Inhibitory Effect of Dehydrocavidine on the Proliferation, Migration, and Invasion of Liver Cancer Cells by Regulating Macrophage Differentiation

Yifeng MO[1], Chun LI[1], Zimeng HUANG[2], Fan YANG[2], Shanshan CHU[2], Yongwen LI[3]*

1. College of Pharmacy, Guilin Medical University, Guilin 530200, China; 2. College of Clinical Medicine, Guilin Medical University, Guilin 530200, China; 3. Department of Pharmacology, College of Pharmacy, Guilin Medical University, Guilin 541199, China

Abstract [**Objectives**] This study was conducted to investigate the effect of dehydrocavidine (DC) on macrophage differentiation and the effect of DC-treated macrophage conditioned medium on the malignant progression of human liver cancer cell lines SK-HEP-1 and Huh-7. [**Methods**] THP-1 cells were induced using PMA and differentiated into M0 macrophages, which were then further polarized into M2-like macrophages by induction with interleukin-4 (IL-4) and interleukin-13 (IL-13), while being treated with different concentrations of DC (5, 10, 20 μM). Cell viability was assessed by the CCK-8 assay. The expression of M2 macrophage-related markers and factors was detected by Western blot and real-time quantitative PCR. The conditioned media from macrophages in each group were collected and co-cultured with SK-HEP-1 and Huh-7 liver cancer cells. The migration, invasion, and proliferation abilities of the liver cancer cells were evaluated by the wound healing assays, Transwell invasion assays, and colony formation assays. Additionally, the expression changes of epithelial-mesenchymal transition (EMT)-related proteins were detected. [**Results**] The CCK-8 assay showed that DC had no significant cytotoxicity against THP-1-derived macrophages within the experimental concentration range. Compared with the model group, DC significantly downregulated the mRNA and protein expression levels of the M2 macrophage markers CD163 and CD206 as well as related factors, thereby inhibiting M2-like polarization of macrophages. Co-culture with conditioned medium from DC-treated macrophages significantly suppressed the migration, invasion, and colony formation abilities of SK-HEP-1 and Huh-7 cells and downregulated the expression of EMT-related proteins such as N-cadherin, Vimentin, Snail, and MMP9. [**Conclusions**] DC can inhibit the polarization of THP-1-derived macrophages toward the M2-like phenotype, thereby weakening their pro-tumor effects and subsequently suppressing the migration, invasion, and proliferation of hepatocellular carcinoma cells.

Key words Liver cancer; Dehydrocavidine; Tumor-associated macrophages; Migration; Invasion; Proliferation

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Liver cancer is one of the most common malignant tumors worldwide, with a mortality rate increasing at an annual rate of approximately 2% - 3%, posing a serious threat to human health[1-2]. Due to its insidious onset, most patients are already at an advanced stage when diagnosed, losing the opportunity for curative surgical treatment. Currently, molecular targeted drugs commonly used in clinic (such as sorafenib) have limitations such as low objective remission rate and easy delopment of drug resistance. Therefore, it is urgent to develop novel anticancer agents with high efficacy and low toxicity[3].

The tumor microenvironment (TME) plays a critical role in the development and progression of liver cancer. The TME is composed of various cell types, including fibroblasts, endothelial cells, and immune cells such as macrophages and microglia, as well as non-cellular components such as collagen and fibronectin[4]. Tumor cells and their microenvironment participate in complex signaling networks that alter both the cellular and non-cellular components of the TME, thereby promoting tumor growth, maintenance, and resistance to therapy[5]. Tumor-associated macrophages (TAMs) are the most abundant immune cells in the TME and can polarize into two main phenotypes: M1 (anti-tumor) and M2 (pro-tumor). The M2-type TAMs promote tumor angiogenesis, matrix remodeling, and epithelial-mesenchymal transition (EMT) by secreting factors such as TGF-β and IL-10, thereby accelerating the proliferation, migration, and invasion of liver cancer cells[6-10]. Targeting the inhibition of macrophage M2 polarization has emerged as a novel strategy for anti-tumor therapy.

Dehydrocavidine (DC), an isoquinoline alkaloid active component derived from the traditional Chinese medicine Corydalis saxicola Bunting, exhibits multiple pharmacological activities, including anti-inflammatory, immunosuppressive, and anti-tumor effects[11-12]. Previous studies have shown that DC directly inhibits various tumor cells. However, whether it indirectly affects the malignant behavior of liver cancer cells by regulating macrophage polarization has not yet been systematically reported.

In this study, PMA-induced THP-1-derived macrophages were used as a model to investigate the effect of DC on IL-4/IL-13-induced M2-like polarization, and conditioned media were collected and co-cultured with human liver cancer cell lines SK-HEP-1 and Huh-7 to assess changes in proliferation, migration, invasion, and EMT-related protein expression. This study provides experimental evidence for DC as a potential candidate drug against liver cancer.

Materials and Methods

Main materials

Human monocytic leukemia cell line THP-1, and human liver cancer cell lines SK-HEP-1 and Huh-7 were all purchased from

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Yifeng MO (2000-), male, P. R. China, master, devoted to research about pathogenesis of liver cancer.

* Corresponding author.

the Cell Resource Center, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. DC was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (batch No. 111667-200401). It is a light yellow needle crystal, soluble in organic solvents such as methanol, ethanol, and DMSO, with a relative molecular weight of 351.4. An appropriate amount of DC was accurately weighed using an electronic balance and dissolved in DMSO to prepare a 20 mM stock solution, which was stored in the dark at a low temperature for subsequent experiments.

Main reagents

DMSO (Sigma-Aldrich, Shanghai, China); IL-4 and IL-13 (PeproTech, USA); CCK-8 kit, 4% paraformaldehyde, crystal violet staining solution, and PMA (Beijing Solarbio Science & Technology Co., Ltd., Beijing, China); Matrigel and Transwell chambers (Corning, USA); penicillin-streptomycin solution, 0.25% trypsin-EDTA digestion solution, RIPA lysis buffer, protease inhibitors, and phosphatase inhibitors (Shanghai Liji Biotechnology Co., Ltd., Shanghai, China); Trizol total RNA extraction reagent, reverse transcription kit, and MonAmp™ SYBR Green qPCR Mix (Tiangen Biotech Co., Ltd., Beijing, China); DMEM high-glucose medium, RPMI-1640 medium, and fetal bovine serum (Gibco, USA).

Main experimental instruments

The main instruments included a CO_2 cell culture incubator (Panasonic, Japan), an inverted microscope (Olympus, Japan), a real-time PCR system (Bio-Rad, USA), a chemiluminescence imaging system (Bio-Rad, USA), a multimode microplate reader (Bio-Rad, USA), and an electronic balance (Mettler Toledo, Switzerland).

Cell culture

SK-HEP-1 cells were cultured in 1640 medium containing 10% fetal bovine serum and 1% penicillin streptomycin mixture. Huh-7 cells were cultured under the same conditions but with DMEM high-glucose medium instead. For THP-1 cells, the FBS was filtered and inactivated before use. All three cell lines were maintained in a humidified incubator at 37 ℃ with 5% CO_2. SK-HEP-1 and Huh-7 cells were subjected to 0.25% trypsin-EDTA digestion and passage. THP-1 cells were subcultured by the half-medium change method. Cells in the logarithmic growth phase were used for subsequent experiments.

Determination of cell viability by CCK-8 assay

THP-1 cells in the logarithmic growth phase were seeded into 96-well plates at a density of 5×10^4 cells per well and induced with 50 ng/ml PMA for 48 h to differentiate into M0-like macrophages. The experiment included a control group and DC treatment groups at various concentrations. Complete media containing 0, 0.1, 0.5, 1, 5, 10, and 20 μM DC were prepared, with the final DMSO concentration kept below 0.1% (*v*/*v*). Each well was added with 100 μl of the respective medium, and each group consisted of six replicate wells. After THP-1 cells were differentiated into M0-like macrophages, each group was treated with the corresponding drug-containing medium for an additional 48 h. Subsequently, 10 μl of CCK-8 solution was added to each well, and the plates were incubated for another 2 h. The optical density (OD) was measured at 450 nm using a microplate reader, and cell viability was calculated according to the following formula:

Cell viability (%) = (OD of experimental group − OD of blank group)/(OD of control group − OD of blank group) × 100%.

SK-HEP-1 and Huh-7 cells in the logarithmic growth phase were seeded into 96-well plates at a density of 1×10^4 cells per well, with 100 μl per well. Six replicate wells were set for each group. The cells were cultured in an incubator for 12 h to allow attachment. Subsequently, the medium was replaced with M2 macrophage conditioned medium (CM) and the cells were cultured for an additional 48 h. The OD values were then measured using the same method, and cell viability was calculated accordingly.

Establishment of PMA-induced M2-like polarization model in THP-1 cells and drug treatment

The experiment was divided into five groups: M0 blank control group (Untreated), M2-like polarization model group (Vehicle), M2-like polarization low-dose group (DC-5 μM), M2-like polarization medium-dose group (DC-10 μM), and M2-like polarization high-dose group (DC-20 μM). THP-1 cells were cultured in RPMI-1640 medium supplemented with 10% filtered and inactivated serum. No differentiation was observed under the microscope. The cells were then induced with PMA for 48 h. After the cells in each group had adhered, the culture medium was replaced with drug-containing media at corresponding concentrations. In addition, the culture media of the vehicle, DC-5 μM, DC-10 μM, and DC-20 μM groups were supplemented with IL-4 (20 ng/ml) and IL-13 (20 ng/ml). The DMSO concentration in all groups was 0.1%, and the cells were cultured for an additional 48 h.

Preparation of macrophage conditioned medium and co-culture

After the macrophages in each group had been co-treated with DC (5, 10, 20 μM) and IL-4/IL-13 for 48 h, the drug-containing medium was discarded. The cells were gently washed three times with pre-warmed PBS for 5 min each time to remove free drugs and non-specifically adsorbed DC. Then, fresh medium containing 10% FBS but no DC was added, and the cells were cultured for an additional 24 h. The supernatant was collected and filtered through a 0.22 μm filter to obtain macrophage conditioned medium (CM), which was used for subsequent co-culture experiments with liver cancer cells. The co-culture duration was 48 h. The experimental groups were set as: untreated CM group, vehicle CM group, DC-5 μM CM group, DC-10 μM CM group, and DC-20 μM CM group.

Detection of related protein expression by Western blot (WB)

Cells from each group after drug treatment were collected, and RIPA lysis buffer containing protease and phosphatase

inhibitors was added. The cells were lysed on ice for 10 min with thorough mixing. Next, the samples were centrifuged at 14 000 rpm for 15 min at 4 ℃. The supernatant from each group was collected for the determination of protein concentrations, and the samples were normalized. Equal amounts of protein were loaded and separated by SDS-PAGE, followed by wet transfer to nitrocellulose (NC) membranes at 300 mA for 120 min. The membranes were blocked with 5% non-fat milk for 1 h, the blocking solution was discarded, and diluted primary antibodies were added. The membranes were incubated overnight at 4 ℃. After washing three times with TBST, 5 min each time, secondary antibody diluted at 1∶10 000 was added, and incubation was performed for 1 h at room temperature, followed by three times of TBST washing. An ECL chemiluminescence kit was used for development, and images were collected with an imaging system. The gray values of the protein bands were analyzed, and the relative protein expression levels were calculated using β-actin as an internal control.

Detection of mRNA expression of relevant factors by RT-qPCR

Cells were collected from each group after drug treatment. Total RNA was extracted using Trizol reagent, reverse-transcribed into cDNA, and then subjected to PCR amplification. The reaction system is shown in the table, and reaction was carried out according to procedures provided by the kit instructions. Data were analyzed using β-actin as an internal reference gene, and the relative mRNA expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method. The data were then normalized. Primers were designed and synthesized by Sangon Biotech (Shanghai) Co., Ltd. The primer sequences are shown in Table 1.

Table 1 Gene primer sequences

Genus	Primer	Forward (5′-3′)	Reverse (5′-3′)
Homo	β-actin	CACTCTTCCAGCCTTCCTTCC	CGTACAGGTCTTTGCGGATGTC
	CD206	TTCGGACACCCATCGGAATTT	CACAAGCGCTGCGTGGAT
	TGF-β	TAAGGCGAAAGCCCTCAAT	ACAATTCCTGGCGATACCTC
	PPAR-γ	AATGATGGGAGAAGATAAAA	TCTACGGATCGAAACTGG
	ARG-1	AGAACGGAAGAATCAGCCTGGTG	CTTGTGGTTGTCAGTGGAGTGTTG

Cell migration assay

SK-HEP-1 and Huh-7 cells in the logarithmic growth phase were evenly seeded into 6-well plates. After the cells had adhered and formed a confluent monolayer, three parallel lines were scratched vertically using 200 μl pipette tips. The wells were rinsed three times with PBS to remove detached cells, and the wash solution was discarded. Macrophage conditioned medium (containing 10% FBS) was then added, and the cells were cultured for 48 h. Images were taken at the same positions at 0 and 48 h, and the cell migration rate was calculated according to the following formula: Migration ratio (%) $=[(W_0 - W_t)/W_0] \times 100\%$.

Transwell invasion assay

SK-HEP-1 and Huh-7 cells in the logarithmic growth phase were seeded into 6-well plates. After overnight adherence, the medium was replaced with macrophage conditioned medium containing 10% FBS, and the cells were cultured for 48 h. Three replicate wells were set for each group. The cells were then digested and resuspended at a density of 2×10^5 cells/ml. After thorough mixing, 200 μl of each cell suspension was transferred to the upper chamber of a Transwell insert, and 500 μl of medium containing 20% FBS was added to the lower chamber. The cells were cultured for 24 h. The Transwell inserts were then washed three times with PBS, fixed with 4% paraformaldehyde for 5 min, and permeabilized with methanol for 10 min. Next, the cells were stained with 0.1% crystal violet for 15 min. The upper side of the insert was gently wiped with a cotton swab. Images were taken under an inverted microscope in three randomly selected fields, and the number of cells was counted.

Colony formation assay

Based on the results of the preliminary proliferation experiment, the most effective dose was selected. Three experimental groups were set: untreated CM group, vehicle CM group, and DC-20 μM CM group. Cells were seeded into 6-well plates at a density of 2×10^3 cells per well. After overnight adherence, the medium was replaced with macrophage conditioned medium, which was refreshed every 3 d. After two weeks of culture, when colonies became visible to the naked eye, the culture medium was discarded. The cells were then fixed with a fixing solution for 15 min, stained with 0.1% crystal violet for 15 min, and washed under running water to remove excess stain. After air drying, the plates were photographed with a camera, and colonies were counted using Image J software.

Statistical analysis

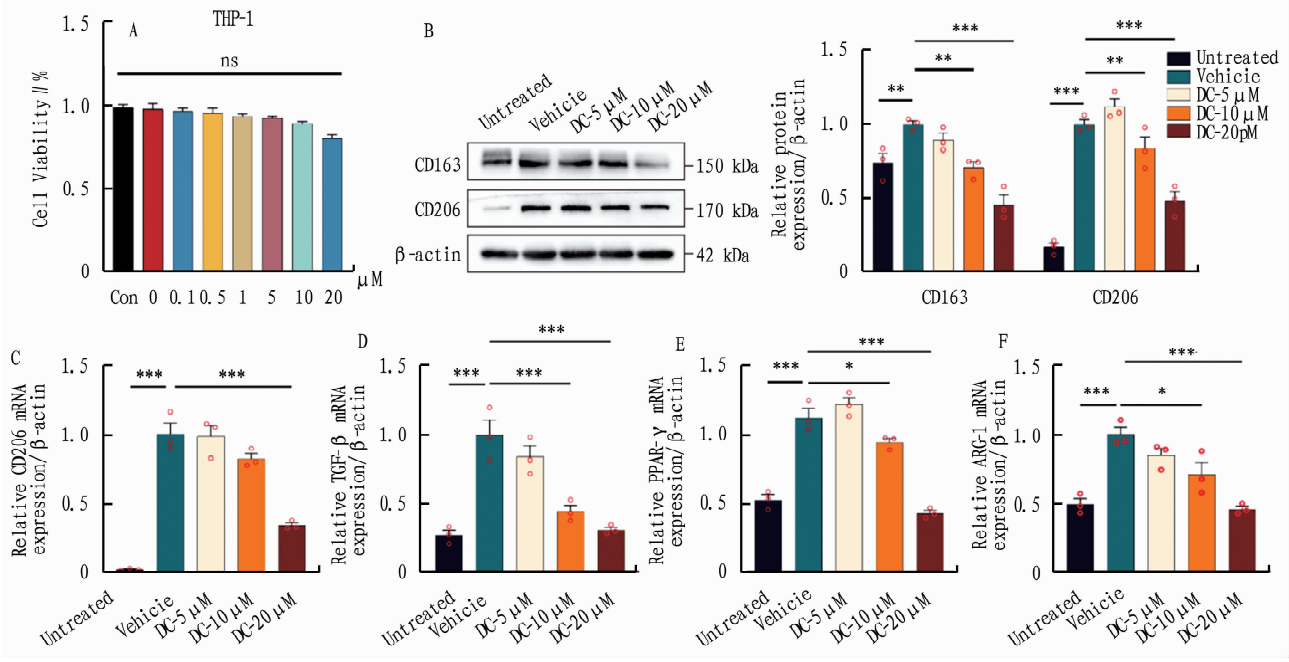
GraphPad Prism 10 was used for data visualization. Statistical analysis was performed using SPSS 20 software, and normal distribution tests were conducted. Comparisons among multiple groups were carried out by one-way analysis of variance (ANOVA), and Tukey's HSD tests were conducted for pairwise comparisons. A P value <0.05 was considered statistically significant.

Results and Analysis

Inhibitory effect of DC on M2-like polarization of macrophages

The viability of macrophages treated with different concentrations of DC for 48 h was evaluated by the CCK-8 assay. Compared with the control group, no significant differences in cell viability were observed in the DC treatment groups ($P>0.05$; Fig. 1 A), indicating that DC had little effect on cell proliferation and toxicity. Compared with the untreated group, the expression levels of the M2-like macrophage marker proteins CD163 and CD206 were

increased significantly in the vehicle group, indicating successful induction of the M2-like polarization model. Furthermore, compared with the vehicle group, the DC-10 and DC-20 μM groups significantly downregulated the expression of CD163 and CD206 ($P<0.01$, $P<0.001$; Fig. 1 B). The mRNA expression levels of the M2-like macrophage marker factors CD206, TGF-β, PPAR-γ, and ARG-1 were detected by RT-qPCR. Compared with the untreated group, the mRNA expression levels of CD163 and CD206 in macrophages were increased significantly in the vehicle group ($P<0.001$). Compared with the vehicle group, the DC-20 μM group significantly downregulated the mRNA expression levels of CD206, TGF-β, PPAR-γ, and ARG-1 ($P<0.001$; Fig. 1 C–F).



(A) The viability of macrophages treated with different concentrations of DC for 48 h was evaluated by thte CCK-8 assay, with the control (con) group as the reference ($n=6$). (B) The relative protein expression levels of CD163 and CD206 were detected by Western blot, with the vehicle group as the reference ($n=3$). (C-F) The relative mRNA expression levels of M2 macrophage markers CD206, TGF-β, PPAR-γ, and ARG-1 were detected by RT-qPCR, with the vehicle group as the reference ($n=3$). Data are presented as mean ± SD. ns, not significant; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

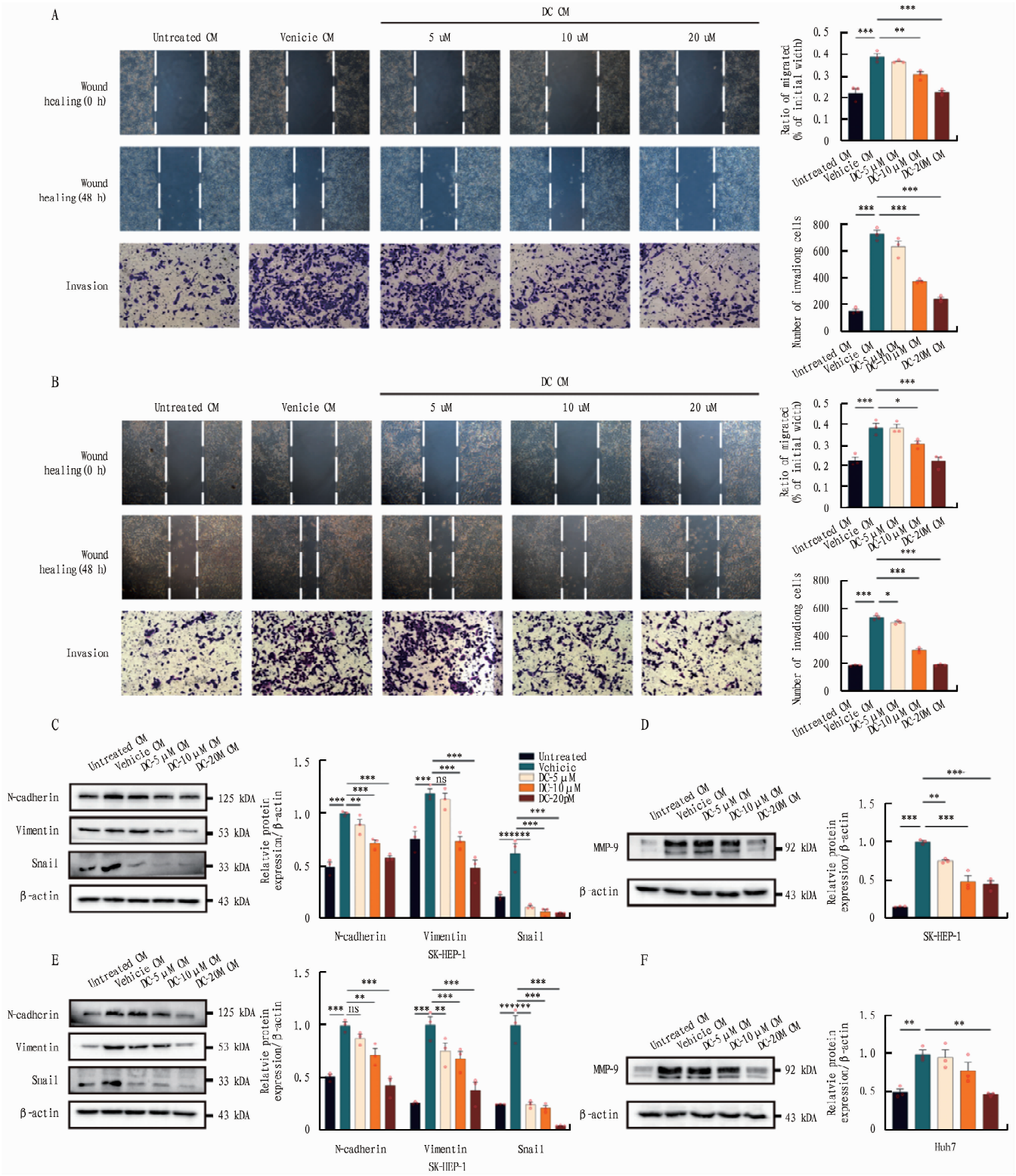
Fig. 1 Inhibitory effect of DC on M2-like polarization of macrophages

Inhibitory effect of DC on the promoting effect of M2-like macrophages on the migration and invasion of liver cancer cells

After co-culture with macrophage conditioned medium, compared with the untreated CM group, the migration and invasion abilities of SK-HEP-1 and Huh-7 cells were significantly increased in the vehicle CM group ($P<0.001$). Compared with the vehicle CM group, the migration and invasion abilities of SK-HEP-1 (Fig. 2 A) and Huh-7 (Fig. 2 B) cells were significantly decreased in the DC-10 μM CM and DC-20 μM CM groups ($P<0.05$). Western blot results showed that compared with the untreated CM group, the vehicle CM group significantly upregulated the expression of N-cadherin, Vimentin, Snail, and MMP9 in SK-HEP-1 and Huh-7 cells ($P<0.01$). Compared with the vehicle CM group, the DC-10 μM CM and DC-20 μM CM groups significantly inhibited EMT in SK-HEP-1 and Huh-7 cells and downregulated the expression of N-cadherin, Vimentin, Snail, and MMP9 ($P<0.01$; Fig. 2 C–F). These results indicate that DC could inhibit the EMT of liver cancer cells by downregulating M2-like polarization of macrophages, thereby suppressing the migration and invasion abilities of liver cancer cells.

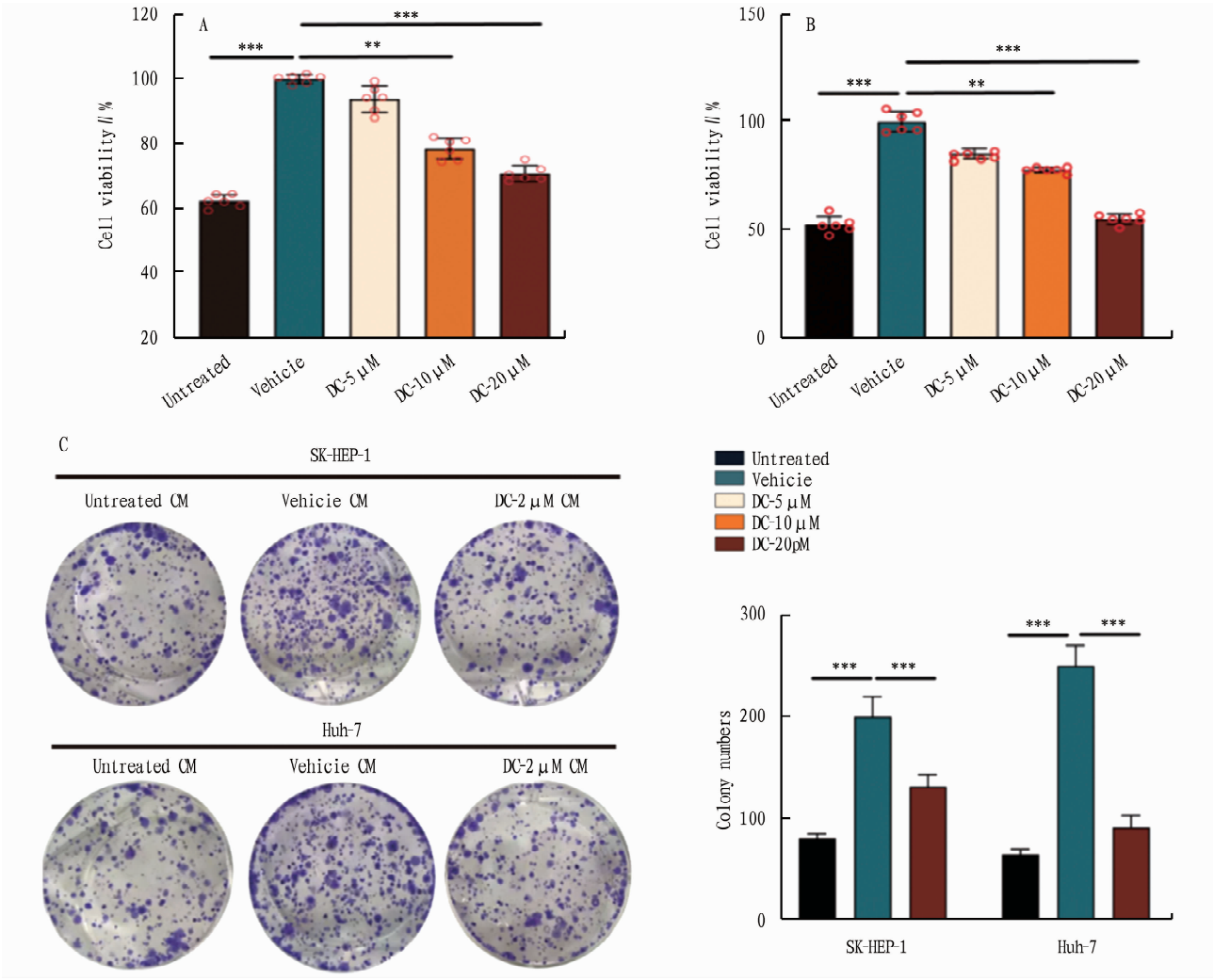
Inhibitory effect of DC on the promoting effect of M2-like macrophages on the proliferation of liver cancer cells

To investigate the effect of DC-treated macrophages on the proliferation of liver cancer cells, the proliferation and colony formation abilities of liver cancer cells co-cultured with macrophage conditioned medium were assessed using the CCK-8 assay and plate colony formation assay. The CCK-8 results showed that compared with the untreated CM group, the proliferation ability of both cell lines was significantly increased in the vehicle CM group ($P<0.001$), indicating that M2-like macrophages could produce factors promoting the proliferation of liver cancer cells. Compared with the vehicle CM group, the proliferation ability of both cell lines was significantly inhibited in the DC-10 μM CM and DC-20 μM CM groups ($P<0.01$; Fig. 2 A and B). The plate colony formation assay showed that compared with the untreated CM group, the number of colonies formed by both cell lines was significantly increased in the vehicle CM group ($P<0.001$). Compared with the vehicle CM group, the number of colonies formed after DC treatment was significantly reduced ($P<0.001$). These results indicated that DC could inhibit the promoting effect of M2-like macrophages on the proliferation of liver cancer cells and reduce the clonogenic ability of liver cancer cells.



(A) The effects of DC-treated macrophage conditioned medium on the migration and invasion abilities of SK-HEP-1 cells were evaluated by the wound healing assay and Transwell invasion assay. (B) The effects of DC-treated macrophage conditioned medium on the migration and invasion abilities of Huh-7 cells were evaluated by the wound healing assay and Transwell invasion assay. (C, D) The relative expression levels of EMT-related proteins in SK-HEP-1 cells after treatment with DC-treated macrophage conditioned medium were detected by Western blot. (E, F) The relative expression levels of EMT-related proteins in Huh-7 cells after treatment with DC-treated macrophage conditioned medium were detected by Western blot. Data are presented as mean ± SD ($n = 3$). With the vehicle CM group as the reference, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Fig. 2 Inhibitory effect of DC-treated macrophage conditioned medium on the migration and invasion of liver cancer cells



(A) The effects of DC-treated macrophage conditioned medium on the proliferation ability of SK-HEP-1 cells were evaluated by the CCK-8 assay. (B) The effects of DC-treated macrophage conditioned medium on the proliferation ability of Huh-7 cells were evaluated by the CCK-8 assay. (C) The effects of DC-treated macrophage conditioned medium on the colony formation ability of SK-HEP-1 and Huh-7 cells were observed by the plate colony formation assay. Data are presented as mean ± SD ($n=3$). The vehicle CM group was used as the reference. $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

Fig. 3 Inhibitory effect of DC-treated macrophage conditioned medium on the proliferation of liver cancer cells

Conclusions and Discussion

Primary liver cancer remains a global health challenge. Most patients are already at an advanced stage when diagnosed, and existing targeted drugs such as sorafenib show limited efficacy in improving overall survival due to drug resistance and low objective response rates[13]. Therefore, exploring novel natural anti-tumor components with wide availability and low toxicity has significant clinical value.

DC, a core alkaloid active component of the traditional Chinese medicine *Corydalis saxicola* Bunting, exhibits multiple pharmacological effects, including hepatoprotective, anti-tumor, antibacterial, and analgesic-sedative activities[11-12]. The present study confirmed that DC can indirectly inhibit the proliferation, migration, invasion, and EMT ability of liver cancer cells by regulating TAMs.

Macrophages are the most abundant immune cell population in the tumor microenvironment (TME). M2-type TAMs promote angiogenesis, matrix remodeling, and EMT by secreting factors such as IL-10 and TGF-β, thereby accelerating liver cancer metastasis[14-16]. The present study showed that DC downregulated the expression of M2 markers CD163 and CD206, as well as the functional factors TGF-β, PPAR-γ, and ARG-1, in a dose-dependent manner. Conditioned medium (CM) from DC-treated macrophages significantly inhibited the proliferation, migration, invasion, and colony formation of SK-HEP-1 and Huh-7 cells, and simultaneously reversed the upregulation of EMT-related proteins (N-cadherin, Vimentin, Snail, MMP9). These results indicated that DC weakened the promoting effect of macrophages on the malignant behavior of liver cancer cells by inhibiting their polarization toward the M2 phenotype.

This is distinct from conventional chemotherapeutic agents. DC can exert indirect effects by modulating immune cell functions, a feature that gives it a potential advantage in the field of cancer immunotherapy. Moreover, previous studies have reported that DC has protective effects against liver fibrosis and acute liver injury[10,17-19], suggesting that DC possesses both hepatoprotective and anti-tumor properties, making it particularly suitable for the treatment of liver cancer in the context of cirrhosis. In addition, DC is derived from natural sources with high safety. In this study, cell viability assays showed no significant cytotoxicity toward THP-1 cells, laying a foundation for its further application.

In summary, DC can inhibit the proliferation, migration, invasion, and EMT ability of liver cancer cells by suppressing M2-like polarization of macrophages, demonstrating its potential as a novel anti-liver cancer drug candidate. Further studies will validate the anti-liver cancer activity of DC in animal models and utilize transcriptomic or proteomic approaches to elucidate its key signaling pathways, thereby providing more robust experimental evidence for the clinical transformation of DC.

References

[1] WANG W, WEI C. Advances in the early diagnosis of hepatocellular carcinoma[J]. Genes & diseases, 2020, 7(3): 308-319.

[2] ZHOU S. Progress in locoregional interventional therapy of primary hepatocellular carcinoma[J]. Cancer Research on Prevention and Treatment, 2022, 49(06): 552-556. (in Chinese).

[3] KIM DW, TALATI C, KIM R. Hepatocellular carcinoma (HCC): Beyond sorafenib-chemotherapy[J]. Journal of gastrointestinal oncology, 2017, 8(2): 256.

[4] BAGHBAN R, ROSHANGAR L, JAHANBAN-ESFAHLAN R, *et al.* Tumor microenvironment complexity and therapeutic implications at aglance[J]. Cell Commun Signal, 2020, 18(1): 59.

[5] FRISCH J, ANGENENDT A, HOTH M, *et al.* STIM-Orai channels and reactive oxygen species in the tumor microenvironment[J]. Cancers (Basel), 2019, 11(4): 457.

[6] DENG L, HE K, PAN Y, *et al.* The role of tumor-associated macrophages in primary hepatocellular carcinoma and its related targeting therapy[J]. Int J Med Sci, 2021, 18(10): 2109-2116.

[7] ZHOU Z, WANG Z, GAO J, *et al.* Noncoding RNA-mediated macrophage and cancer cell crosstalk in hepatocellular carcinoma[J]. Mol Ther Oncolytics, 2022, 25: 98-120.

[8] YANG Y, YE YC, CHEN Y, *et al.* Crosstalk between hepatic tumor cells and macrophages via Wnt/beta-catenin signaling promotes M2-like macrophage polarization and reinforces tumor malignant behaviors[J]. Cell death & disease, 2018, 9: 793.

[9] ZHANG J, ZHANG Q, LOU Y, *et al.* Hypoxia-inducible factor-1alpha/interleukin-1beta signaling enhances hepatoma epithelial-mesenchymal transition through macrophages in a hypoxic-inflammatory microenvironment[J]. Hepatology, 2018, 67: 1872-89.

[10] YEUNG OW, LO CM, LING CC, *et al.* Alternatively activated (M2) macrophages promote tumour growth and invasiveness inhepatocellular carcinoma[J]. Journal of hepatology, 2015, 62: 607-616.

[11] ZENG YZ, ZHONG HS, SU XD, *et al.* Chemical constituents, pharmacological effects and clinical applications of *Corydalis saxicola* Bunting and predictive analysis on quality marker[J]. Chinese Journal of New Drugs, 2023, 32(13): 1325-1335. (in Chinese).

[12] PASTUSHENKO I, BLANPAIN C. EMT transition states during tumor progression and metastasis[J]. Trends Cell Biol, 2019, 29(3): 212-226.

[13] NICOLÁS-ÁVILA JÁ, ADROVER JM, HIDALGO A. Neutrophils in homeostasis, immunity, and cancer[J]. Immunity, 2017, 46(1): 15-28.

[14] NARAYANAN S, KAWAGUCHI T, PENG X, *et al.* Tumor infiltrating lymphocytes and macrophages improve survival in microsatellite unstable colorectal cancer[J]. Sci Rep, 2019, 9(1): 13455.

[15] ARAS S, ZAIDI MR. TAMeless traitors: Macrophages in cancer progression and metastasis[J]. Br J Cancer, 2017, 117(11): 1583-1591.

[16] SHEN M, CHEN Y, XU L, *et al.* Increased infiltration of macrophages-to radioresistant lung cancer cells contributes to the development of the additional resistance of tumor cells to thecytotoxic effects of NKcells[J]. Int J Oncol, 2018, 53(1): 317-328.

[17] MANTOVANI A, SICA A. Macrophages, innate immunity and cancer: Balance, tolerance, and diversity[J]. Curr Opin Immunol, 2010, 22: 231-237.

[18] BABAEI G, AZIZ SG, JAGHI NZZ. EMT, cancer stem cells and autophagy; The three main axes of metastasis[J]. Biomed Pharmacother, 2021, 133: 110909.

[19] SUAREZ-CARMONA M, LESAGE J, CATALDO D, *et al.* EMT and inflammation: Inseparable actors of cancer progression[J]. Mol Oncol, 2017, 11(7): 805-823.

Editor: Yingzhi GUANG Proofreader: Xinxiu ZHU

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[13] YANG YX, MING J, LYU ZZ, *et al.* Optimization of detection methods for 40 pesticides based on GC-MS/MS and screening of vegetable substrates[J]. Shandong Chemical Industry, 2023, 52(12): 110-117. (in Chinese).

[14] REN JP. Study on matrix effects in determination of pesticide residues in vegetables by QuEChERSgas chromatographytandem mass spectrometry[J]. Agriculture and Technology, 2021, 41(4): 27-36. (in Chinese).

[15] MA YF, LIU SD, CHENG Q, *et al.* Influence of matrix effect on pesticide residues detection in vegetables[J]. Agricultural Research and Application, 2023, 36(3): 27-36. (in Chinese).

Editor: Yingzhi GUANG Proofreader: Xinxiu ZHU