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Original Article

Peptostreptococcus anaerobius promotes cervical cancer angiogenesis by upregulating SCD to activate ERK pathway

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Abstract: Accumulating evidence indicates that virginal microbiota dysbiosis is a distinct feature of cervical cancer. As cervical lesions progress towards malignancy, the dominance of *Lactobacillus* species within the vaginal microbiota is progressively replaced by anaerobic bacteria, with *Peptostreptococcus anaerobius* (*P. anaerobius*) being a noticeable one. Despite this well-documented microbial shift, the precise functional role of *P. anaerobius* in cervical cancer development and progression has remained unclear. Our study demonstrated that *P. anaerobius* promoted cervical cancer cells proliferation and enhanced tube formation of human umbilical vein endothelial cells (HUVECs). Furthermore, we identified a significant upregulation of stearoyl-CoA desaturase 1 (SCD) following the introduction of *P. anaerobius*, leading to subsequent activation of the extracellular signal-regulated kinase (ERK) signaling pathway. Moreover, supplement with *P. anaerobius* failed to reverse the ERK1/2 inhibitor-induced suppression of the tube-formation. *In vivo* validation revealed that *P. anaerobius* exerted its influence on angiogenesis by regulating SCD expression and ERK pathway acvivation. Collectively, these findings reveal an oncogenic role of *P. anaerobius* in cervical cancer, mediated by the SCD-ERK signaling axis to drive angiogenesis. This work provides novel mechanistic insights into the contribution of vaginal microbiota to gynecologic malignancies.

Keywords: Cervical cancer, angiogenesis, *Peptostreptococcus anaerobius*, SCD, ERK pathway

Introduction

The tumor microenvironment (TME) plays a pivotal role in the initiation and progression of cancer. It's a complex ecosystem that influences all stages of oncogenesis. Recent research has established that the local microbiota as an essential component of the TME. While the impact of gut flora on colorectal carcinogenesis and therapy response is well-documented [1], the vaginal microbiota is crucial in maintaining the homeostasis of the female reproductive system. In healthy states, *Lactobacillus* species dominate, maintaining an acidic pH that serves as a natural barrier against exogenous pathogens. Studies have identified associations between alterations in vaginal microbiota composition and the severity of cervical lesions [2-5]. Specifically, the progression of cervical lesions correlates with increased microbial diversity and a decline in *Lactobacillus* dominance, replaced by anaerobic bacteria characteristic of community state type IV [4, 5]. This shift becomes particularly pronounced in advance, irreversible high-grade squamous intraepithelial lesions (HSILs) and cervical cancer. Nevertheless, the direct mechanistic impact of vaginal microbiota on cervical lesions progression remains poorly understood.

Peptostreptococcus anaerobius (*P. anaerobius*) has emerged as a significant factor in carcinogenesis. It contributes to colorectal cancer development by modulating lipid metabolism and the immune responses [6, 7], and mediates resistance to chemotherapy and immunotherapy in this context [8, 9]. An increased abundance of *P. anaerobius* has also been

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observed in cervical HSIL patients [2], although the underlying mechanism has not been elucidated.

Malignant tumors exhibit high demands for oxygen and nutrients. Rapid tumor growth necessitates angiogenesis to supply these resources. Consequently, the TME is frequently characterized by hypoxia, ischemia and acidosis. These conditions simulate the release of cytokines and growth factors that promote blood and lymphatic vessel formation, facilitating tumor growth and metastasis [10]. Consequently, angiogenesis is crucial not only for tumor growth but also tightly linked to tumor invasion and migration, significantly influencing overall tumor progression. Anti-angiogenesis therapies, such as bevacizumab for advanced cervical cancer, are well-established clinical strategies [11]. However, the potential influence vaginal microbiota on angiogenesis in cervical cancer remains unexplored.

Stearoyl-CoA desaturase 1 (SCD), a key regulator of lipid metabolism, maintains the balance between saturated and monounsaturated fatty acids. Appropriate SCD expression levels are essential for cellular homeostasis and lipogenesis. Elevated SCD levels are detected in tumors of various origins, and SCD inhibition represents a promising anti-neoplastic strategy [12-15]. Recent research demonstrates that SCD overexpression promotes proliferation, metastasis, and lipid metabolism in cervical cancer [16]. However, its role in modulating cervical cancer angiogenesis is unclear.

In this study, we elucidated the carcinogenic effects of *P. anaerobius* in cervical cancer. We demonstrate that *P. anaerobius* promotes tumor angiogenesis by upregulating SCD expression and subsequently activating the extracellular signal-regulated kinase (ERK) pathway. These findings reveal the specific mechanism by which the vaginal microbiota influences cervical cancer progression and identify potential novel therapeutic targets.

Material and methods

Clinical sample collection

Vaginal secretion samples were collected from the Gynecology and Obstetrics Hospital of Fudan University between October 2023 and April 2024. The cohort comprised 12 patients with histopathologically confirmed cervical cancer and 12 healthy controls. The exclusion criteria were as follows: (1) usage of antibiotics within 14 days before sampling; (2) co-existence of other gynecological malignancies; (3) patients with vaginitis; (4) history of sexual intercourse or vaginal douching within 3 days. Informed consents were obtained from all patients, and all participants were anonymized. The study complied with the Declaration of Helsinki and was approved by the hospital's ethics committee (Approval number: kyy2023-136). Samples were stored at -80°C and DNA extraction was perfoemed in a single batch following complete sample collections.

Cell culture and animal experiments

Cervical cancer cell lines Hela and SiHa were purchased from the Chinese Academy of Sciences Shanghai cellular library. Human umbilical vein endothelial cells (HUVECs) were kindly provided by the Gynecology and Obstetrics Hospital of Fudan University. Cells were cultured in DMEM (Servicebio, Wuhan, Hubei, China) supplemented with 10% fetal bovine serum (Gibco, Guangzhou, Guangdong, China) and 1% penicillin-streptomycin (Servicebio, Wuhan, Hubei, China) at 37°C in a humidified incubator with 5% CO_2.

Animal procedures were approved by the Animal Welfare and Ethics Group of the Laboratory Animal Science Department of Fudan University (approval number: 2024-FCKYY-023). Female BALB/c-nu mice (4-6 weeks old) were purchase from Shanghai Model Organisms Center, Inc in Shanghai, China. Animals were housed in a specific-pathogen-free (SPF) facility under a 12-hour light/dark cycle and 50-55% relative humidity. SiHa cells in the logarithmic growth phase were collected and numbered. A cell suspension of 1-5 × 10^5/100 μl was subcutaneously injected into the left axilla of each mouse. The mice were humanely euthanized by cervical dislocation when the maximum tumor size reached 1.2-1.5 cm, and the tumors were then excised.

Culture of P. anaerobius

P. anaerobius strain was a gift from the Gynecology and Obstetrics Hospital of Fudan University. The strain was revived on anaerobic

agar plates and cultured at 37°C under anaerobic conditions. After 48 hours, single colonies were inoculated into broth and incubated anaerobically at 37°C with 160 rpm shaking for about 36 hours. The optical density (OD) value of the *P. anaerobius* cultures was measured using a microplate reader to standardize consistent bacterial concentration in each batch. Cultures were centrifuged at 4000 rpm for 20 minutes and filtered through a 0.22-μm-pore-sized sterile-filter to obtain the supernatant.

Tube formation experiment

Matrigel (Corning Incorporate, NY, USA) was stored at -20°C and thawed overnight on ice at 4°C. Matrigel was dispensed into a 96-well plate and placed at 37°C for 30-60 minutes to solidify. Early-passage HUVECs (3-5 × 10^4/well) were seeded onto each well and incubated in an atmosphere of 5% CO_2 at 37°C. Tube formation was monitored every 2-3 hours. Calcein AM (Beyotime Biotechnology, Baoshan, Shanghai, China) staining was applied to visualize the tube formation of HUVECs.

Quantitative polymerase chain reaction

Quantitative polymerase chain reaction (qPCR) was performed using Taq Pro Universal SYBR qPCR Master Mix (Nanjing Vazyme Biotech Co., Ltd., Jiangsu, China). The specific primers for *P. anaerobius* were forward 5'-CTGGTGGATAGGAGGCAAAG-3' and reverse 5'-CCACAATATTGGCATTTGGA-3'. The primers for SCD were forward 5'-TTCCTACCTGCAAGTTCTACACC-3' and reverse 5'-CCGAGCTTTGTAAGAGCGGT-3'. And the primers for β-actin were forward 5'-TGTCACCAACTGGGACGATA-3' and reverse 5'-GGGGTGTTGAAGGTCTCAAA-3'. The PCR was carried out in a 20 μl volume with the procedure of degeneration at 95°C for 30 seconds, followed by 40 cycles of amplification with parameters of 95°C for 10 seconds and 60°C for 30 seconds, and then a melting curve analysis with settings of 95°C for 15 seconds, 60°C for 60 seconds and 95°C for 15 seconds.

Western blot

Total protein was extracted using RIPA Lysis Buffer (Beyotime Biotechnology, Baoshan, Shanghai, China). Lysates were mixed with loading buffer, separated by Tris-glycine SDS-PAGE. Tris-glycine electrophoresis was performed after loading the samples into the lanes at a constant voltage of 90 V in the stacking gel and 120 V in the separating gel. The proteins were transferred to polyvinylidene fluoride (PVDF) membranes at a constant current of 400 mA for 40 minutes. Membranes were then blocked in 5% non-fat milk at room temperature for two hours on a slow-speed shaker. After washing with Tris buffered saline with Tween-20 (TBST), the membrane was incubated with the primary antibody overnight at 4°C. Then the membrane was washed with TBST for 5 minutes × 5 times and incubated with the secondary antibody at room temperature for 1 hour. After another round of washing with TBST for 5 minutes × 5 times, the proteins was detected using electrochemiluminescence (ECL) substrate. The primary antibodies included anti-SCD (Proteintech, 1:10000 dilution), anti-p-ERK1/2 (Abmart, 1:1000 dilution), anti-ERK1/2 (Abclonal, 1:1000 dilution), anti-Tubulin (Proteintech, 1:20000 dilution). The secondary antibodies included HRP-labeled Goat Anti-Mouse IgG (H+L) (Beyotime, 1:10000 dilution) and HRP-labeled Goat Anti-Rabbit IgG (H+L) (ZSGB-Bio, 1:10000 dilution).

Immunofluorescence staining

Tumor tissues were fixed in 4% paraformaldehyde and embedded in paraffin. After paraffin sectioning, the tissue sections were dewaxed by xylene and hydrated through a series of ethanol solutions with decreasing concentrations. Antigen retrieval was performed followed by permeabilization with 0.5% TritonX-10. After washing with phosphate buffered saline with Tween-20 (PBST), the sections were blocked with goat serum for one hour at room temperature. The primary antibody of CD31 (Proteintech, 1:200 dilution) was applied to cover the surface of the tissue and incubated at 4°C overnight. After washing with PBST, the sections were incubated with the secondary antibody Alexa Fluor® 594-conjugated Goat Anti-Rabbit IgG (H+L) (Servicebio, 1:800 dilution) for one hour at room temperature. After washing, the DAPI-containing anti-fluorescence quenching tablet encapsulation was added, and a coverslip was gently placed on top. The sections were examined under a fluorescence microscope with an excitation wavelength of 591 nm.

Statistical analysis

One-way analysis of variance (ANOVA) was applied for multi-group comparisons and pair-

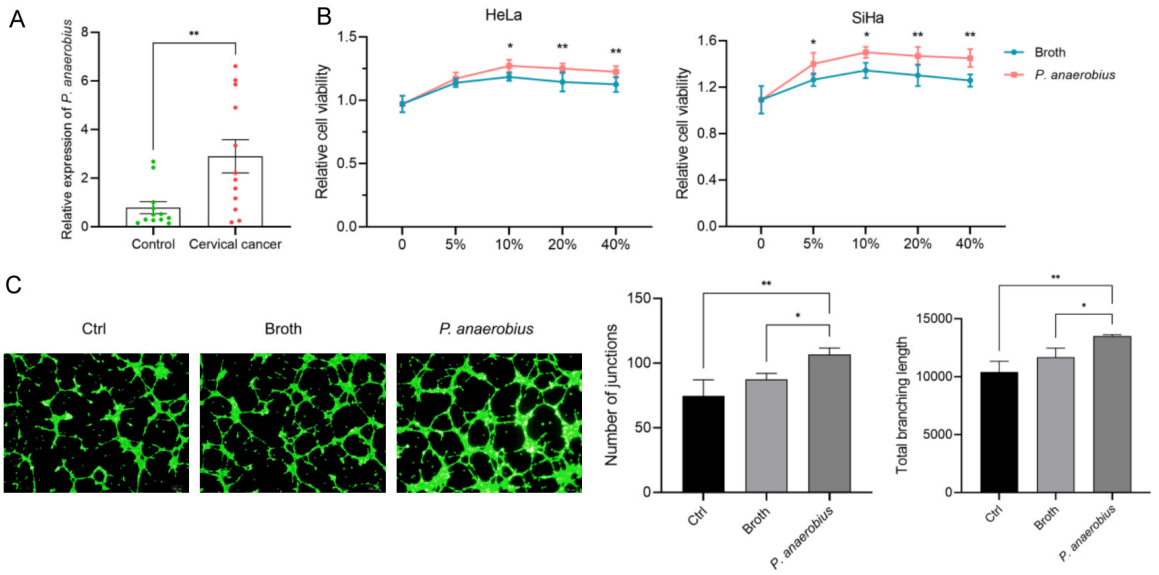

Figure 1. *P. anaerobius* promotes the angiogenesis of cervical cancer. A. The concentration of *P. anaerobius* was elevated in cervical cancer patients; B. *P. anaerobius* promoted the proliferation of Hela and SiHa cells; C. The medium derived from *P. anaerobius* treated SiHa cells promoted the tube formation of HUVECs (Magnification: 40×). Results are presented as mean ± SD. *P < 0.05, **P < 0.01.

wise comparison was conducted using Tukey's multiple comparisons test. Data was visualized using GraphPad Prism 9. HUVEC tube formation was quantified using the Angiogenesis Analyzer plugin in ImageJ software. Statistical analysis was conducted in SPSS v25.0. A *P*-value < 0.05 was considered statistically significant.

Results

P. anaerobius promotes the angiogenesis of cervical cancer

To investigate the role of *P. anaerobius* in cervical carcinogenesis, we quantified its abundance in vaginal samples from cervical cancer patients and healthy controls using qPCR. The abundance of *P. anaerobius* was significantly elevated in cancer patients (**Figure 1A**). This initial finding was a strong indication that *P. anaerobius* involved in the development of cervical cancer. We next assessed the direct impact of *P. anaerobius* supernatant on cervical cancer cell proliferation. As shown in **Figure 1B**, the treatment of the *P. anaerobius* supernatant significantly enhanced growth in both Hela and SiHa cervical cancer cell lines. Given angiogenesis is critical for tumor progression, we evaluated the pro-angiogenic potential of *P. anaerobius* using a HUVEC tube formation assay with conditioned media from *P. anaerobius*-treated SiHa cells. The results showed that the medium significantly accelerated the growth of junctions and the branching of HUVECs (**Figure 1C**). This indicated that *P. anaerobius*, through its interaction with cervical cancer cells, could enhance the angiogenic potential of endothelial cells, providing tumors with the necessary blood supply for their growth and spread.

P. anaerobius promotes angiogenesis by regulating the expression of SCD

To elucidate the mechanism of the pro-angiogenic effect of *P. anaerobius*, we performed proteomic analysis. The analysis of SiHa cells treated with *P. anaerobius* supernatant revealed significant upregulation of SCD (**Figure 2A**), validated by Western blot (**Figure 2B**). To establish SCD's functional role, we performed SCD knockdown using short hairpin RNA targeting SCD (shSCD) and conducted RNA-sequencing (**Figure 2C**, **2D**). Transcriptomic analysis demonstrated enrichment of angiogenesis-related pathways such as blood vessel morphogenesis and remodeling upon SCD perturbation (**Figure 2E**). Conditioned media from shSCD SiHa cells significantly reduced HUVEC tube complexity (junction number and branch length) compared to shNC controls (**Figure 2F**).

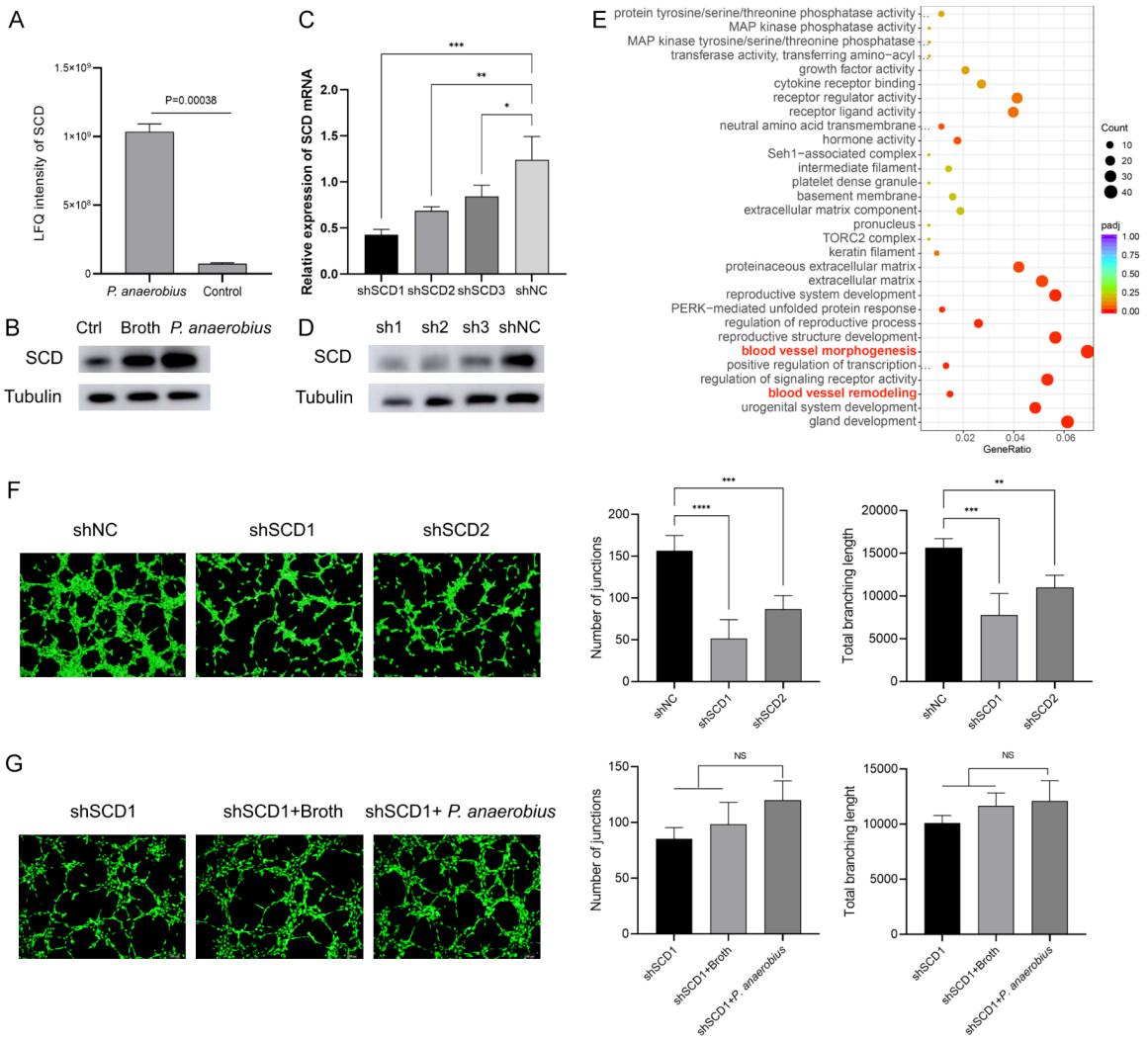

Figure 2. *P. anaerobius* promotes angiogenesis by regulating the expression of SCD. A. Proteome analysis uncovered the significant elevation in the expression of the SCD protein in SiHa cells treated with *P. anaerobius* supernatant; B. The expression of SCD protein was increased after treatment with *P. anaerobius* supernatant; C, D. The expression of SCD mRNA and SCD protein was downregulated by shSCD; E. The Gene Ontology enrichment analysis of RNA-seq showed that processes related to blood vessel morphogenesis and blood vessel remodeling were highly enriched; F. SCD knock-down hindered the tube formation of HUVECs (Magnification: 40×); G. *P. anaerobius* supernatant failed to reverse the inhibition of tube formation resulted from SCD knockdown (Magnification: 40×). Results are presented as mean ± SD. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Crucially, *P. anaerobius* supernatant failed to rescue this angiogenic impairment in shSCD cells (shSCD1 + *P. anaerobius* vs. shSCD1 or shSCD1 + broth groups; **Figure 2G**), confirming SCD as the essential mediator of *P. anaerobius*-induced angiogenesis.

P. anaerobius promotes angiogenesis by activating the ERK signaling pathway through SCD regulation

RNA-seq analysis following SCD knockdown indicated significant suppression of ERK signaling (**Figure 3A**). To probe into the downstream signaling cascade through which SCD regulates angiogenesis, we detected the activation status of the ERK pathway. We observed that *P. anaerobius* supernatant increased phosphorylated ERK1/2 (p-ERK1/2) levels in SiHa cells, while SCD knockdown reduced p-ERK1/2 expression relative to shNC controls (**Figure 3B**). To further clarify the role of the ERK pathway in angiogenesis, an ERK1/2 inhibitor was administrated to SiHa cells. Subsequently, the culture medium from these treated SiHa cells was used to culture HUVECs. Pharmacological inhi-

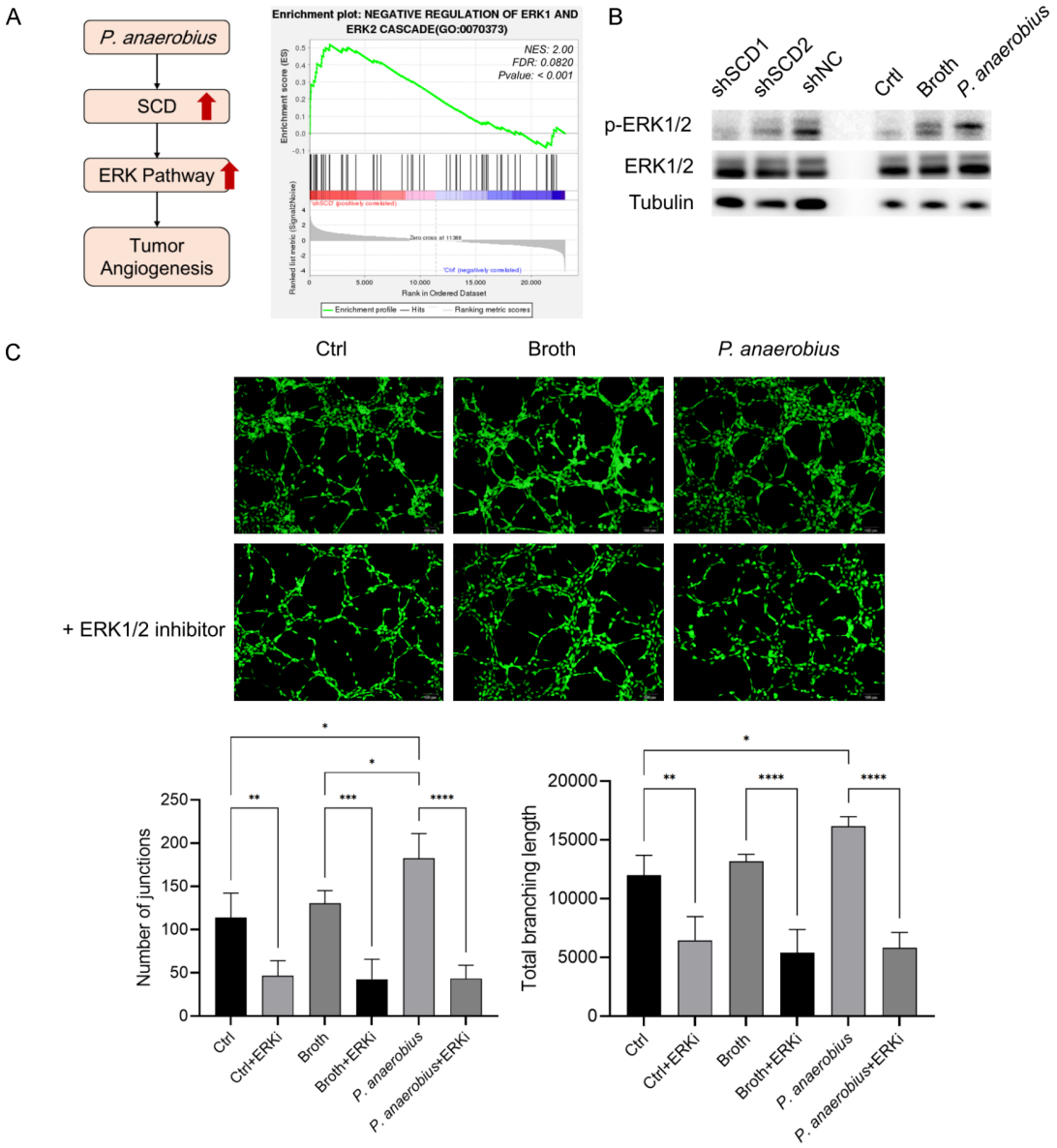

Figure 3. *P. anaerobius* promotes angiogenesis by activating the ERK signaling pathway through SCD regulation. A. The negative regulation of the ERK pathway was enriched after SCD knock-down management; B. Treatment with *P. anaerobius* supernatant (PA) led to the activation of the ERK signaling pathway. However, when SCD was knocked down, this activation was reversed, and the activation of ERK pathway was downregulated; C. The tube formation of HUVECs was effectively restrained by ERK1/2 inhibitor (ERKi) of the ERK pathway, which cannot be reversed by *P. anaerobius* supernatant administration (Magnification: 40×). Results are presented as mean ± SD. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

bition of ERK1/2 in SiHa cells profoundly suppressed the junction formation and branching in HUVECs (**Figure 3C**). Furthermore, the addition of the supernatant of *P. anaerobius* could not reverse the inhibitory effect of the ERK1/2 inhibitor on the tube-forming ability of HUVECs. The findings suggested that *P. anaerobius* stimulates angiogenesis by regulating SCD, which in turn activates the ERK signaling pathway.

P. anaerobius promotes tumor angiogenesis in tumor-bearing mice

To elucidate the *in vivo* role of *P. anaerobius*, the tumor-bearing model in nude mice was employed. CD31 staining was used to visualize and quantify blood vessel density. In tumor-bearing mouse models, *P. anaerobius* administration significantly increased tumor microves-

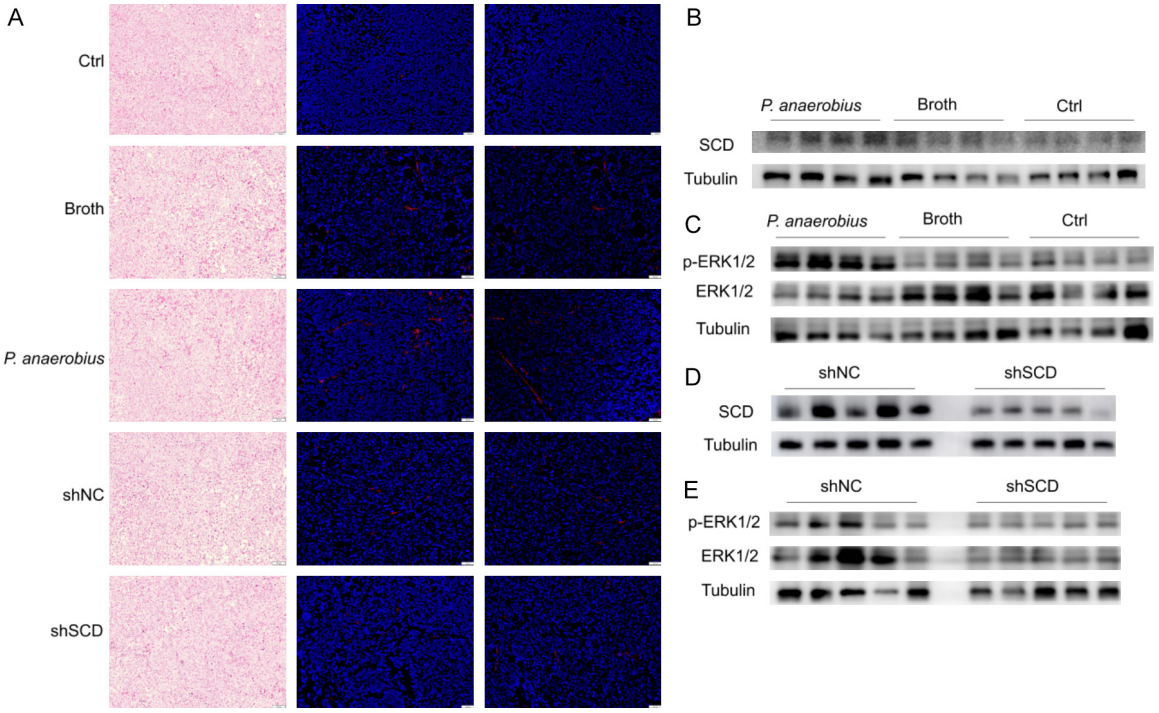

Figure 4. *P. anaerobius* promotes tumor angiogenesis in tumor-bearing mice. A. The H&E staining and blood vessels (in red color) in xenograft tumors visualized by CD31 staining (Magnification: 200×) were more densely packed in *P. anaerobius*-treated group (PA) compared to those in both the broth-treated group (Broth) and the control group (Ctrl). The vascular density in the xenograft tumors created using SiHa shSCD was notably lower than that in the control shNC-constructed xenograft tumors; B, C. In the tumors of nude mice treated with *P. anaerobius* supernatant, the expression level of both SCD and p-ERK1/2 proteins were significantly increased; D, E. The expression of SCD and p-ERK1/2 proteins were downregulated in tumor of nude mice constructed by SiHa shSCD compared to the control SiHa shNC.

sel density ($CD31^+$ staining) compared to broth-treated and untreated controls (**Figure 4A**). In the *P. anaerobius*-treated group, we witnessed an up-regulation of SCD and p-ERK1/2, which coincided with the increased growth of blood vessels (**Figure 4B**, **4C**). Conversely, xenografts derived from SCD-knockdown SiHa cells exhibited reduced vascularization (**Figure 4A**) and decreased expression level of SCD and p-ERK1/2 (**Figure 4D**, **4E**). This demonstrated that *P. anaerobius* promotes tumor angiogenesis in tumor-bearing mice by upregulating SCD and activating the ERK signaling pathway.

Discussion

Previous research established *P. anaerobius* as oncogenic and immunosuppressive agent in colorectal cancer [6, 7]. While increased abundance of anaerobes, including *P. anaerobius*, has been documented in HSILs and cervical cancer, the specific role of *P. anaerobius* in the progression from cervical lesions to malignancy remains poorly defined. This study aimed to elucidate the carcinogenic effects of *P. anaerobius* outside of the intestinal tract and provide deeper insight into the impact of vaginal microbiota on cervical cancer pathogenesis. Utilizing proteomic and transcriptomic analyses, we identified significant upregulation of SCD and subsequent activation of the ERK pathway following *P. anaerobius* administration, which further contributes to cervical cancer angiogenesis.

The association between anaerobic flora and cervical neoplasia development is well-supported [2-5], with *P. anaerobius* abundance notably elevated in HSIL patients [2]. Consistent with these clinical observations, our analysis of patient samples revealed a correlation between *P. anaerobius* and cervical cancer. *In vitro* studies further demonstrate that *P. anaerobius* promotes both cervical cancer cell proliferation and the tube-forming capacity of HUVECs.

Given that rapid tumor growth demands substantial oxygen and nutrients, angiogenesis is essential for sustaining proliferating malignancies and is critically implicated in cervical cancer progression [17, 18]. To validate these findings *in vivo*, we established a tumor-bearing mouse model. Immunofluorescence staining of CD31 revealed a significant increase in tumor microvessel density following administration of *P. anaerobius*, strongly indicating its pro-angiogenic capacity *in vivo*. Our study provides substantial mechanistic evidence linking the vaginal microbiota, specifically *P. anaerobius*, to angiogenesis in cervical cancer.

SCD overexpression is firmly associated with progression in multiple tumor types [19], and has been implicated in angiogenesis during myocardial infarction repair [20]. To further delve into the underlying molecular mechanisms, we employed proteomic and transcriptomic profiling. These analyses demonstrated a marked elevation in SCD expression levels in cervical cancer cells following *P. anaerobius* treatment. *In vivo* studies corroborated this finding, showing significant SCD upregulation upon intraperitoneal *P. anaerobius* administration. To investigate SCD's regulatory role in angiogenesis, we performed lentiviral-mediated short-hairpin RNA (shRNA) knockdown of SCD. Transcriptome sequencing in SCD-knockdown cells revealed a clear link between SCD expression and angiogenesis-related pathways in cervical cancer. Functional assessment confirmed that SCD knockdown substantially inhibited HUVECs tube formation *in vitro*. Moreover, reduced vascular density in xenograft tumors derived from SCD-knockdown cells further validated the regulatory role of SCD in cervical cancer angiogenesis *in vivo*.

The involvement of SCD in regulating the ERK pathway, significantly impacting cancer cell proliferation and survival, has been observed in renal carcinoma and lung carcinomas [21, 22]. Integrating our RNA-seq results, we found that SCD knockdown negatively regulated the ERK pathway. Conversely, *P. anaerobius* treatment, which upregulates SCD, effectively activated the ERK pathway both *in vitro* and *in vivo*. As growth factors and the ERK pathway are integral to angiogenesis regulation [10], our study further established a direct relationship between ERK pathway activation and cervical cancer angiogenesis. Critically, supplementation with *P. anaerobius* supernatant failed to rescue the inhibition of tube formation caused by an ERK inhibitor, highlighting the essential role of ERK signaling in *P. anaerobius*-induced angiogenesis. Consistent with *in vitro* results, SCD-dependent activation of the ERK pathway was also observed *in vivo*, elucidating a key downstream mechanism by which SCD promotes angiogenesis.

In summary, this study demonstrated that vaginal *P. anaerobius* promotes cervical cancer progression by upregulating SCD expression. Elevated SCD levels subsequently activate the downstream ERK signaling pathway, accelerating tumor angiogenesis. The marked expression of vascular growth by ERK inhibition confirms the pathway's critical role. Our findings provide compelling evidence for the direct carcinogenic effect of specific vaginal microbiota constituents on cervical cancer and delineate the pivotal role of SCD in mediating this tumorigenicity through angiogenesis.

Acknowledgements

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Disclosure of conflict of interest

None.

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