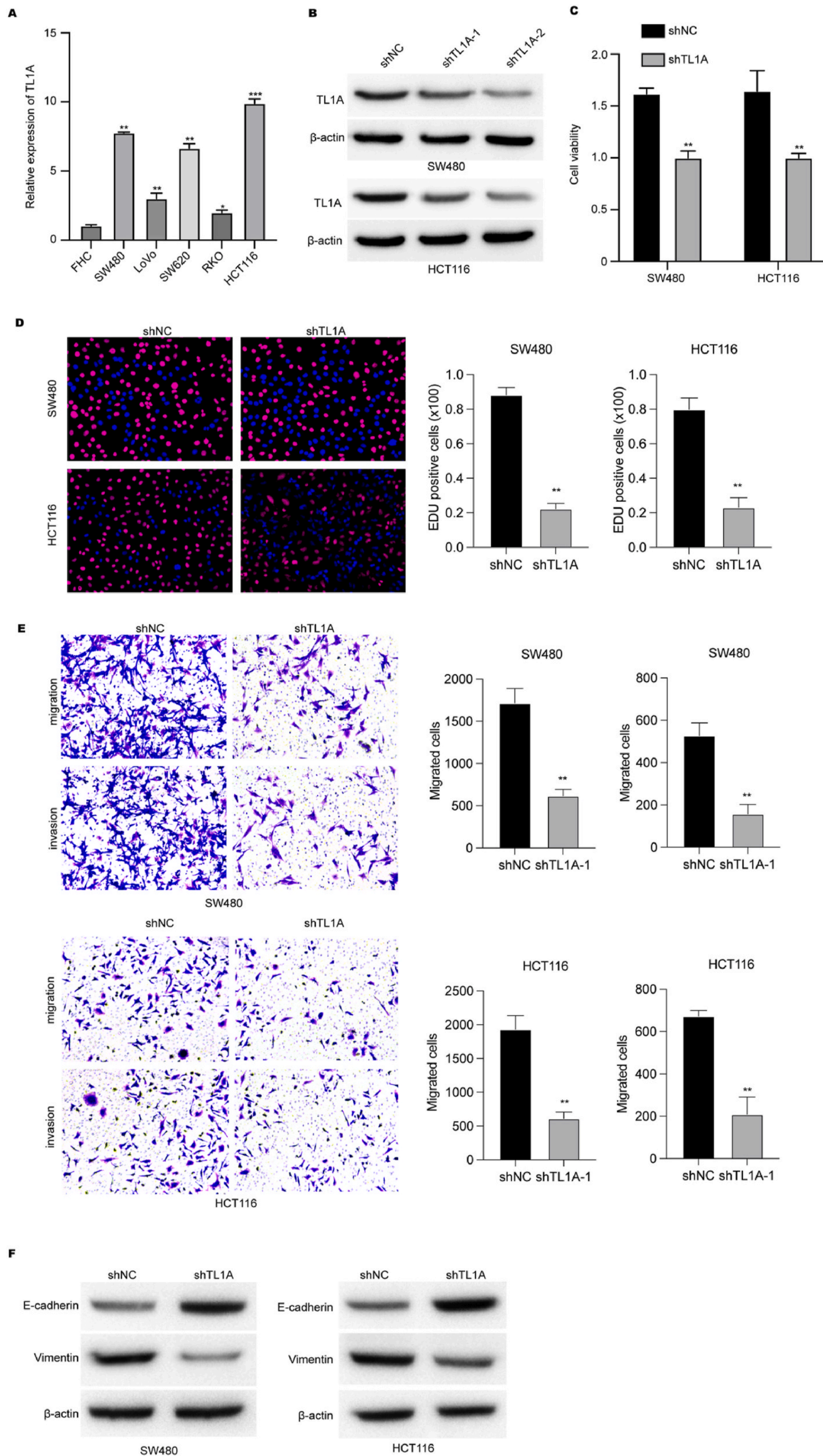

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Fig. 3. TL1A depletion suppressed the *in vitro* growth and metastasis of CRC cells. (A) The RNA level of TL1A in cell lines was detected using qPCR assay. (B–F) SW480 and HCT116 cells were transfected with shTL1A or shNC, then (B) protein level of TL1A, (C) cell viability, (D) cell proliferation, (E) cell migration and invasion, and (F) protein levels of E-cadherin and Vimentin were assessed using western blotting, CCK-8, EdU, and Transwell, respectively. $^{**}p < 0.01$vs shNC.

2.10. Statistical analysis

The statistical analyses in this study were performed using GraphPad Prism 7.0 software. The differences between two or multiple groups were analyzed using the Student's *t*-test or one-way ANOVA test. The *p* value < 0.05 was set as statistically significant.

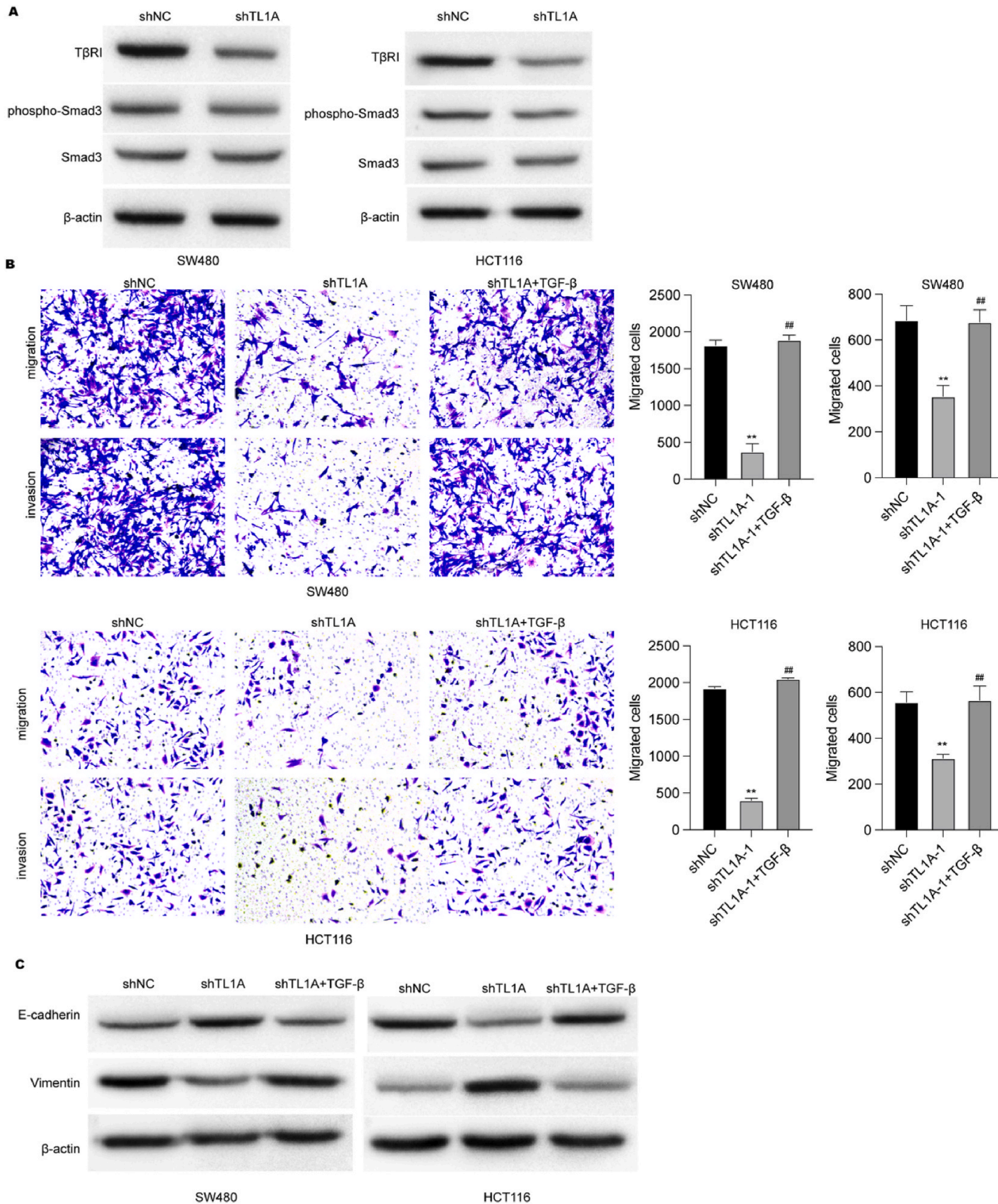

Fig. 4. TL1A regulates CRC cell phenotypes via TGF-β/Smad3 signaling. (A) The protein levels of TβRI and phosphorylated Smad3 in CRC cells were detected by western blotting assay. (B) CRC cells were transfected with shTL1A and stimulated with TGF-β, then (B) cell migration and invasion were detected by Transwell experiment and (C) expression of E-cadherin and Vimentin was checked by western blotting assay. $^{**}P < 0.01$ vs shNC; $^{##}P < 0.01$ vs shTL1A.

3. Results

3.1. TL1A regulates the AOM/DSS-induced CRC progression in vivo

We used a well-established AOM/DSS mouse model to mimics chronic intestinal inflammation to investigate the role of TL1A in colitis-associated CRC development. We performed depletion of TL1A in AOM/DSS mouse and observed that the mice in model group exhibited notable higher level of TL1A compared with the control mice, whereas shTL1A significantly repressed TL1A expression in colon tissues (Fig. S1A). We observed decreased length of colon and multiple tumors in colon and rectum (Fig. 1A) in AOM/DSS-induced mice. Histological analysis revealed destructed structure of crypt and massive inflammatory cell infiltration (Fig. 1B), along with increased expression of Ki-67 protein (Fig. 1C) in colon tissues from AOM/DSS-induced mice, as compared with the mice in control group. Moreover, the production of inflammatory factors including IL-1β, IL-6, and TGF-β1, were notably elevated compared with control mice (Fig. 1D). In contrast, the depletion of TL1A with shRNAs markedly recovered the length of colon, reduced the tumor number, improved the crypt structure, and alleviated infiltration of inflammatory cells (Fig. 1). Moreover, analysis with online GEPIA website indicated the significant higher level of TL1A in CRC tumor tissues compared with the non-tumor tissues (Fig. S2). These data indicated that TL1A knockdown significantly alleviated colitis-associated CRC development *in vivo*.

3.2. TL1A regulates the growth and metastasis of CRC in mouse models

We nest investigated the effects of TL1A on CRC using xenograft tumor model and metastatic model. The results from xenograft mouse model manifested that depletion of TL1A notably suppressed the tumor size (Fig. 2A), tumor growth (Fig. 2B), and tumor weight (Fig. 2C) compared with the control group. Besides, shTL1A did not affect the body weight of mice, which suggested its safety (Fig. 2B). Noteworthy, the level of E-cadherin was significantly increased, and Vimentin was decreased in tumor tissues along with the knockdown of TL1A (Fig. 2D). Furthermore, the observation using IVIS system manifested that the mice received tail vein injection of HCT116 cells developed notable tumors at lung and liver tissues in control group, whereas the cells depleted of TL1A exhibited significantly suppressed metastasis ability (Fig. 2E). Results from HE analysis on liver tissues confirmed the less metastatic foci in lung and liver tissues from shTL1A group compared with the control group (Fig. 2F).

3.3. TL1A depletion suppressed the in vitro growth and metastasis of CRC cells

Subsequently, we examined the *in vitro* effects of TL1A in CRC cells. First, we observed notably increased expression of TL1A in CRC cells, including SW480, LoVo, SW620, RKO, and HCT116, compared with the normal FHC cell line (Fig. 3A), among which the SW480 and HCT116 exhibited the highest level and were hence used for following shRNA transfection. The efficacy of shTL1A in SW480 and HCT116 cells was verified by notably decreased level of TL1A (Fig. 3B). To investigate the role of TL1A in CRC cell proliferation and metastasis, we performed CCK-8, EdU assay, and Transwell experiment. Depletion of TL1A significantly suppressed the proliferation (Fig. 3C and D), as well as suppressed the number of migrated and invaded CRC cells (Fig. 3E), compared with the control group. The elevated E-cadherin and deceased Vimentin level under TL1A knockdown further indicated the suppressed metastatic ability of CRC cells under TL1A depletion (Fig. 3F).

3.4. TL1A regulates CRC cell phenotypes via TGF-β/Smad3 signaling

We observed decreased level of TβRI (the TGF-β1 receptor) and suppressed phosphorylation of Smad3 in CRC cells that depleted of TL1A, compared with the control cells (Fig. 4A). To determine whether TGF-β signaling mediate the function of TL1A in CRC cells, we stimulated CRC cells that depleted of TL1A with TGF-β and determined cell migration and invasion. As shown in Fig. 4B, the shTL1A-suppressed migration and invasion of CRC cells through Transwell membranes were recovered by TGF-β stimulation, simultaneously repressed the E-cadherin level and elevated Vimentin expression (Fig. 4C). These data suggested that TL1A regulates CRC cell phenotypes via TGF-β/Smad3 signaling.

4. Discussion

In this study, we identified TL1A as a promoter of metastatic CRC and depletion of TL1A alleviated the development of CRC in colitis-associated CRC murine model and xenograft tumor model, along with suppressed infiltration of inflammatory cells. The evaluation on metastatic CRC murine model further confirmed that TL1A knockdown suppressed the liver and lung metastasis of CRC cells. In recent years, TL1A as a critical regulatory factor of inflammation response has been widely studied in various diseases [23] and anti-TL1A antibody treatment may be an effective treatment manner in inflammatory disorders [20,24,25]. For examples, in the dextran sodium sulfate (DSS) and adoptive T-cell transfer models, myeloid- and T-cell-expressing Tl1a transgenic mice showed elevated collagen deposition, elevated T-cell activation markers and IL-17 expression compared to wild-type mice [26]. TL1A binds to activate the death receptor 3 (DR3) and downstream signaling, consequently participates in gut inflammation and intestinal fibrosis [27,28]. In an asthma mouse model, this TL1A/DR3 axis contributes to the airway inflammation, remodeling, and tissue destruction and may be a promising therapeutic target in asthma [29]. Consistent with these published articles, we suggested that depletion of TL1A reduced the production of inflammatory cytokines including IL-1β, IL-6, and TGF-β1 in both CRC cells and *in vivo* tumor tissues. A recent article revealed that Nonylphenol (NP), an endocrine-disruptor chemical, regulated CRC growth and angiogenesis via

regulating the TL1A [19]. Moreover, TL1A is previously reported to facilitates the lymph angiogenesis via activating VEGFC signaling in lung cancer cells, which contributes to the lymphatic metastasis in lung tumor-bearing mice [30]. However, the effects of TL1A on metastasis of CRC cells as not been elucidated. We for the first time determined that knockdown of TL1A repressed the tumor growth and lung and liver metastasis of CRC cells.

We next explored the potential mechanisms. The EMT process is modulated by a complicated signaling pathways and gene expression [31,32]. And TGF-β1/Smad3 pathway is one of the most classic signaling pathway involving TGF-β1 [33]. For example, rat intestinal epithelial cells that exposed to TGF-β1 for 7 days displayed *in vitro* EMT, as manifested by shift from irregular polygonal shape to the spindle-shaped morphology [34]. Administration with recombinant human bone morphogenetic protein-7 (BMP-7), the member of TGF-β superfamily, could abolish the TGF-β1-induced EMT in intestinal fibrosis both *in vitro* and *in vivo* [34]. It is worth to be noted that the TGF-β1/Smad3 pathway may be involved in TL1A-induced EMT and correlated with the expression of IL-13 and EMT-related transcriptional molecules such as ZEB1 and Snail1 in intestinal tissues of transgenic mice [12]. Besides, Zhang and colleagues showed that anti-TL1A antibodies could ameliorate the inflammation and fibrosis of intestinal tissues in colitic mice with adoptively transferred T cells, which decreased the expression of vimentin and α-SMA and suppressed the TGF-β1/smad3 signaling pathway [35]. Here, in our work, we found that TL1A knockdown inhibited the phosphorylation of Smad3 and stimulation with TGF-β1 reversed the level of phosphorylated Smad3 and abolished the shTL1A-suppressed migration and invasion of CRC cells. These findings suggested that TL1A may modulate the EMT and inflammation response for CRC via the TGF-β1/Smad3 signaling.

5. Conclusion

To summarize, we demonstrated that suppression of TL1A ameliorated the CRC metastasis via inactivating the TGF-β1/smad3 signaling pathway. Our findings raise the possibility that metastatic CRC patients may benefit from TL1A inhibition and provide novel insight into the clinical treatment of CRC.

Data availability statement

No data was used for the research described in the article.

Ethics declarations

All experimental procedures were reviewed and approved by the Hebei Medical University Animal Care and Use Committee (approval No. 2021.R.139) and were carried out in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals.

CRediT authorship contribution statement

Weiwei Niu: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Qian Liu:** Validation, Methodology, Investigation. **Xiaoxia Huo:** Validation, Methodology, Investigation. **Yuxin Luo:** Validation, Software, Methodology, Investigation. **Xiaolan Zhang:** Software, Resources.

Declaration of competing interest

There are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24392.

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