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Research article

A novel hsa_circ_0006903 circular RNA promotes tumor development and dendritic cells activated expression in infantile hemangioma

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ABSTRACT

Background: Increasing reports revealed that circular RNAs (circRNAs) and immune cells infiltration were related with tumor development. However, its role in infantile hemangioma (IH) is unknown. We will explore a novel hsa_circ_0006903-based ceRNA network and investigate the landscape of dendritic cells activated expression in IH.

Material and methods: Differentially expressed circRNAs (DECs) were identified from Gene Expression Omnibus (GEO) database. Regulatory networks and functional enrichment analysis were constructed. CIBERSORT was used to characterize immune cells composition. qRT-PCR was performed to detect the expression of hsa_circ_0006903 in cell lines. Then, the role of hsa_circ_0006903 in IH were validated in vitro using transwell assay. Immunofluorescence was applied to the colocalization of CD11b for dendritic cells activated as a biomarker in IH tissues.

Results: Using GEO database, a total of 67 DECs were screened out in IH. Hsa_circ_0006903 was the most significant DECs. Then, a novel hsa_circ_0006903 circular RNA-ceRNA network was constructed. Mechanistically, functional enrichment analysis showed that the p53 signaling pathway played the most important roles, and hsa_circ_0006903/miR-6721-5p/CACNA2D2 and hsa_circ_0006903/miR-4786-3p/ATP13A4 axis were identified. CACNA2D2, ATP13A4, and P53 were significantly downregulated in IH cell lines. We validated that dendritic cell activated was significantly overexpressed. Moreover, CD11b as a biomarker of dendritic cells activated were tested in IH tissues. Finally, hsa_circ_0006903 was significantly overexpressed, and hsa_circ_0006903 promoted infantile hemangioma cell proliferation, invasion, and migration in vitro.

Conclusion: Overall, our study revealed that a novel hsa_circ_0006903 promoted tumor progression, and indicated a potential biomarker CD11b of dendritic cells activated in IH.

Abbreviations: IH, infantile hemangioma; ceRNA, competing endogenous RNA; NCBI, National Centre of Biotechnology Information; DECs, differentially expressed circRNAs; MRE, microRNA response element; ORF, RNA binding protein and open reading frame; HemECs, hemangioma-derived endothelial cells; HUVEC, human umbilical vein endothelial cells.

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1. Introduction

Infantile hemangioma (IH) is the most common benign tumor in childhood with an increasing incidence of 3–10 % [1,2]. There are many clinical complications in IHs, including pain, functional impairment, or permanent disfigurement [3]. Many novel therapeutic pathways are used in IHs, such as surgical treatment [4], oral beta-blockers [5] and laser treatment [6]. Despite previous report showed that angiogenesis have been recognized as underlying characteristics in IH [7], the molecular mechanism of infantile hemangiomas is still unknown.

Increasing evidences showed that non-coding RNAs (ncRNAs) including miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) participated in numerous biological processes of IH. For example, the previous study reported that miR-139-5p affected the proliferation, migration and adipogenesis of IH [8]. In addition, Liu, Z. et al. showed that long noncoding RNA LINC00342 ponging miR-3619-5p promoted growth of infantile hemangioma [9].

CircRNAs as a new type of ncRNAs played an essential role in tumor progression [10]. The mechanism of circRNAs focused mostly on competing endogenous RNA (ceRNAs) to regulate the expression of target genes by microRNA response element (MREs) [11]. Yan, L et al. found that hsa_circ_0035483 promoted the gemcitabine-resistance of human renal cancer cells by sponging hsa-miR-335 [12]. Zhang, X et al. showed that circular RNA circNRIP1 sponged microRNA-149-5p promoting gastric cancer progression [13]. Many studies revealed that circRNAs could bind to miRNAs altering the expression of target genes of those miRNAs [14]. At present, some researchers found that circRNA could bind to proteins to form specific circRNA-protein complexes (circRNPs) regulating the action of associated protein [15].

Tumor microenvironment (TME) can affect tumor epigenetics, tumor differentiation, immune escape, and infiltration metastasis [16]. Tumor-infiltrating immune cells (TIICs) in tumor microenvironment plays an important role in tumor development. Therefore, there exists an urgent need to explore the mechanism of circRNAs as a valuable biomarker and immune infiltrating cells in IH.

Here, firstly, hsa_circ_0006903 was identified as the most significantly expressed in IH from GEO dataset GSE98795, and constructed a ceRNAs network of hsa_circ_0006903-mediated for the first time in IH. Then, hsa_circ_0006903 regulatory axis in infantile hemangioma treated with propranolol was identified, and CACNA2D2, ATP13A4, and P53 were significantly upregulated in IH cell lines. Moreover, we evaluated the landscape of immune cells infiltration and found that dendritic cells activated was significantly expressed in IH. Moreover, CD11b as a biomarker of dendritic cells activated were validated in IH samples. Finally, we demonstrated the expression and function of hsa_circ_0006903 promoting cell progression. Our study provides evidences for elucidating the roles of hsa_circ_0006903 and the landscape of immune cells infiltration, especially dendritic cells activated in IH.

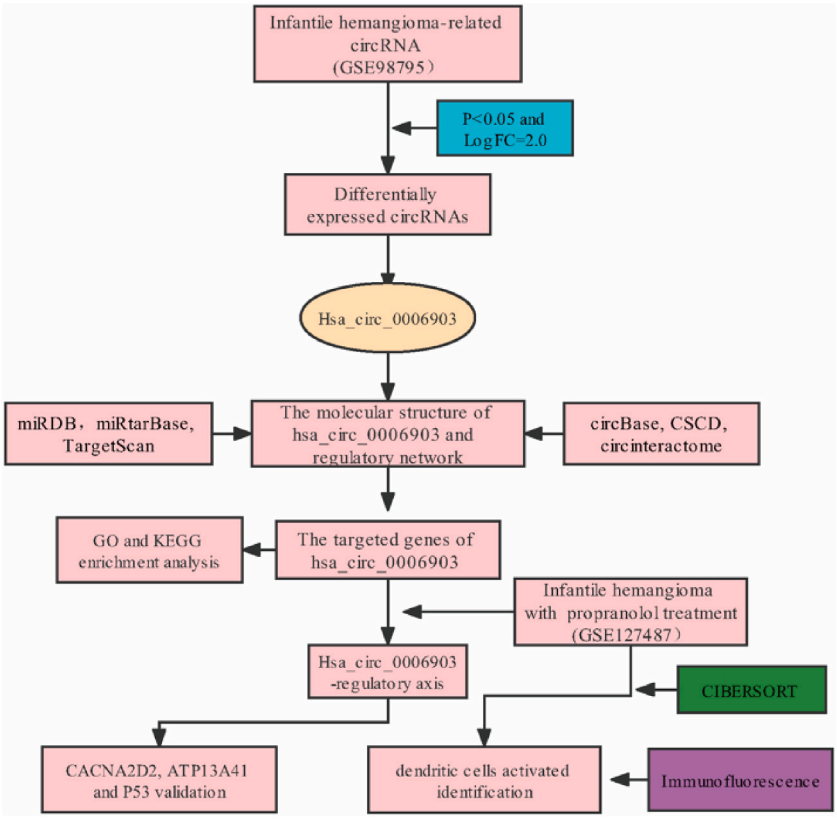

Fig. 1. The workflow of this study (The original image is provided in the Supplementary material file).

2. Materials and methods

The detailed workflow is presented in Fig. 1.

2.1. Microarray analysis of gene expression

We searched "infantile hemangioma circRNA or mRNAs array" in the National Centre of Biotechnology Information (NCBI) Gene Expression Omnibus database (GEO, http://www.ncbi.nlm.nih.gov/geo/).

Datasets GSE98795 (https://www.ncbi.nlm.nih.gov/gds/?term=GSE98795) and GSE127487 (https://www.ncbi.nlm.nih.gov/gds/?term=GSE127487) associated with IH were acquired. The original files (.CEL files) and platform files of GSE98795 [17] and GSE127487 [18]were downloaded. In this study, GSE98795 datasets contained four IH tumor tissues and four adjacent skin normal tissues. In addition, GSE127487 datasets included 18 IH tumor tissues, 5 normal skin tissues, and 5 IH tumor tissues with propranolol treatment.

2.2. Identification of DECs and differentially expressed genes (DEGs)

Differentially expressed circRNAs and mRNAs were identified using the limma package with a corrected P-value of < 0.05 and log | fold change (FC)| > 2 between tumor and normal samples. Volcano plots and heat maps were performed using limma and pheatmap packages, respectively.

2.3. Functional enrichment analysis

GO (GO Ontology) term is one of the most widely used tools in molecular and cellular biology providing an ontology of defined terms to represent specific gene product properties [19]. KEGG (Kyoto Encyclopedia of Genes and Genomes) is a database dealing with genomes, diseases, biological pathways, drugs, and chemical materials [20]. GO and KEGG were performed to analyze biological function and pathway enrichment using R language and Perl software. The packages ("colorspace"), ("dose"), biocLite ("DOSE"), ("clusterProfiler"), and ("pathview") were installed for next analysis.

2.4. Hsa_circ_0006903 circular RNA-mediated ceRNA network construction

To explore MREs, RNA binding protein and open reading frame (ORF) information, hsa_circ_0006903 was predicted in Cancer-Specific CircRNA database (CSCD) (http://gb.whu.edu.cn/CSCD/). Targeted miRNAs of hsa_circ_0006903 were obtained from the CSCD database. miRDB database, miRTarBase database, and TargetScan database were used to identify targeted genes of miRNAs binding hsa_circ_0006903 ci. Cytoscape is one of the most popular open-source software tools for the visual exploration of biomedical networks composed of protein, gene, and other types of interactions. Type and network txt files were designed to visualize hsa_circ_0006903-miRNAs-mRNAs using Cytoscape software 3.6.0 [21].

2.5. Composition of immune cell infiltration

Cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT), is a computational method characterizing cell composition of complex tissues from their gene expression profiles [22]. The set value for permutations is 1000. The packages ('e1071') and ('parallel') of R software were performed for CIBERSORT analysis. The infiltration levels of 22 immune cell types were estimated in this study.

2.6. Cell culture and CCK-8 cell proliferation assay

IH cell line hemangioma-derived endothelial cells (HemECs) and human umbilical vein endothelial cells (HUVEC) were gained from the Createch Biology (Tianjin, China). All cells were cultured in DMEM medium (Gibco, USA) at 37 °C containing 5 % CO_2 under saturated humidity. The proliferation ability of HemECs cells was assessed using CCK8 assay (Ameresco. USA). After 24 h of incubation, transfected cells were plated onto 96-well plates and cultured for 48 h. Every well contained 4000 cells. CCK8 solution was added to each well, and the absorbance at a wavelength of 450 nm was spectrophotometrically measured by an automatic microplate reader (Synergy 4; BioTek, Winooski, VT, USA).

2.7. qRT-PCR validation

Total RNA was extracted using TRIzol reagent (Invitrogen, USA) and the cDNA was generated using M-MLV reverse transcriptase (TaKaRa Bio, Japan) according to the manufacturer's instructions. qRT-PCR was performed using SYBR Green assay (Roche, Switzerland). GAPDH was used as controls. The hsa_circ_0006903 siRNAs and NC-hsa_circ_0006903 as well as the non-targeting negative control, were purchased from Createch Biology (Tianjin, China). Lipofectamine 2000 (Invitrogen) was used for transfection.

2.8. Transwell assay

Transwell assay was used to evaluate cell migration and invasion ability according to the manufacturer's instructions. Cells were incubated for 24 h. At least three microscopy fields were randomly selected to acquire images under a 200 × magnification microscope. HemECs were transfected with plasmids using Lipofectamine 2000 reagent (Invitrogen, USA) based on the manufacturer's instructions for 24 h.

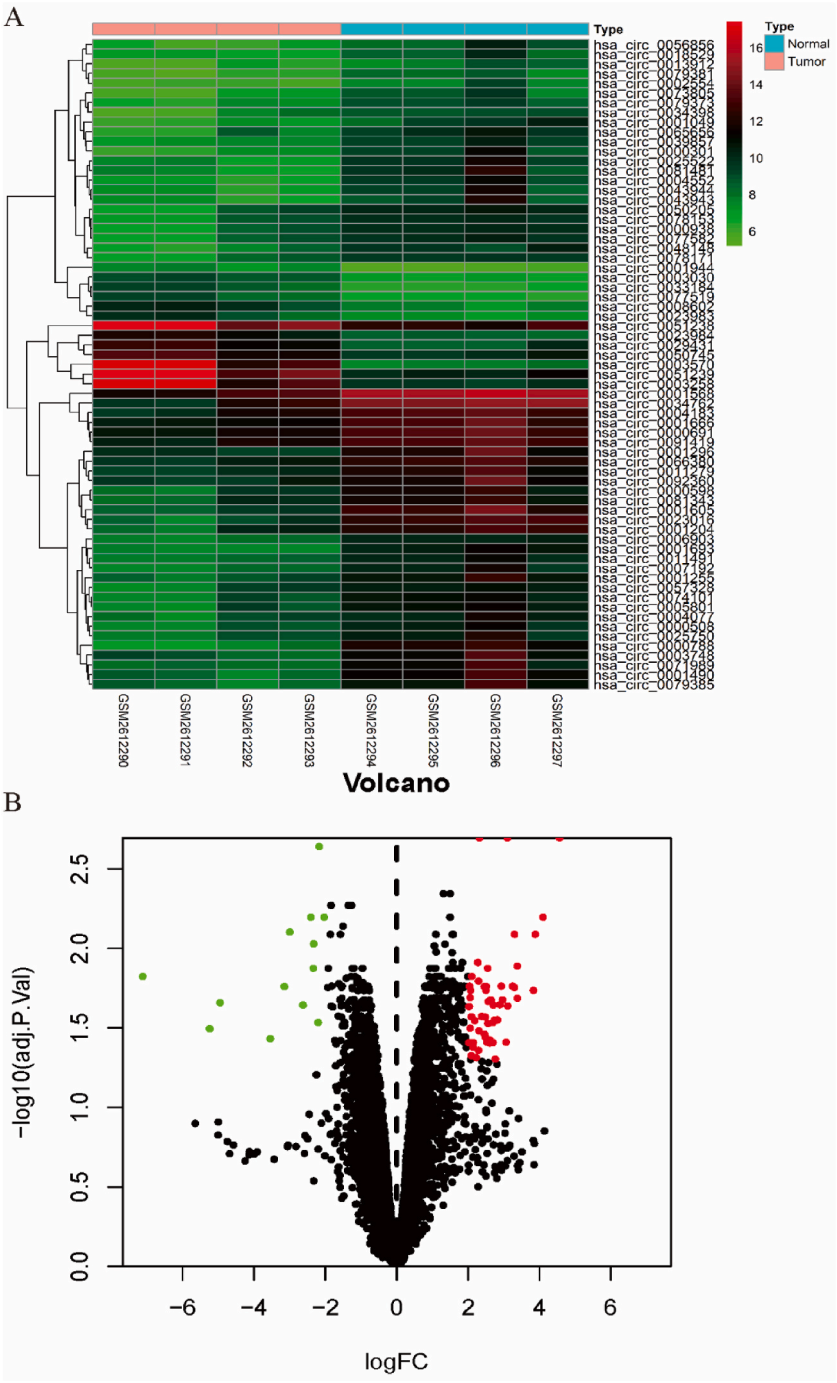

Fig. 2. CircRNAs and miRNAs expression profiles in infantile hemangioma. (A) The heat map and (B) volcano map of the expression of 67 differentially expressed circRNAs in IH (The original image is provided in the Supplementary material file).

2.9. Western blot

The proteins were extracted from cells using RIPA buffer (Beyotime) with protease inhibitors. The membranes were blocked in TBST with 5 % non-fat milk for 2 h and then incubated with rabbit anti-human primary antibodies against CACNA2D2 (1:1000

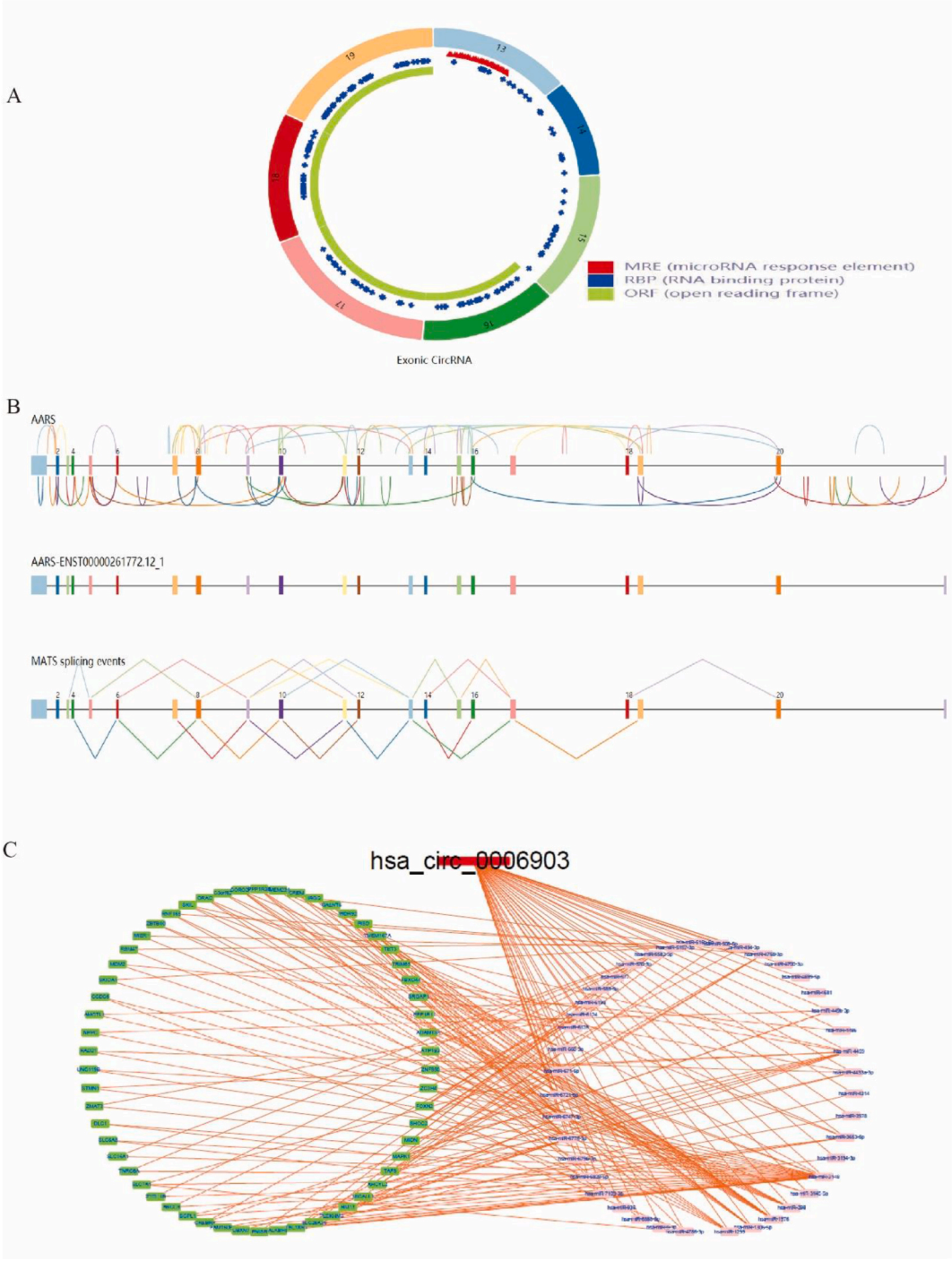

Fig. 3. Schema graphs of hsa_circ_0006903 and ceRNA network. (A) and (B) presenting the molecular structure of hsa_circ_0006903 circular RNA were downloaded from Cancer-Specific CircRNA database (CSCD). Red spots represent miRNA response elements (MRE), blue spots represent RNA binding protein (RBP), and green curves represent open reading frame (ORF). (C) Hsa_circ_0006903 circular RNA-mediated regulatory network (The original image is provided in the Supplementary material file).

dilution, Abcam), ATP13A4 (1:1000 dilution, Abcam), P53 (1:1000 dilution, Abcam) or NADPH (1:1000 dilution, Abcam) as a loading control at 4 °C overnight and goat anti-rabbit secondary antibody (1:10000 dilution, Abcam) at room temperature for 1.5 h.

2.10. Immunofluorescence

For immunofluorescence double staining, the sections were incubated with 0.1 % Triton for 15 min for permeabilization, and then were blocked for 30 min. The previous study showed that CD11b could represent a biomarker of dendritic cells activated [23]. The sections were incubated with rabbit anti-human primary antibodies against CD11b (ab133357, 1:500 dilution, Abcam). Nuclei were visualized using 4′,6-diamidino-2-phenylindole (DAPI).

2.11. Statistical analyses

All analyses were performed using R 3.6.1 and Graphpad Prism 8.0.1. $P < 0.05$ was considered as be statistically significant. The

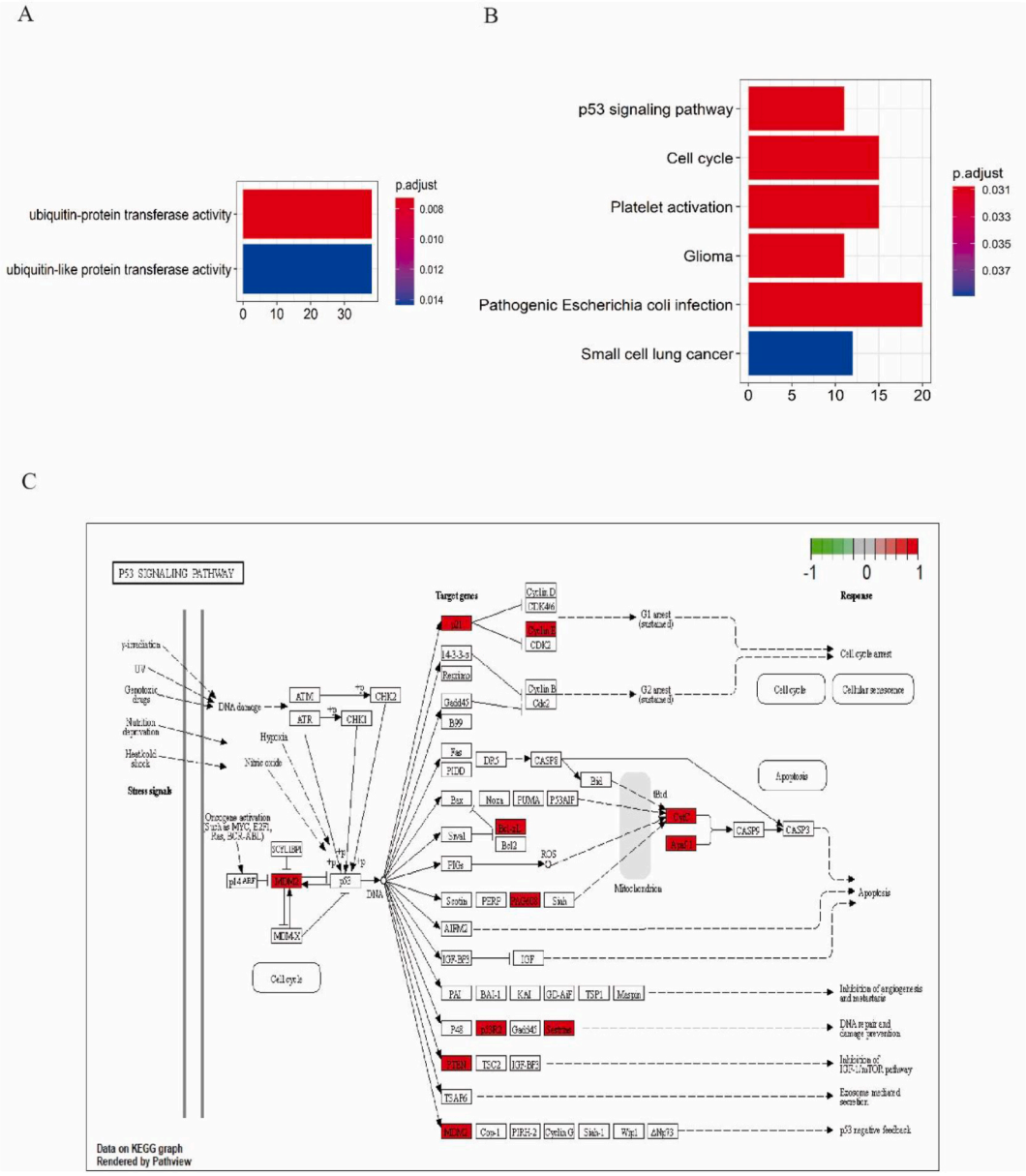

Fig. 4. Functional enrichment analysis. (A) GO enrichment items of target genes. (B) Gene ratio and KEGG pathway items. (C) revealed upregulated genes in p53 signal pathway (The original image is provided in the Supplementary material file).

student's t-test was used to analyze the difference between groups and $P < 0.05$ (or FDR <0.05) was considered statistically significant. One-way analysis of variance was used to compare immune-cell type proportions among the GEO cohort. The experiments were repeated at least three times.

3. Results

3.1. DECs identification in infantile hemangioma

In GSE98795 datasets, a total of 67 circRNAs were differentially expressed in the IH samples compared to the normal samples. Among these DECs, 13 were downregulated and 54 were upregulated. The top 6 upregulated circRNAs with the most significant expression were hsa_circ_0006903, hsa_circ_0000788, hsa_circ_0001693, hsa_circ_0023016, hsa_circ_0001605, hsa_circ_0001568. These results were presented in the heat map (Fig. 2A) and volcano plot (Fig. 2B).

3.2. Schema graph of hsa_circ_0006903 and construction of ceRNA network

To explore the molecular structure of hsa_circ_0006903, we analyzed the basic structure of hsa_circ_0006903 downloaded from CSCD database online (Fig. 3A and B). CircRNAs functioning as the ceRNA have been most widely reported [24]. Then, we explored the target miRNAs of "hsa_circ_0006903" in the CSCD database and screen out 41 miRNAs for next study. Target genes of 41 miRNAs interacting with hsa_circ_0006903 were identified using miRDB database, miRTarBase database, and TargetScan database. In the present study, 41 miRNAs and 1002 target genes were screened out to construct ceRNA network using Cytoscape software 3.6.0. The result was shown in Supplementary Table 1. The hsa_circ_0006903-mediated ceRNA network was presented in Fig. 3C.

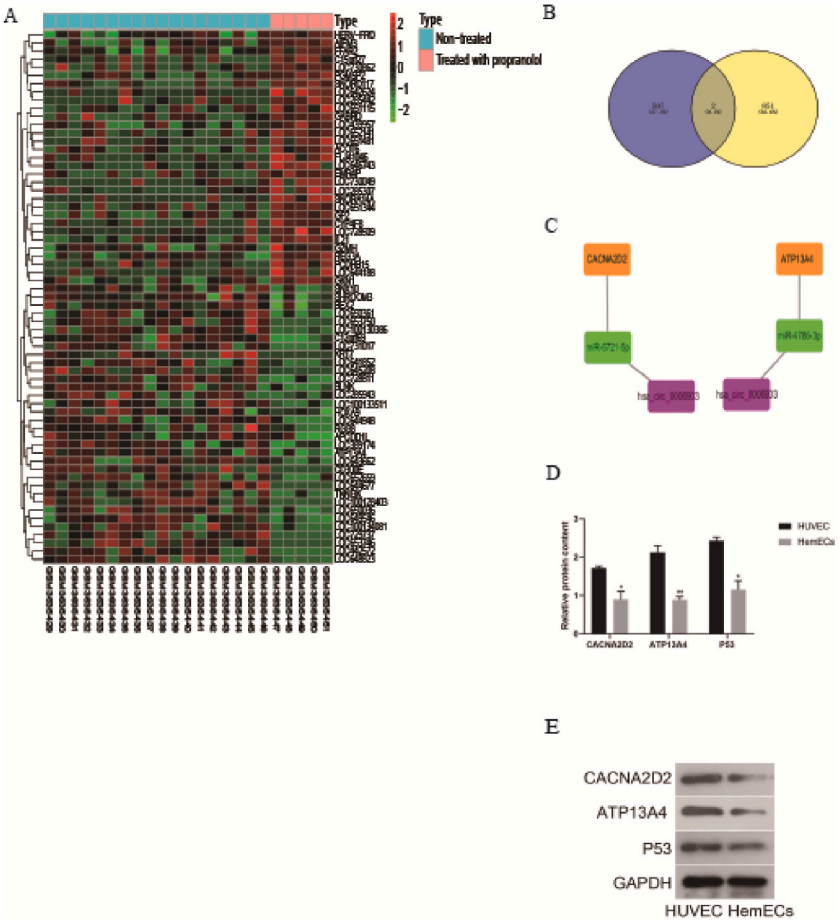

Fig. 5. Hsa_circ_0006903 regulatory axis in IH with propranolol treatment and validation. (A) Heatmap of DEGs in infantile hemangioma with propranolol treatment. (B) Common genes between DEGs and target genes of hsa_circ_0006903 using VENNY.2.1 online database. (C) Regulatory axis of hsa_circ_0006903/miR-6721-5p/CACNA2D2 and hsa_circ_0006903/miR-4786-3p/ATP13A4. (D) The expression of CACNA2D2, ATP13A4, and P53 in HemECs and HUVEC cell lines. (E) The expression of ATP13A4, CACNA2D2, and P53 in IH (The original image is provided in the Supplementary material file).

3.3. Functional enrichment analysis of target genes of hsa_circ_0006903

GO enrichment and KEGG pathway analysis were performed to explore the biological function of target genes of hsa_circ_0006903. GO enrichment analysis revealed that ubiquitin-protein transferase activity and ubiquitin-like protein transferase activity were closely associated with IH (Fig. 4A). KEGG signaling pathways showed that target genes of hsa_circ_0006903 were mainly enriched in the p53

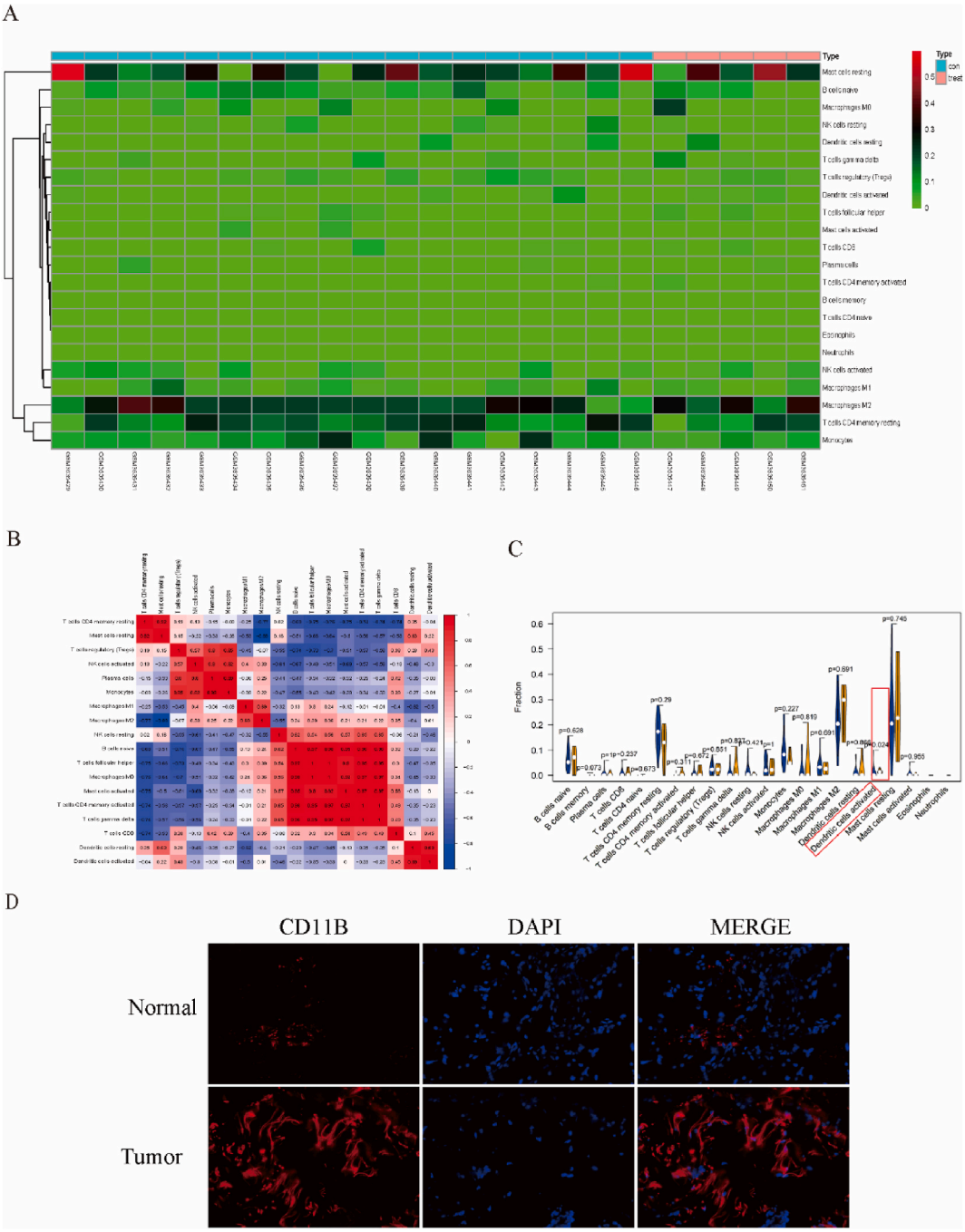

Fig. 6. Immune cells infiltration and dendritic cells activated identification. (A) Heatmap of 22 immune-cell types identified by estimating mRNAs expression in IH with propranolol treatment from the GEO database. (B) Pearson correlation analysis revealing the correlation of 22 immune-cell types. (C) The vioplot showing the expression of 22 immune-cell types and dendritic cells activated was significant differentially expressed. (D) CD11b and DAPI Colocalization in IH samples using immunofluorescence double staining (The original image is provided in the Supplementary material file).

signaling pathway, cell cycle, platelet activation, glioma, pathogenic escherichia coli infection, shigellosis, small cell lung cancer (Fig. 4B). Subsequently, considering P53 was involved in the development of many tumors, we analyzed genes associated with the p53 signaling pathway, which were presented in Fig. 4C. The expression of P53 in infantile hemangioma was evaluation in the next analysis.

3.4. Hsa_circ_0006903 regulatory axis in infantile hemangioma treated with propranolol and validation

Now, propranolol treatment of infantile hemangioma (IH) has been widely investigated in recent years. We explored DEGs between IH and IH with propranolol treatment. Firstly, a total of 509 DEGs were identified from GSE127487 datasets including IH and IH with propranolol treatment. Among the DEGs, 247 genes were downregulated and 262 genes were upregulated. These results were presented in the heat map (Fig. 5A). Then, we used online database VENNY.2.1.0 [25] to screen out common genes between target genes of hsa_circ_0006903 circular RNA and DEGs in GSE127487 cohort. CACNA2D2 and ATP13A4 were the common genes presented in Fig. 5B. We showed that CACNA2D2 and ATP13A4 played important role in IH with propranolol treatment. Therefore, we analyzed the regulatory axis of hsa_circ_0006903 functioning as a ceRNA hsa_circ_0006903/miR-6721-5p/CACNA2D2 and hsa_circ_0006903/miR-4786-3p/ATP13A4 axis in Fig. 5C. Finally, we validated the expression of CACNA2D2, ATP13A4, and P53. Our results revealed that CACNA2D2, ATP13A4, and P53 were significantly downregulated in HemECs compared to HUVEC (Fig. 5D and E).

3.5. Immune cells infiltration and dendritic cells activated identification

Immune cells are important components of the tumor microenvironment and are closely associated with tumor development. In this study, we used the CIBERSORT algorithm to evaluate the proportions of immune-cell types in the IH samples from GEO database

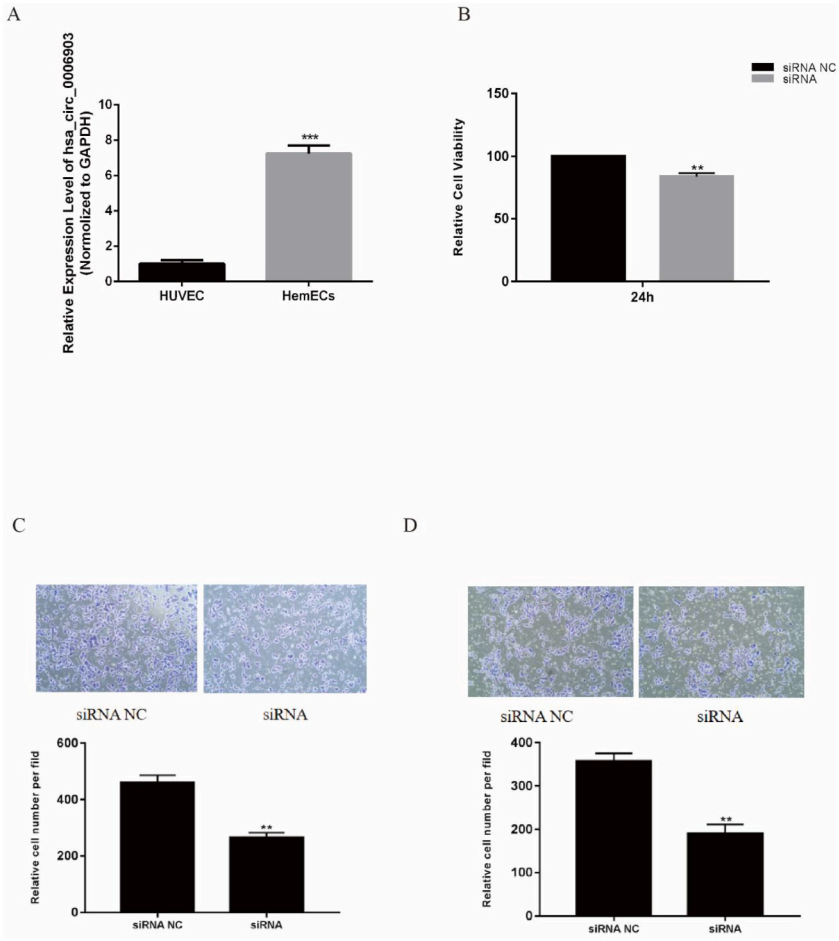

Fig. 7. Knockdown of hsa_circ_0006903 circular RNA inhibits proliferation, migration, and invasion in IH cells. (A) The expression of hsa_circ_0006903 in IH. Proliferation (B), migration (C), and invasion (D) were investigated in cells transfected with siRNA-NC or siRNA by Transwell assays. *P < 0.05, **P < 0.01, ***P < 0.001, Scalebar, 100 mm (The original image is provided in the Supplementary material file).

(Fig. 6A). Pearson correlation analysis revealed plasma cells was the most positively correlated with Monocytes (R = 0.99). However, Macrophages M2 was the most negatively correlated with Mast cells resting (R = −0.88) (Fig. 6B). We found that dendritic cells activated was significantly overexpressed in IH samples than with propranolol treatment sample (Fig. 6C). CD11b was a marker for dendritic cells activated [26]. Immunofluorescence colocalization staining revealed that CD11b was upregulated in tissues compared to normal tissues (Fig. 6D).

3.6. Ha_circ_0006903 expression and functional experiment in vitro

We validated the expression of hsa_circ_0006903 in IH. The result showed that hsa_circ_0006903 was significantly overexpressed in HemECs compared to HUVEC (Fig. 7A). To explore the role of hsa_circ_0006903 in IH cells, CCK8 assay showed that si-hsa_circ_0006903 could significantly inhibit cell proliferation in HemECs (Fig. 7B). To further examine the effect of hsa_circ_0006903 in IH, we showed that hsa_circ_0006903 affected cell migration and invasion (Fig. 7C and D) using transwell assays. The result revealed that hsa_circ_0006903 could play an important role in the development of IH.

4. Discussion

IH is a vascular tumor commonly affecting children, known as infantile capillary hemangiomas, strawberry hemangiomas, or strawberry nevi [27]. IH is characterized by a proliferative rapid growth phase [28]. Previous studies confirmed that ncRNAs regulated the pathogenesis in tumors [29].

CircRNA was first found as highly base-paired rod-like structures [30]. Increasing studies showed that circRNAs played critical roles in cancer development [31]. Numerous circRNAs may function as the competitive endogenous RNA (ceRNA) mechanism. Kulcheski, F. R. et al. found that circular RNAs were miRNA sponges as a new class of biomarker [32]. Rong, D. et al. showed that circPSMC3 could act as a competitive endogenous RNA through sponging miR-296-5p to inhibit the proliferation and metastasis of gastric cancer [33]. Xia, T.et al. thought that circPDZD8 promoted gastric cancer progression via sponging miR-197-5p [34]. However, the expression pattern and regulatory roles of circRNAs in IH are unclear.

Our study showed that hsa_circ_0006903 was significantly overexpressed in IH. However, there is no report elucidating the role of hsa_circ_0006903 in IH. In this study, hsa_circ_0006903 were selected for further study.

Increasing studies reported that miRNAs played crucial roles in keloid [35]. To explore the role of miRNAs in IH, we downloaded miRNAs expression data GSE100682. We found that hsa-miR-210-3p was the most significantly upregulated in IH. Many studies elucidated the role of hsa-miR-210-3p in tumor [36]. Our result showed that miR-6721-5p and miR-4786-3p were significantly expressed in IH. Previous study displayed that miR-6721-5p was associated with Osseous-associated cervical spondylomyelopathy (OA-CSM) [37]. Moreover, miR-4786-3p played an important role in the efficacy of chemotherapy for oral squamous cell carcinoma (OSCC) [38]. We will collect many clinical samples to validate the expression of miR-6721-5p and miR-4786-3p, and to investigate the mechanism in IH.

By the integrated analysis of many databases, we constructed a novel hsa_circ_0006903 -mediated ceRNA network using bioinformatics tools. In the present study, we found that target genes of hsa_circ_0006903 were enriched in P53 signaling pathway. Additionally, P53 was significantly downregulated in IH. Some reports thought that P53 signaling pathway was indicated to play a critical role in cancers [39]. Moreover, P53 expression is significantly enhanced in HemECs following treatment with propranolol [40], which was also consistent with this work.

There are different approaches for IH treatment. Indications for IH with propranolol treatment were ulceration, risk of disfigurement and functional impairment [41]. However, the molecular mechanism of propranolol in IH treatment is unclear. Recent studies have shown that the mechanism of IH with propranolol treatment was associated with the inhibition of cell cycle [42]. Platelet activation may affect the process of IH [43].

In the present study, we identified DEGs in IH with propranolol treatment and constructed the hsa_circ_0006903 regulatory axis. The molecular mechanism of IH with propranolol treatment needs further investigation in the future. In addition, CACNA2D2 and ATP13A4 attracted our interest. The CACNA2D2 gene, a new subunit of the Ca2+ channel complex, was identified in the homozygous deletion region of chromosome 3p21.3 in human lung and breast cancers [44]. CACNA2D2 was implicated in cancer development. Warnier, M. et al. found that CACNA2D2 promoted tumorigenesis by stimulating cell proliferation and angiogenesis [45]. ATPase Type 13A4 (ATP13A4) is a cation-transporting, P_5-type ATPase that has been reported in neurodevelopmental disorders [46]. Until now, the role of CACNA2D2 and ATP13A4 which were associated with propranolol treatment in IH were not reported.

Tumor immune cells infiltration accounts for the progression and aggressiveness of tumors. Previous studies found that tumor immune cells played an important role in pancreatic ductal adenocarcinoma [47], colorectal cancer [48]. In this study, we explored immune cells infiltration and revealed that dendritic cells activated was significantly overexpressed. Dendritic cells (DCs) are a diverse group of specialized antigen-presenting cells with key roles in cancer immunology and immunotherapy [49]. Duong et al. revealed that an activation state of CD11b + conventional DCs (DC2) was characterized by expression of interferon (IFN)-stimulated genes (ISG + DCs) [50].

In this research, we evaluated the expression of CD11b in IH samples and found that CD11b was overexpressed in IH tissues. We investigated the role of dendritic cells activated in IH for the first time. YC Zhang. et al. found that FOXF1 was identified as a novel biomarker related with dendritic cells activated in IH [51]. This study verified that dendritic cells activated was expected to be explored as a therapeutic target in further work.

CircRNAs are demonstrated to be closely associated with tumor development. To validate the expression of hsa_circ_0006903 in IH,

RT-qPCR was applied. The result showed that hsa_circ_0006903 was significantly overexpressed in IH. Subsequently, we investigated the function of hsa_circ_0006903 and found that hsa_circ_0006903 promoted the proliferation and migration of HemECs cells. Previous study showed circRNA could be as vaccine in different diseases treatment [52]. This study revealed that hsa_circ_0006903 could be as a therapeutic target in IH. However, the regulatory mechanism of hsa_circ_0006903 in IH needs further to be explored.

There are two limits in this study. Firstly, our study should collect many IH samples to verify the expression of hsa_circ_0006903. Secondly, this study needs to elucidate the mechanism of hsa_circ_0006903 in regulating the development of IH. In conclusion, we revealed a novel hsa_circ_0006903-mediated ceRNA network and promoted tumor progression. In addition, we explored the landscape of immune cells infiltration and a biomarker CD11b overexpression of dendritic cells as a promising therapeutic strategy for IH.

Funding

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

The datasets analyzed in this study were publicly available from the GEO database, GSE98795, GSE127487, CSCD database, miRDB database, miRTarBase database, and TargetScan database.

CRediT authorship contribution statement

Xibo Gao: Writing – original draft. **Lixin Chen:** Formal analysis. **Hailiang Zuo:** Validation. **Qinfeng Li:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Qinfeng Li reports financial support was provided by Tianjin Children's Hospital. Qinfeng Li reports a relationship with Tianjin Children's Hospital that includes: employment. Qinfeng Li has patent pending to Tianjin Children's Hospital. Xibo Gao et al. were employed by Tianjin Children's Hospital If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34186.

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