lncRNA NEAT1 promotes the proliferation of hemangioma cells by transcriptionally activating β-catenin via enhancing H3K18 lactylation

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Received May 13, 2025; Accepted October 17, 2025

DOI: 10.3892/mmr.2025.13763

Abstract. Infantile hemangioma (IH), a common vascular tumor, occurs in childhood; however, its pathogenesis has not been fully elucidated. In the present study, the roles and detailed mechanisms of long non-coding RNA (lncRNA) NEAT1 in the progression of hemangioma were further explored. The NEAT1-interacting proteins were selected by analyzing the catRAPID database and lactate dehydrogenase B (LDHB) was predicted to bind with NEAT1. The binding between NEAT1 and LDHB was validated using an RNA immunoprecipitation assay and it was further found that knocking down NEAT1 expression destabilized LDHB by regulating the proteasome pathway. The knocking down of lncRNA NEAT1 also inhibited cellular protein lactylation and downregulated β-catenin. Furthermore, blockade of lactylation via 2-DG and oxamate attenuated the viability and colony formation of hemangioma cells. NEAT1 promoted the lactylation of H3K18 in the promoter region of β-catenin, and blockade of lactylation downregulated β-catenin expression in hemangioma cells. The lactyltransferases alanyl-tRNA synthetase 1 and P300 were regulated by NEAT1 and also positively regulated β-catenin. The levels of β-catenin mRNA and H3K18 lactylation were also found to be elevated in IH tissues. Taken together, the results of the present study revealed that lncRNA NEAT1, which is upregulated in hemangioma, binds with and stabilizes LDHB, subsequently elevates the levels of cellular lactate and H3K18 lactylation, potentiates β-catenin transcription and ultimately enhances the proliferation of hemangioma cells.

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Key words: NEAT1, lactylation, H3K18, lactate dehydrogenase B, β-catenin

Introduction

Infantile hemangioma (IH) is the most common vascular tumor in children, with an incidence of 3-10% (1). Due to its rapid growth, some IHs lead to long-term residual permanent skin damage and might affect the physical and mental health of children (2). Although a number of studies have focused on the mechanisms underlying IH progression, the detailed regulatory mechanisms are still not fully understood.

Long non-coding RNAs (lncRNAs), with a length of >200 nucleotides, have crucial roles in hemangioma cell proliferation and invasion (3,4). A recent study reported that CTBP1-AS2 sponges microRNA (miR)-335-5p, upregulates C-C motif chemokine ligand 2 and subsequently enhances hemangioma angiogenesis and progression (5). MIR4435-2HG, which is secreted by M2 macrophages, targets Heterogeneous nuclear ribonucleoprotein A1 and promotes IH progression (4). Most notably, our previous study revealed that knocking down lncRNA NEAT1 repressed IH progression by sponging miR-33a-5p and regulating the downstream hypoxia inducible factor 1 subunit α (HIF1α)/NF-κB pathway (6). Additional studies have further reported that in hemangioma, lncRNA NEAT1 is positively regulated by alkB homolog 5, RNA demethylase in an m6A modification-dependent manner and promotes hemangioma development by regulating the miR-361-5p/VEGFA pathway (7,8). However, the exact regulatory roles of lncRNA NEAT1 in hemangioma progression are still largely unknown.

Histone lactylation (addition of a lactyl group to a lysine residue) by P300 and KAT8 is a protein modification newly discovered in 2019 that affects transcription (9,10), and has been found to widely participate in disease progression including cancer, atrial fibrillation and keloids (11,12). Recent studies have shown that H3 lysine 18 lactylation (H3K18la) can activate gene transcription (13,14). However, the roles of protein lactylation in hemangioma development are still unclear.

In the present study, the effects of the lncRNA NEAT1/H3K18la/β-catenin signaling pathway on the colony formation ability and viability of hemangioma cells were investigated. Additionally, the detailed mechanism by which NEAT1 regulates β-catenin in hemangioma cells was further investigated.

Materials and methods

Tissue sample information. IH tissues (proliferating stage; median age, 7 months; n=10, Table I) and normal adjacent subcutaneous tissues (n=10) were collected from the Kunming Children's Hospital (Kunming, China) between February 2022 and September 2024. Samples were kept at -80˚C until analysis. Informed consent was obtained from the parents/legal guardians of each patient. The patients received no treatment before surgery. The Ethics Committee of Kunming Children's Hospital approved the present study (approval no. 2021-03-181-K01). The inclusion criteria were as follows: i) The patients were diagnosed with IH (proliferating stage); ii) age of <1 years old; and iii) The hemangioma lesion was located in concealed areas such as the trunk and limbs, and the parents voluntarily opted for surgical removal. The exclusion criteria were as follows: i) Multiple hemangiomas; ii) vascular malformation; and iii) the patients had received any other treatment.

Cell culture and treatments. Hemangioma endothelial cells (HemECs) were prepared following the protocol described in a previous study (15) using the hemangioma sample from patient no. 4 in Table I. The HemECs were cultured in human endothelial serum-free medium (Gibco; Thermo Fisher Scientific, Inc.) supplemented with 10% FBS (Gibco; Thermo Fisher Scientific, Inc.) at 5% CO_2 and 37˚C.

Lipofectamine 3000 (Thermo Fisher Scientific, Inc.) was used to transfect small interfering RNAs (siRNA; 50 nM; Shanghai GenePharma Co., Ltd.) into the cells at 37˚C for 48 h. Then, the cells were collected for reverse transcription-quantitative PCR (RT-qPCR), western blotting, chromatin immunoprecipitation (ChIP)-PCR and cell viability assays. Table SI lists the sequences of the siRNAs.

2-Deoxy-D-glucose (2-DG), oxamate, lactate, MG132, bafilomycin A1 (BafA1), cycloheximide (CHX) and A-485 were purchased from Selleck Chemicals. In the present study, 10 mM 2-DG, 20 mM oxamate and 10 mM lactate were used to treat the HemECs (16-19) (RT-qPCR, western blotting, ChIP-PCR and cell viability assays: 37˚C for 48 h; colony formation assay: 37˚C for 7-9 days), and the protein lactylation was inactivated (2-DG and oxamate) and activated (lactate). At 46.5 and 46 h after transfection of NEAT1 siRNA, 20 μM MG132 (treatment: 1.5 h at 37˚C) and 100 nM BafA1 (treatment: 2 h at 37˚C) were used to suppress the proteosome and lysosome, respectively (20), and the cells were harvested for western blotting after a total time of 48 h of transfection with NEAT1 siRNA. At 33, 36, 39, 42 and 45 h after transfection of NEAT1 siRNA (corresponding to the 15, 12, 9, 6 and 3 h treatment group), 100 μg/ml CHX was used to treat the cells (20), and the cells were harvested for western blotting after a total time of 48 h of transfection with NEAT1 siRNA. Additionally, 5 μM A-485 (RT-qPCR, western blotting, cell viability assays: 37˚C for 48 h; colony formation assay: 37˚C for 7-9 days) were applied to block p300 (21).

RT-qPCR assay. Total RNA from tissues and cells was extracted using RNAiso Esay Plus (Wuhan Servicebio Technology Co., Ltd.) according to the manufacturer's instructions. First-strand cDNA synthesis and qPCR were performed using the HifiScript cDNA Synthesis Kit (Cwbiotech) and PowerUp™ SYBR™ Green Master Mix (Thermo Fisher Scientific, Inc.), respectively, according to the manufacturer's protocol. The qPCR program was as follows: 95˚C for 2 min, followed by 40 cycles of 95˚C for 15 sec and 60˚C for 1 min. The $2^{-\Delta\Delta cq}$ method was used to calculate the relative expression of the genes (22). GAPDH was used for normalization. Table SII lists the primer sequences.

Colony formation and cell viability assays. A total of 500 cells per well were plated in 12-well plate and then incubated for 7-9 days [lactate dehydrogenase B (LDHB)-knock down cells: cells were seeded after transfection for 24 h; 2-DG/oxamate/lactate/A-485 treated cells: drugs were used to treat after seeding for 24 h]. At the end of the experiment, the cells were fixed with 4% paraformaldehyde for 15 min at room temperature and then stained with 0.1% crystal violet (Beyotime Biotechnology) for 30 min at room temperature. Colonies (>50 cells) were visualized and quantified by light microscopy. The cell viability was detected using Cell Counting Kit-8 (Dojindo Laboratories, Inc.) assays as previously described (6).

RNA immunoprecipitation (RIP) assay. According to the protocol previously described (23), the hemangioma cells were harvested and washed twice with ice-cold PBS. The hemangioma cells were suspended in RIP buffer (1 ml) containing 50 mmol/l Tris pH 7.4, 0.5% NP-40, 1X RNasin plus (Promega Corporation), 150 mmol/l NaCl, 2 mmol/l ribonucleoside vanadyl complex (New England BioLabs, Inc.), 1X protease inhibitor cocktail (MilliporeSigma) and 1 mmol/l PMSF. After brief sonication, cell lysates were centrifuged at 10,000 x g for 10 min at 4˚C and the supernatants were precleared using 10 μl Dynabeads Protein G (Thermo Fisher Scientific, Inc.). The precleared supernatants were divided into two equal parts, and one part was incubated with 1 μg LDHB antibody (cat. no. 14824-1-AP; Proteintech Group, Inc.) and 20 μl Protein A/G Magnetic Beads (cat. No. HY-K0202; MedChemExpress) overnight at 4˚C. The other part was incubated with 1 μg IgG control antibody (cat. no. 30000-0-AP; Proteintech Group, Inc.) and 20 μl Protein A/G Magnetic Beads overnight at 4˚C. After washing the beads three times with RIP buffer, the samples were decrosslinked by proteinase K buffer (50 mmol/l Tris pH 7.4, 150 mmol/l NaCl, 1X RNasin plus, 0.5% SDS and 200 μg/ml proteinase K) at room temperature for 30 min. Then, the RNA was extracted and RT-qPCR was performed.

ChIP-PCR. The SimpleChIP Enzymatic Chromatin IP Kit (Magnetic Beads) (cat. no. CST-9003; Cell Signaling Technology, Inc.) were used to analyze the H3K18 lactylation level of the promoter of the β-catenin

Table I. Clinical features of the patients with infantile hemangioma included in the present study.

Patient no.	Sex	Age (months)	Location of tumor	Growth phase
1	Male	9	Abdominal wall	Proliferating
2	Female	4	Waist	Proliferating
3	Female	3	Neck	Proliferating
4	Male	6	Abdominal wall	Proliferating
5	Female	7	Abdominal wall	Proliferating
6	Male	7	Neck	Proliferating
7	Female	9	Waist	Proliferating
8	Female	4	Neck	Proliferating
9	Male	8	Abdominal wall	Proliferating
10	Female	8	Waist	Proliferating

gene (*CTNNB1*) following the manufacturer's protocol. The 2-DG/oxamate-treated cells, lactate-treated cells, NEAT1-knockdown cells and LDHB-knockdown cells were crosslinked with 1% formaldehyde for 10 min at room temperature, then collected after washing twice using PBS (containing 0.5 mM EDTA). The cell pellet was lysed with 0.3 ml of cell lysis buffer (50 mM Tris-HCl pH 8.1, 10 mM EDTA, 1% SDS and protease inhibitor) and incubated for 10 min on ice. The cell lysates were sonicated (sonication for 15 sec, with a 10-sec interval, totaling 3 min of sonication) to obtain DNA fragments (150-900 base pair in length) and ~50 μg of cross-linked sheared chromatin solution was then used for immunoprecipitation. The L-lactyl-histone H3 (Lys18) antibody (cat. no. PTM-1427RM; PTM BIO LLC; 6 μg/5x10^6 cells) was incubated with the sample overnight at 4˚C on a rotating shaker. Magnetic beads were added to the solution, incubated at 4˚C for 1 h and then washed with washing buffer. The cross-linking was reversed by adding NaCl at a final concentration of 200 mM and heating at 65˚C for 30 min. The DNA fragments were purified using a spin column and qPCR was performed. The sequences of the primers used were as follows: *CTNNB1* promoter forward primer, 5'-CCTAGTGACAAGTGGAACCAGA-3'; and reverse primer, 5'-GAACTCTCCGTAGAACGGGC-3'.

Western blot assay. The western blot procedure was described in our previous study (6). The primary antibodies used were LDHB (cat. no. 14824-1-AP; 1:5,000), β-catenin (cat. no. 51067-2-AP; 1:5,000), alanyl-tRNA synthetase 1 (AARS1; cat. no. 17394-1-AP; 1:2,000), P300 (cat. no. 20695-1-AP; 1:1,000) and GAPDH (cat. no. 60004-1-Ig; 1:50,000) from Proteintech Group, Inc., and L-lactyl-Histone H3 (Lys18) (cat. no. PTM-1406RM; 1:1,000), L-lactyl lysine (pan-lac; cat. no. PTM-1401RM; 1:1,000) and Histone H3 (cat. no. PTM-1002RM; 1:1,000) from PTM BIO LLC. All primary antibodies were incubated overnight at 4˚C. The secondary antibodies used were HRP-conjugated Goat Anti-Mouse IgG (H+L) (cat. no. SA00001-1; 1:10,000; Proteintech Group, Inc.) and HRP-conjugated Goat Anti-Rabbit IgG (H+L) (cat, no. SA00001-2; 1:10,000; Proteintech Group, Inc.), which were incubated for 1 h at room temperature.

Cellular lactate detection. The cellular lactate concentrations were detected using a Lactic Acid assay kit (cat. no. BC2230; Beijing Solarbio Science & Technology Co., Ltd.) according to the manufacturer's protocol.

Bioinformatics analysis. The NEAT1-interacting proteins were predicted using catRAPID software (http://s.tartaglialab.com/page/catrapid_group; accessed on September 5, 2024). Based on the NEAT1-interacting proteins (predicted by catRAPID; Interaction Propensity >50), Gene Oncology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed using the DAVID platform (24,25).

Statistical analysis. GraphPad Prism 10 software (Dotmatics) was used for data analysis. The quantitative data are shown as the mean ± SD and were analyzed via one-way with Tukey's multiple comparisons test (multiple groups) or unpaired Student's t-test (two groups). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Identification of lncRNA NEAT1-interacting proteins. Our previous study reported that NEAT1 was highly expressed in IH tissues (6). In the present study, to investigate the regulatory mechanisms underlying NEAT1-affected hemangioma progression, the proteins that interact with NEAT1 were analyzed using catRAPID software. In total, 2,064 proteins (such as HSP90B1 and CDK11B) were predicted to interact with NEAT1. GO and pathway enrichment analyses of these genes were subsequently performed using DAVID. The biological process enrichment analysis revealed that NEAT1-interacting proteins were associated with processes such as 'mRNA processing', 'mRNA splicing, via spliceosome', 'RNA splicing', 'Translation' and 'rRNA processing' (Fig. 1A). Cellular component enrichment analysis revealed that NEAT1-interacting proteins were associated with components such as 'Nucleoplasm', 'Nucleolus', 'Ribonucleoprotein complex', 'Nucleus' and 'Nuclear speck' (Fig. 1B). Molecular function enrichment analysis revealed that NEAT1-interacting proteins were associated with functions such as 'RNA binding',

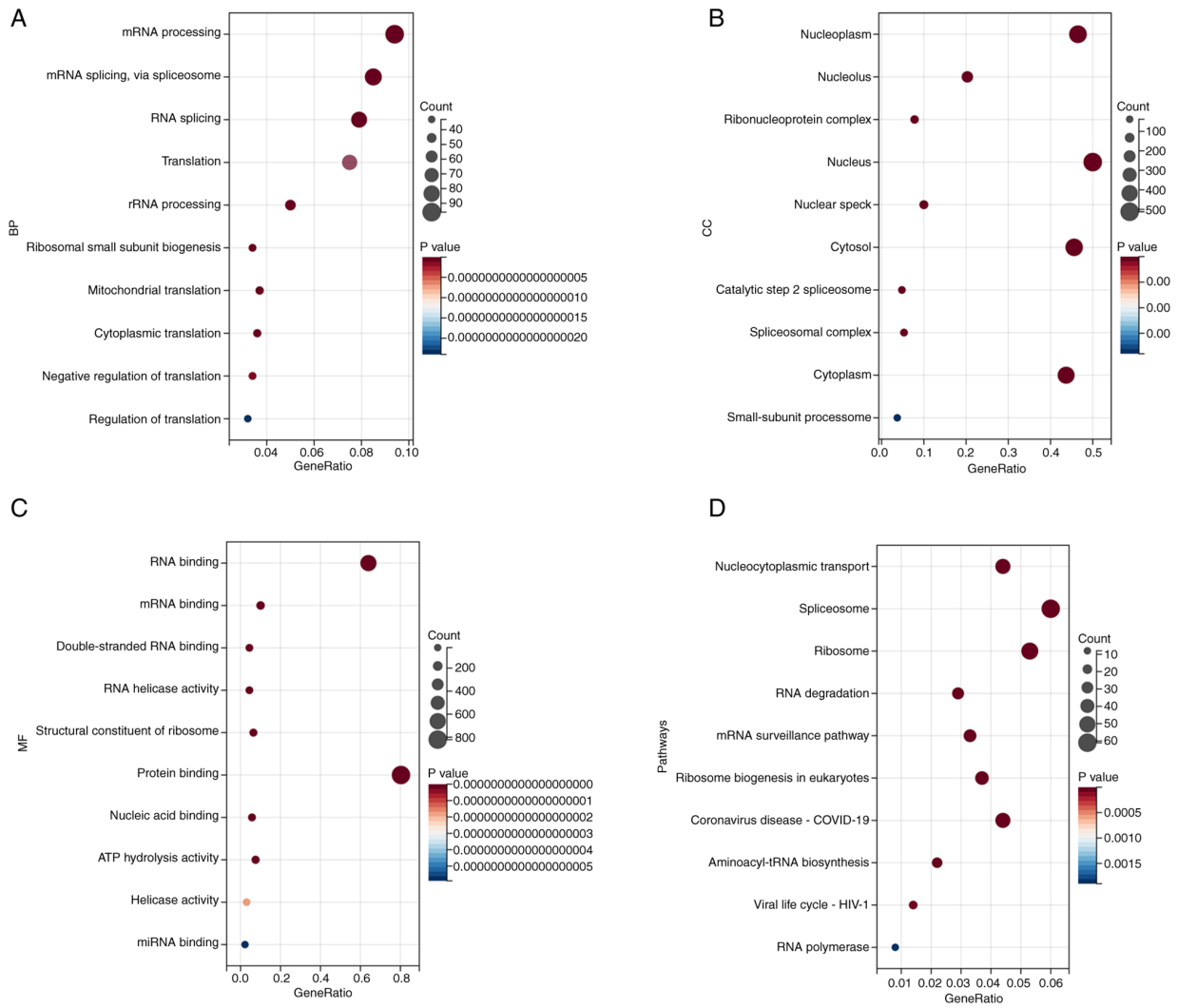

Figure 1. Identification of proteins that interact with the long non-coding RNA NEAT1. (A) BP enrichment analysis of NEAT1-interacting proteins. (B) CC enrichment analysis of NEAT1-interacting proteins. (C) MF enrichment analysis of NEAT1-interacting proteins. (D) KEGG enrichment analysis of NEAT1-interacting proteins. BP, Biological Process; CC, Cellular Component; MF, Molecular Function; KEGG, Kyoto Encyclopedia of Genes and Genomes.

'mRNA binding', 'Double-stranded RNA binding', 'RNA helicase activity' and 'Structural constituent of ribosome' (Fig. 1C). KEGG enrichment analysis revealed that NEAT1-interacting proteins were associated with 'Nucleocytoplasmic transport', 'Spliceosome,' 'Ribosome', 'RNA degradation' and 'mRNA surveillance pathway' (Fig. 1D).

lncRNA NEAT1 interacts with and positively regulates LDHB in hemangioma cells. Notably, it was found that LDHB was predicted to bind with NEAT1 using catRAPID software (Fig. 2A and B). The interaction between NEAT1 and LDHB in hemangioma cells was validated using a RIP assay (Fig. 2C). Additionally, after knocking down NEAT1 expression (Fig. 2D), the protein level (Fig. 2E) but not the mRNA level of LDHB (Fig. 2F) was reduced, indicating that NEAT1 may regulate LDHB at the protein level. After protein translation was inhibited via CHX, LDHB degradation occurred faster in NEAT1-knock down cells than in the negative control cells (Fig. 2G). The proteasome inhibitor MG132, but not the lysosome inhibitor BafA1, reversed the effect of NEAT1 knockdown on the protein level of LDHB, indicating that NEAT1 knockdown reduced the LDHB protein levels via activation of the proteasome activity (Fig. 2H). These results suggested that the lncRNA NEAT1 interacted with and positively regulated LDHB in hemangioma cells.

Knockdown of lncRNA NEAT1 inhibits cellular protein lactylation and downregulates β-catenin in hemangioma cells. LDHB and LDHA have critical roles in converting pyruvate to lactate during glycolysis and are involved in regulating protein lactylation (26,27). In the present study, the knockdown of NEAT1 reduced the cellular lactate concentration and attenuated the levels of both pan lactylation (pan-lac) and H3K18 lactylation in HemECs (Fig. 3A-D). After LDHB expression was knocked down (Fig. 3E), the viability and colony formation ability of HemECs was decreased (Fig. 3F and G).

Activation of the Wnt/β-catenin pathway potentiates the invasion, migration, proliferation and epithelial-mesenchymal transition (EMT) of HemECs (28,29). Therefore, it was next evaluated whether lncRNA NEAT1 promotes the colony formation and viability of HemECs by regulating the Wnt/β-catenin signaling pathway. The results revealed that

A

Protein ID	RNA ID	Interaction Propensity	Z-score	Interaction Matrix	RBP propensity	RNA-Binding Domains	RNA-Binding Motifs	Conserved Interactions	Ranking
P07195 LDHB	NR.028272.1	77.83	2.04	table|plot	1	0	0	0/0	★★☆
Q9UPU9 SAMD4A	NR.028272.1	77.77	2.03	table|plot	1	0	0	0/0	★★☆
Q9P275 USP36	NR.028272.1	77.75	2.03	table|plot	1	0	0	0/0	★★☆
Q9Y6K5 OAS3	NR.028272.1	77.75	2.03	table|plot	1	3	0	0/0	★★☆
P11388 TOP2A	NR.028272.1	77.73	2.03	table|plot	1	1	0	0/0	★★☆

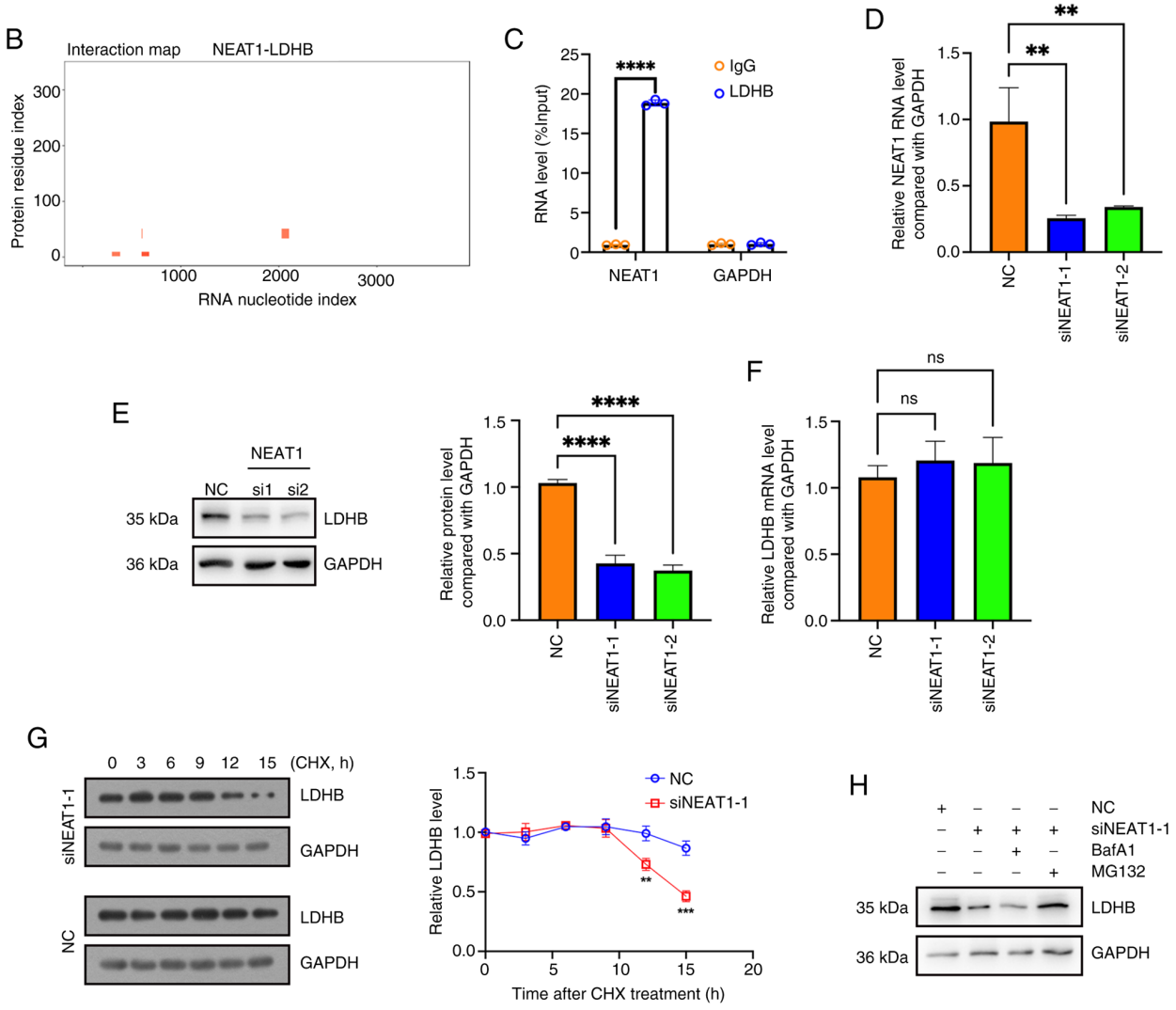

Figure 2. Long non-coding RNA NEAT1 interacts with and positively regulates LDHB in hemangioma cells. (A) The interaction propensity between NEAT1 and LDHB was predicted by the catRAPID software. (B) The interaction map between NEAT1 and LDHB was predicted by the catRAPID software. (C) The binding between NEAT1 and LDHB was measured by the RNA immunoprecipitation assay; ****P<0.0001 (n=3). (D) The knockdown efficiency of NEAT1 was detected by RT-qPCR assay; **P<0.01 vs. NC (n=3). (E) The protein level of LDHB in NEAT1-knock down cells was detected by western blotting; ****P<0.0001 vs. NC (n=3). (F) The LDHB mRNA levels in NEAT1-knock down cells were detected by RT-qPCR (n=3). (G) After CHX treatment, the protein expression level of LDHB in NEAT1-knock down cells was detected by western blotting; **P<0.01, ***P<0.001 (n=3). (H) The proteasome inhibitor MG132 and the lysosome inhibitor BafA1 were used to treat the NEAT1-knock down cells, and the protein expression level of LDHB was detected by western blotting. ns, not significant; CHX, cycloheximide; BafA1, bafilomycin A1; NC, negative control; si, small interfering (RNA); LDHB, lactate dehydrogenase B.

knocking down NEAT1 downregulated β-catenin at both the mRNA and protein levels, and that knocking down LDHB also reduced the mRNA and protein levels of β-catenin in HemECs (Fig. 3H-L). These data revealed that knocking down of lncRNA NEAT1 inhibited cellular protein lactylation and downregulated β-catenin in hemangioma cells.

Blockade of lactylation using 2-DG and oxamate attenuates the viability and colony formation of hemangioma cells and lactate treatment has the opposite effects. Oxamate suppressed cellular protein and H3K18 lactylation in hemangioma cells and 2-DG slightly reduced the H3K18 lactylation level and inhibited cellular protein lactylation in hemangioma

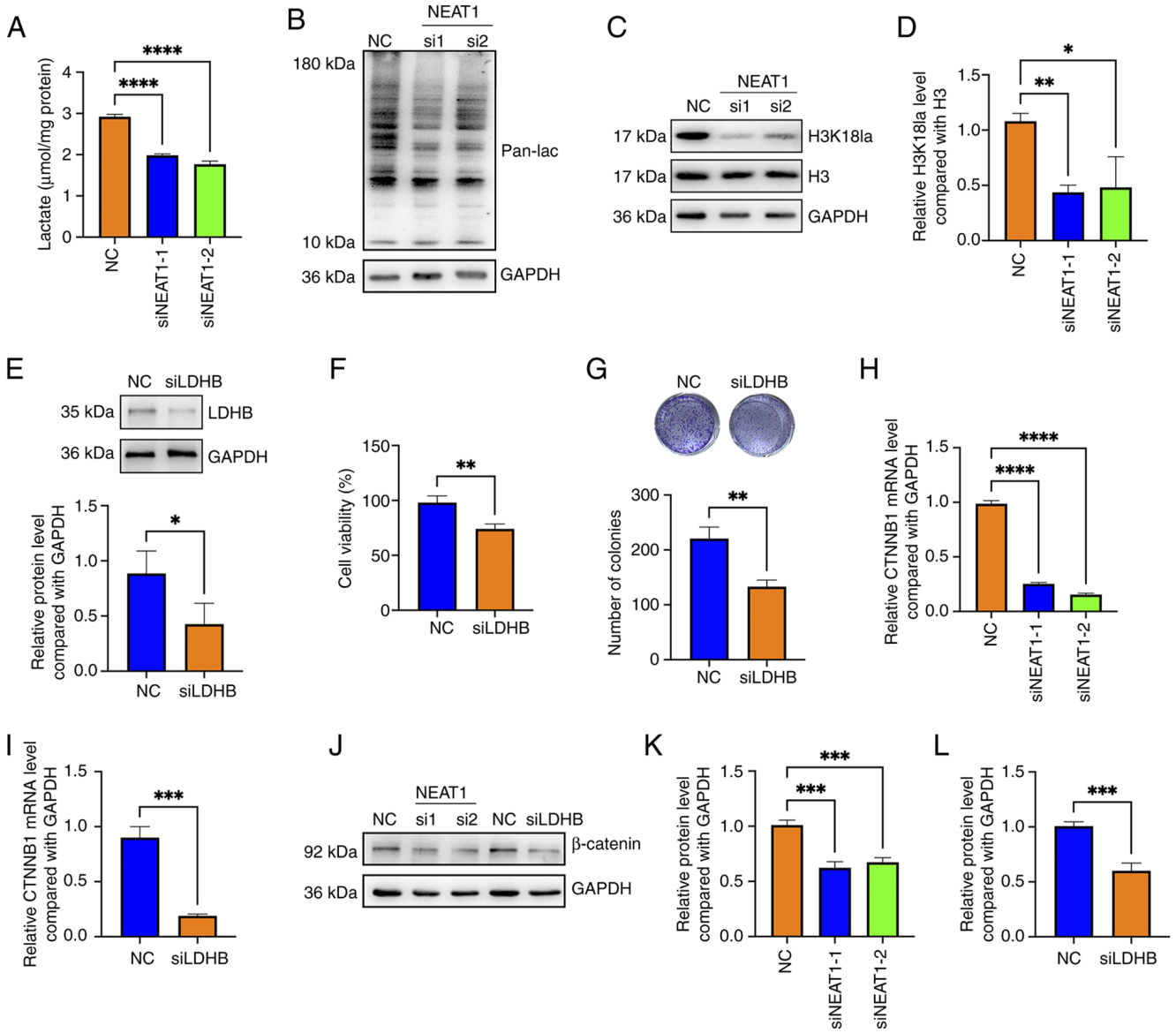

Figure 3. Knocking down long non-coding RNA NEAT1 inhibits cellular protein lactylation and downregulates β-catenin in hemangioma cells. (A) Cellular lactate levels were measured after NEAT1 knockdown; ****P<0.0001 vs. NC (n=3). (B) The level of pan-lactylation in NEAT1-knock down cells were detected by western blotting (n=3). (C) H3K18 lactylation in NEAT1-knock down cells was detected by western blotting (n=3). (D) Quantitative analysis of the levels of H3K18la in the western blotting results; *P<0.05, **P<0.01 vs. NC (n=3). (E) The knockdown efficiency of LDHB was detected by western blotting; *P<0.05 (n=3). (F) The viability of LDHB-knock down cells was detected via Cell Counting Kit-8 assay; **P<0.01 (n=3). (G) Colony formation ability of LDHB-knock down cells was detected via a colony formation assay; **P<0.01 (n=3). (H) The mRNA levels of *CTNNB1* in NEAT1-knock down cells were detected using RT-qPCR. ****P<0.0001 vs. NC (n=3). (I) The mRNA levels of *CTNNB1* in LDHB-knock down cells were detected using RT-qPCR. ***P<0.001 vs. NC (n=3). (J) The protein levels of β-catenin in NEAT1-knock down and LDHB-knock down cells were measured using western blotting (n=3). (K) Semi-quantitative analysis of the levels of β-catenin in NEAT1-knock down cells detected by western blotting; ***P<0.001 vs. NC (n=3). (L) Semi-quantitative analysis of the levels of β-catenin in LDHB-knock down cells detected by western blotting; ***P<0.001 vs. NC (n=3). NC, negative control; H3K18la, Histone H3K18 lactylation; si, small interfering (RNA); LDHB, lactate dehydrogenase B; CTNNB1, β-catenin gene; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

cells (Fig. 4A and B). Conversely, lactate addition markedly increased cellular protein lactylation and H3K18 lactylation in hemangioma cells (Fig. 4C). Both 2-DG and oxamate significantly impeded the viability and colony formation of hemangioma cells (Fig. 4D, E, G and H), and lactate significantly enhanced the viability and colony formation of hemangioma cells (Fig. 4F and I). These data indicated that inhibition of lactylation suppressed the viability and colony formation of hemangioma cells and that promotion of lactylation exhibited promotive effects.

lncRNA NEAT1 promotes H3K18 lactylation of the CTNNB1 promoter and the blockade of lactylation downregulates β-catenin in hemangioma cells. Lactylation of promoters or enhancers is an indication of transcription activation (13); hence, whether NEAT1 regulates β-catenin by affecting lactylation of the *CTNNB1* promoter was investigated. The results showed that both 2-DG and oxamate treatment reduced the H3K18 lactylation level of the *CTNNB1* promoter; conversely, lactate addition increased the H3K18 lactylation level (Fig. 5A and B). Notably, knocking down NEAT1 or LDHB

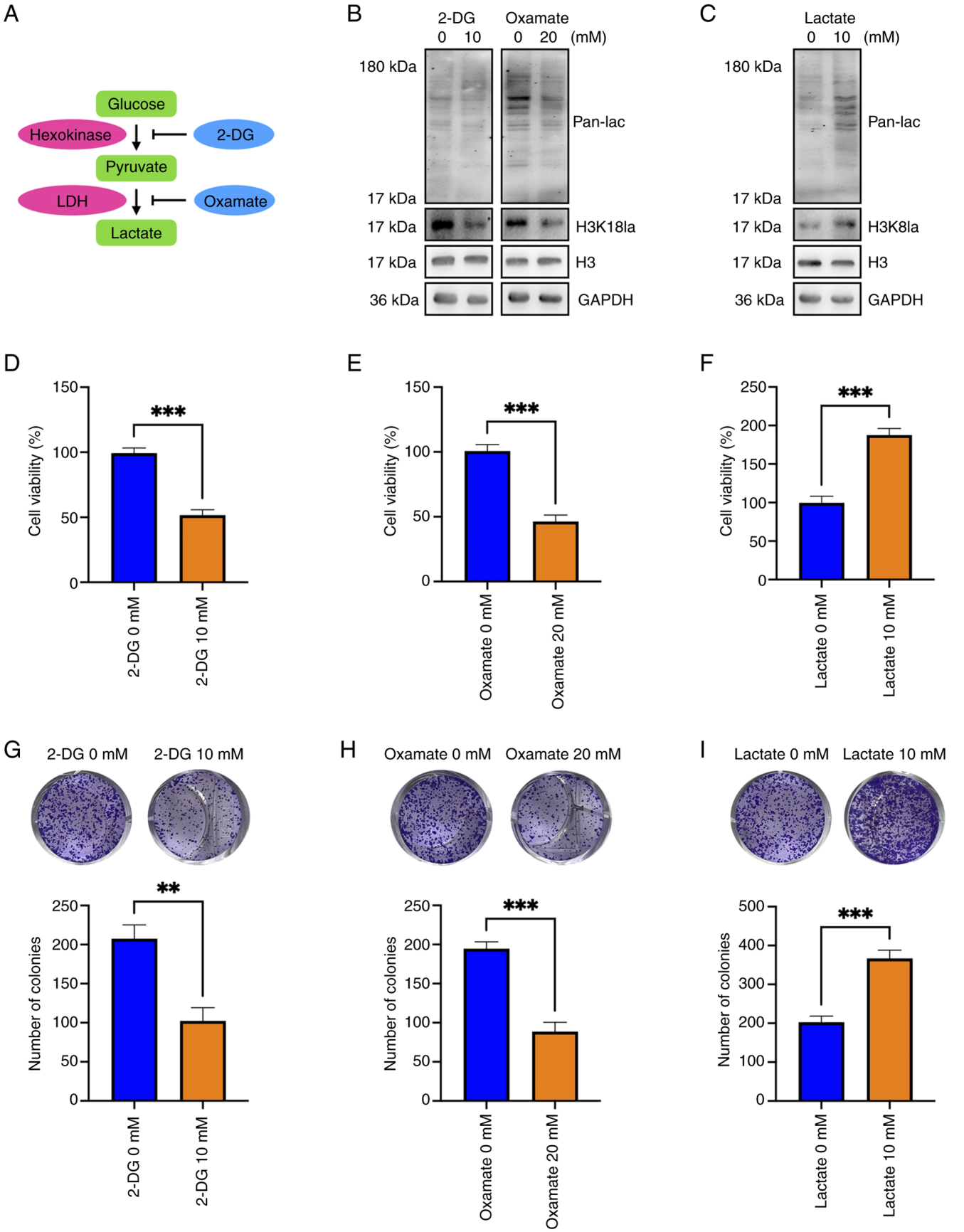

Figure 4. Blockade of lactylation using 2-DG and oxamate attenuates the viability and colony formation of hemangioma cells, and lactate treatment has the opposite effects. (A) 2-DG and oxamate suppress lactate production by blocking glycolysis. (B) Western blotting was used to detect pan-lac in hemangioma cells after 2-DG and oxamate treatment. (C) Western blotting was used to detect the pan-lactylation in hemangioma cells after the addition of lactate. The viability of hemangioma cells under (D) 2-DG, (E) oxamate and (F) lactate treatment; ***P<0.001 (n=3). Colony formation ability of hemangioma cells under (G) 2-DG, (H) oxamate and (I) lactate treatment; **P<0.01, ***P<0.001 (n=3). 2-DG, 2-Deoxy-D-glucose; LDH, lactate dehydrogenase; pan-lac, pan-lactylation; H3K18la, Histone H3K18 lactylation.

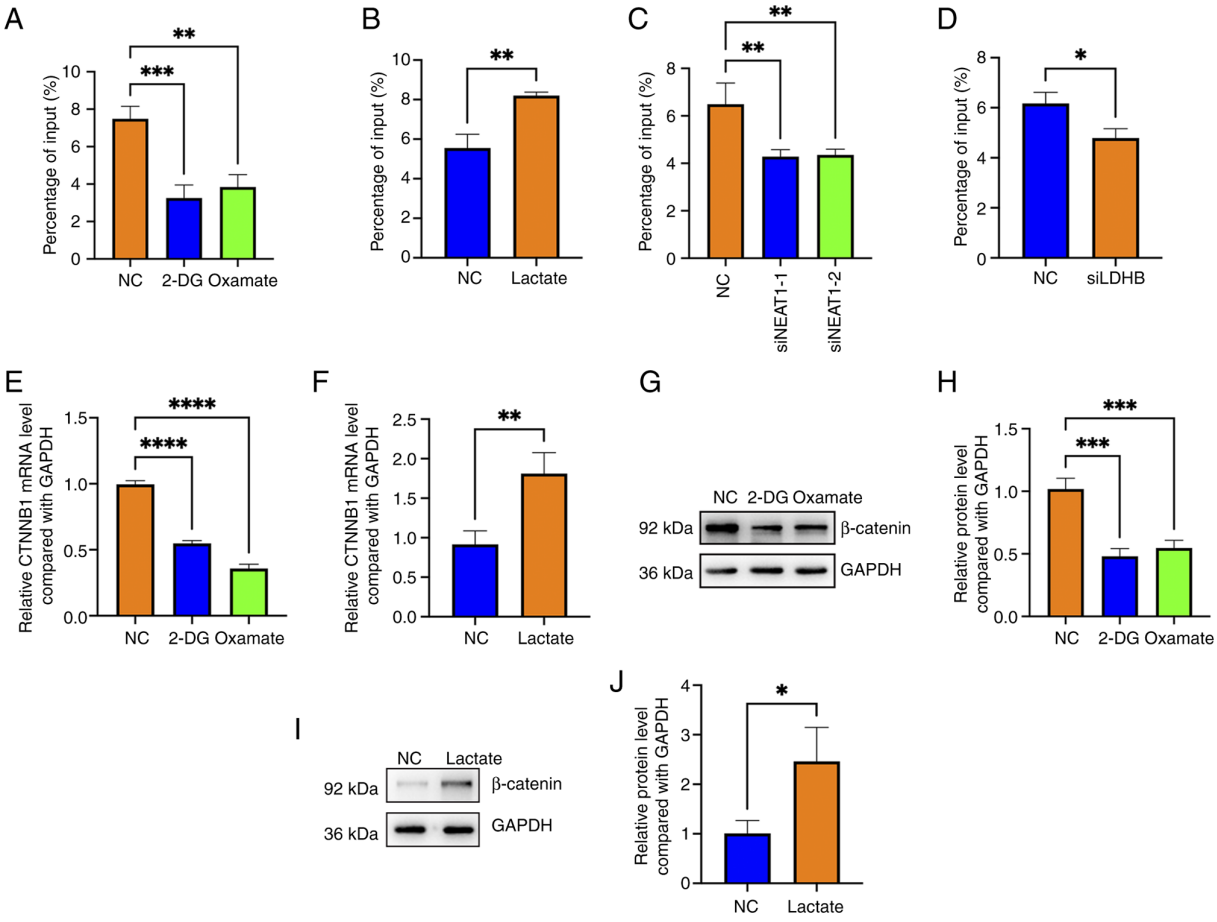

Figure 5. Long non-coding RNA NEAT1 promotes the H3K18 lactylation of the *CTNNB1* promoter and the blockade of lactylation downregulates β-catenin in hemangioma cells. H3K18 lactylation levels of the *CTNNB1* promoter in (A) 2-DG- or oxamate-treated cells and (B) lactate-treated, (C) NEAT1-knock down and (D) LDHB-knock down hemangioma cells were evaluated using ChIP-PCR; *P<0.05, **P<0.01, ***P<0.001 vs. NC (n=3). The *CTNNB1* mRNA levels in (E) 2-DG- and oxamate-treated cells as well as (F) lactate-treated cells were detected by RT-qPCR; **P<0.01, ****P<0.0001 vs. NC (n=3). The protein levels of β-catenin in (G) 2-DG- and oxamate-treated cells were detected by western blotting (n=3). (H) Semi-quantitative analysis of the levels of β-catenin in 2-DG and oxamate-treated cells detected by western blotting; ***P<0.001 vs. NC (n=3). (I) The protein levels of β-catenin in lactate-treated cells were detected by western blotting (n=3). (J) Semi-quantitative analysis of the levels of β-catenin in lactate-treated cells detected by western blotting; *P<0.05 vs. NC (n=3). 2-DG, 2-Deoxy-D-glucose; NC, negative control; CTNNB1, β-catenin gene; LDHB, lactate dehydrogenase B; ChIP, chromatin immunoprecipitation; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; si, small interfering (RNA).

inhibited the H3K18 lactylation of the *CTNNB1* promoter (Fig. 5C and D).

Both 2-DG and oxamate treatment reduced the *CTNNB1* mRNA level; by contrast, lactate increased *CTNNB1* mRNA expression (Fig. 5E and F). Additionally, western blotting revealed that 2-DG and oxamate treatment downregulated β-catenin at the protein level (Fig. 5G and H) and that lactate upregulated β-catenin at the protein level (Fig. 5I and J). These findings suggested that NEAT1 promoted H3K18 lactylation of the *CTNNB1* promoter and that blocking lactylation downregulated β-catenin expression in hemangioma cells.

Lactyltransferases AARS1 and P300 are indirectly regulated by lncRNA NEAT1 and further regulate β-catenin in hemangioma cells. AARS1, AARS2, CREB binding lysine acetyltransferase (CBP), lysine acetyltransferase (KAT) 5, KAT8 and P300 are reported to positively regulate protein lactylation as lactyltransferases, and Sirtuin (SIRT) 1, SIRT2, SIRT3, Histone deacetylase (HDAC) 1, HDAC2 and HDAC3 have been found to negatively affect protein lactylation as delactyltransferases (30). Hence, which molecules regulate β-catenin in hemangioma cells were screened next. Notably, after separately knocking down every lactyltransferase (Fig. 6A) and delactyltransferase (Fig. 6C), it was found that the knockdown of AARS1 and P300 reduced the mRNA level of *CTNNB1* (Fig. 6B). Additionally, knocking down HDAC1 also downregulated *CTNNB1* at the mRNA level in hemangioma cells (Fig. 6D). The knockdown efficiency of AARS1 and P300 was further confirmed using western blotting (Fig. 6E and F). It was subsequently found that the knocking down of AARS1 and P300 in hemangioma cells also downregulated β-catenin at the protein level (Fig. 6G and H). Furthermore, knockdown of NEAT1 significantly decreased the mRNA and protein levels of AARS1 and P300 (Fig. 6I-K). Notably, blocking P300 using A-485 suppressed the viability and colony formation of HemECs (Fig. 7A-C), and A-485 treatment also decreased the mRNA and protein levels of β-catenin (Fig. 7D-F). These results indicated that NEAT1 regulates β-catenin in hemangioma cells possibly by positively affecting the lactyltransferases AARS1 and P300.

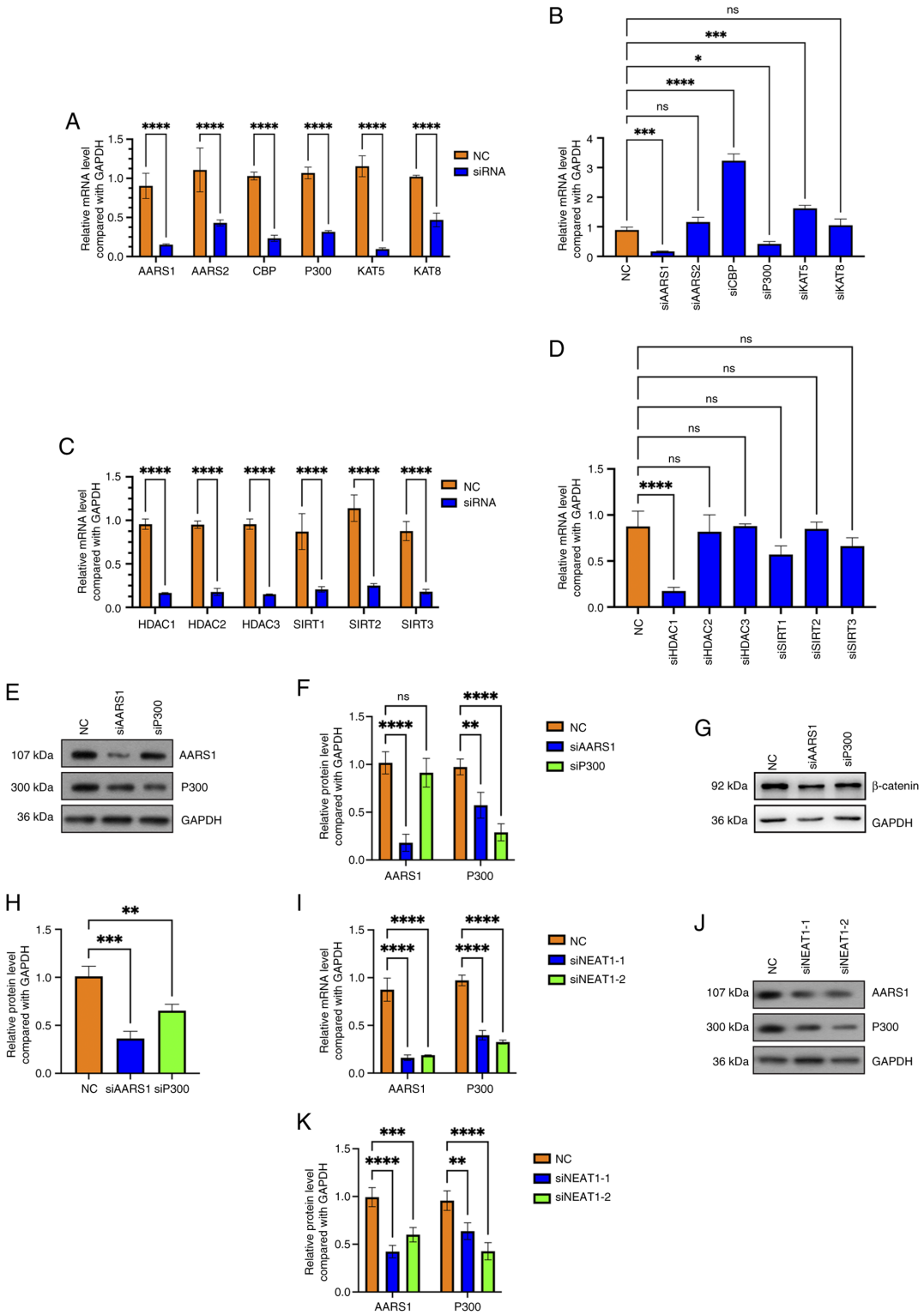

Figure 6. Long non-coding RNA NEAT1 regulates β-catenin by positively affecting the lactyltransferases AARS1 and P300 in hemangioma cells. (A) The knockdown efficiencies of AARS1, AARS2, CBP, KAT5, KAT8 and P300 were confirmed by RT-qPCR; ****P<0.0001 vs. NC (n=3). (B) After AARS1, AARS2, CBP, KAT5, KAT8 and P300 were knocked down, the *CTNNB1* mRNA level was detected using RT-qPCR; *P<0.05, ***P<0.001, ****P<0.0001 vs. NC (n=3). (C) The knockdown efficiencies of SIRT1, SIRT2, SIRT3, HDAC1, HDAC2 and HDAC3 were confirmed by RT-qPCR; ****P<0.0001 vs. NC (n=3). (D) After SIRT1, SIRT2, SIRT3, HDAC1, HDAC2 and HDAC3 were knocked down, the *CTNNB1* mRNA level was detected using RT-qPCR; ****P<0.0001 vs. NC (n=3). (E) The knockdown efficiency of AARS1 and P300 was confirmed by western blotting (n=3). (F) Semi-quantitative analysis of the levels of AARS1 and P300 in AARS1-knock down and P300-knock down cells detected by western blotting; **P<0.01, ****P<0.0001 vs. NC (n=3). (G) The protein level of β-catenin after AARS1 and P300 knockdown was detected using western blotting (n=3). (H) Semi-quantitative analysis of the levels of β-catenin in AARS1-knock down and P300-knock down cells detected by western blotting; **P<0.01, ***P<0.001 vs. NC (n=3). (I) The mRNA levels of AARS1 and P300 after NEAT1 knockdown were detected using RT-qPCR; ****P<0.0001 vs. NC (n=3). (J) The protein levels of AARS1 and P300 after NEAT1 knockdown were detected using western blotting (n=3). (K) Semi-quantitative analysis of the levels of AARS1 and P300 in NEAT1-knock down cells detected by western blotting; **P<0.01, ***P<0.001, ****P<0.0001 vs. NC (n=3). ns, not significant; NC, negative control; AARS, alany-tRNA synthetase; CBP, CREB binding lysine acetyltransferase; KAT, lysine acetyltransferase; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; CTNNB1, β-catenin gene; SIRT, sirtuin; HDAC, histone deacetylase; siRNA, small interfering RNA.

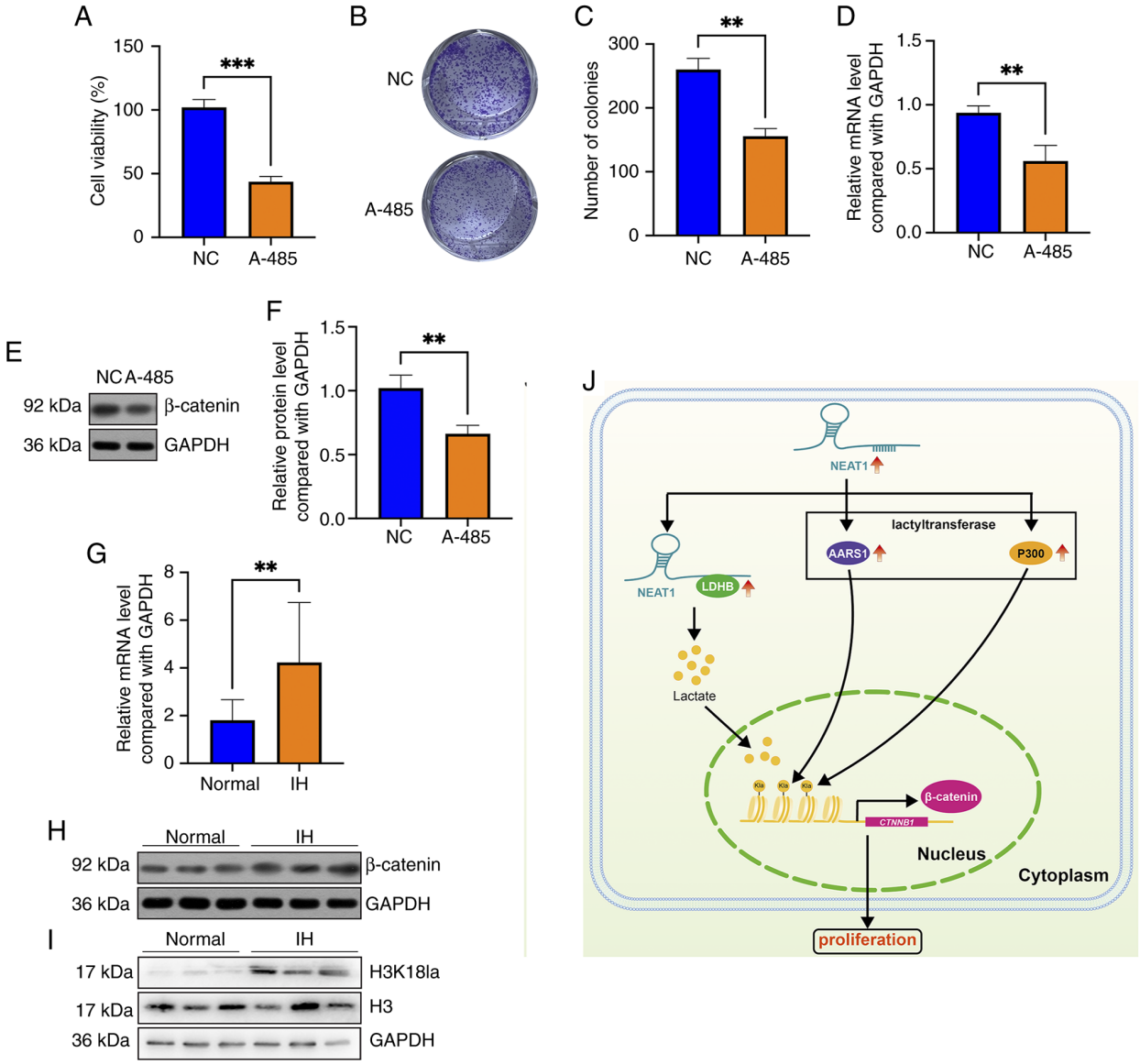

Figure 7. β-catenin and H3K18 lactylation levels were elevated in IH tissues. (A) The viability of hemangioma cells treated with a P300 inhibitor (A-485) were measured via Cell Counting Kit-8 assay; ***P<0.001 (n=3). (B) The colony formation ability of hemangioma cells treated with a P300 inhibitor (A-485) were measured via colony formation assays (n=3). (C) Quantitative analysis of the colony formation results; **P<0.01 (n=3). (D) The *CTNNB1* mRNA level after A-485 treatment was detected using RT-qPCR; **P<0.01 (n=3). (E) The protein level of β-catenin after A-485 treatment was detected using western blotting (n=3). (F) Semi-quantitative analysis of the levels of β-catenin in A-485-treated cells detected by western blotting; **P<0.01 (n=3). (G) The *CTNNB1* mRNA level in IH tissues was detected using RT-qPCR; **P<0.01 (n=10). (H) The level of β-catenin protein in IH tissues was detected using western blotting. (I) The level of H3K18 lactylation in IH tissues was detected using western blotting. (J) Proposed model of long non-coding RNA NEAT1 regulation of the LDHB/H3K18-lactylation/β-catenin signaling cascade. IH, infantile hemangioma; NC, negative control; CTNNB1, β-catenin gene; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; AARS1, alany-tRNA synthetase 1; LDHB, lactate dehydrogenase B.

β-catenin and H3K18 lactylation levels are elevated in IH tissues. The status of β-catenin expression and H3K18 lactylation levels in IH tissues were further evaluated. The RT-qPCR and western blotting results revealed that both the mRNA and protein levels of β-catenin were greater in the IH tissues than in normal tissues (Fig. 7G and H). Additionally, western blotting indicated that the H3K18 lactylation level was greater in IH tissues than in normal tissues (Fig. 7I). In summary, the results revealed that lncRNA NEAT1, which is upregulated in hemangioma, binds with and upregulates LDHB, subsequently elevates the levels of cellular lactate and H3K18 lactylation, potentiates β-catenin transcription and ultimately enhances the proliferation of hemangioma cells (Fig. 7G).

Discussion

Our previous study revealed that lncRNA NEAT1 is highly expressed in IH tissues and promotes the proliferation, migration and invasion of hemangioma cells by sponging miR-33a-5p and regulating the downstream HIF1α/NF-κB pathway (6). Nevertheless, the functional roles and detailed mechanisms of NEAT1 in hemangioma are still not fully understood.

The Wnt/β-catenin pathway plays critical promotional roles in hemangioma progression, and inactivation of the Wnt/β-catenin pathway has therapeutic effects on hemangioma (28,29). IL13RA2 was overexpressed in IH tissues, and exogenous expression of IL13RA2 potentiated hemangioma

progression by interacting with and activating the β-catenin pathway (28). Renin has been shown to promote the proliferation of IH cells by activating the Wnt pathway (31). Additionally, blockade of the Wnt/β-catenin pathway by fucoidan has been shown to inhibit the proliferation and EMT of hemangioma cells (29). Dai *et al* (32) reported that luteolin suppresses IH progression by blocking the Wnt signaling pathway. Notably, the results of the present study indicated that lncRNA NEAT1, which is upregulated in IH tissues, upregulated β-catenin expression in an H3K18 lactylation-dependent manner.

Lactic acid was first discovered in 1780 and was formerly considered a byproduct of metabolism (33). However, at present, lactate is considered to act as both a metabolic substance and a signaling molecule (34,35). In 2019, Zhang *et al* (9) discovered protein lysine lactylation, a new posttranslational modification, and provided a new insight into the novel function of lactate. H3K18 lactylation is a critical type of histone lactylation that typically activates gene transcription (36) and is recognized as a biomarker for poor prognosis in epithelial ovarian cancer (37). In non-small cell lung carcinoma, H3K18 lactylation directly transcriptionally activates POM121 transmembrane nucleoporin and ultimately induces programmed cell death protein 1 expression and enhances immune escape (27). In ovarian cancer, lactate-induced H3K18 lactylation increases CCL18 expression (38). In pancreatic ductal adenocarcinoma (PDAC), H3K18 lactylation, which is elevated in PDAC, promotes the transcription of BUB1 mitotic checkpoint serine/threonine kinase B and TTK protein kinase and eventually causes tumorigenesis (39). H3K18 lactylation transcriptionally activates SOX9 and facilitates liver fibrosis development (40). Notably, the present study revealed that H3K18 lactylation transcriptionally activates β-catenin in hemangioma.

H3K18 lactylation is typically regulated by glycolysis, lactyltransferases and delactyltransferases. In breast cancer, potassium two pore domain channel subfamily K member 1 binds with LDHA and affects histone lysine lactylation (41). In PDAC, HDAC2 and P300 regulate histone lactylation as the eraser and writer of protein lactylation (39). The present study revealed that NEAT1 binds to LDHB and positively regulates LDHB expression in hemangioma cells. A previous study reported that LDHA was highly expressed in HemECs compared with human umbilical vein endothelial cells (42). Another study revealed that the protein expression of phosphofructokinase-1 (FPK-1) is greater in proliferating IHs than in involuting IHs, and that suppression of FPK-1 impedes the proliferation and migration of HemECs and reduces lactate production (43). However, the role of LDHB in hemangioma progression is still unclear.

The proliferative (first 6-12 months after birth), involuting (starting at ~13 months) and involuted (4-7 years of age) phases are the three stages of the self-limiting disease course in IH (44). Unraveling the mechanisms underlying IH development from proliferation to involution is crucial for developing a new therapeutic strategy for IH. The findings of the present study suggest that the levels of H3K18la and β-catenin are increased in proliferating IH tissues. Molecular analysis further revealed that H3K18la-driven transcriptional activation of *CTNNB1* enhances the proliferation of hemangioma cells. Therefore, blocking this mechanism might be a benefit for IH therapy.

Taken together, the results of the present study revealed that lncRNA NEAT1, which is upregulated in hemangioma, binds with and stabilizes LDHB, subsequently elevates the levels of cellular lactate and H3K18 lactylation, potentiates *CTNNB1* transcription and finally enhances the proliferation of hemangioma cells. Nevertheless, several limitations of the present study remain. First, when the candidate lactyltransferases or delactyltransferases that may regulate β-catenin expression were screened, the changes in expression were only examined at the mRNA level and not the protein level. Second, in addition to H3K18 lactylation, NEAT1 also regulates the lactylation of non-histone proteins; therefore, whether the lactylation of non-histone proteins is also involved in the NEAT1-affected hemangioma cell proliferation still needs to be investigated. Third, how NEAT1 regulates AARS1 and P300 requires further exploration.

Acknowledgements

Not applicable.

Funding

This study was funded by the Joint Special Funds for the Department of Science and Technology of Yunnan Province-Kunming Medical University (grant no. 202201AY070001-202).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HS conceived and designed the research. LY performed the experiments and wrote the manuscript. NZ, XLZ, XJP, LX, YJP, LZ and JNW analyzed the data. All authors read and approved the final version of the manuscript. HS and LY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The Ethics Committee of Kunming Children's Hospital (Kunming, China) approved this study (approval no. 2021-03-181-K01). Informed consent was obtained from the parents/legal guardians of each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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