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The Inflammatory Chemokine CCL20 Modulates the Phosphorylation of Key Proteins in Stem Cell-Like Properties of Non-Small Cell Lung Cancer *via* the PI3K/AKT/mTOR Signaling Pathway

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ABSTRACT

Objective: Investigate the effect of CCL20 on the stem cell-like properties of non-small cell lung cancer and its mechanism.

Methods: By culturing A549 cells under serum-free conditions, to establish stem cell-like properties non-small cell lung cancer model. Using RT-qPCR and tube formation to validate the stemness characteristics of NSCLCSCs. The CCK-8 assay was used to determine cell viability, and the optimal concentration of CCL20 was determined. Western blotting was used to detect the phosphorylation levels of pathway proteins in response to CCL20, and the CCK8 assay was employed to assess the resistance to cisplatin and gefitinib following CCL20 treatment.

Results: NSCLCSCs treated with CCL20 exhibited increased stemness gene expression, PI3K, AKT, and mTOR phosphorylation levels were significantly elevated. The IC_{50} values for Cisplatin and Gefitinib treated with CCL20 were significantly higher than those in the control group.

Conclusion: CCL20 significantly promotes stem cell-like characteristics in NSCLC cells, including enhancing self-renewal capacity, upregulating expression of stem cell markers, and increasing drug resistance. CCL20 regulates the stem cell-like characteristics of NSCLC through activation of the PI3K/AKT/mTOR signaling pathway. CCL20 holds promise as a novel therapeutic target for the treatment of NSCLC, offering new strategies for clinical management.

Keywords: CCL20, NSCLC, Drug Resistance, Stemness Markers, Western Bloating, PI3K/AKT/mTOR Signaling Pathway

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INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 80%-85% of all lung cancer cases and remains a leading cause of cancer-related mortality worldwide, despite continuous advancements in multimodal therapeutic strategies including surgery, radiotherapy, chemotherapy, and molecularly targeted agents [1,2]. A primary factor contributing to treatment failure is the profound intratumoral heterogeneity and the persistence of a therapy-resistant cell population, which often leads to disease recurrence and metastatic progression. In this context, the cancer stem cell (CSC) hypothesis has gained substantial traction as a conceptual framework to explain the recalcitrant nature of NSCLC [3]. CSCs represent a minor subpopulation within tumors that possess self-renewal capacity, multilineage differentiation potential, and are posited to be responsible for tumor initiation, propagation, therapeutic resistance, and relapse [4]. These cells maintain their stem-like state through the activation of evolutionarily conserved developmental signaling pathways, such as Wnt/β-catenin, Notch, and Hedgehog, and can enhance their invasive and metastatic potential via processes like the epithelial-mesenchymal transition (EMT) [5,6]. Consequently, a detailed understanding of the regulatory mechanisms governing CSCs in NSCLC is imperative for the development of novel therapeutic approaches aimed at eradicating this resilient cell compartment and improving patient survival.

The tumor microenvironment (TME) plays a crucial role in sustaining CSCs and fostering therapeutic resistance [7,8]. Among the various components of the TME, chemokines have emerged as key mediators of intercellular communication. Chemokine ligand 20 (CCL20), a member of the CC-chemokine family, exerts its biological functions primarily by binding to its sole known receptor, CCR6. While classically involved in immune cell trafficking (e.g., dendritic cells and lymphocytes) and mucosal immunity, CCL20 is frequently dysregulated in the TME of various malignancies, including NSCLC [9-11]. In cancer, CCL20 contributes to the formation of an immunosuppressive niche by recruiting regulatory T cells (Tregs) and tumor-associated macrophages (TAMs). Beyond its immunomodulatory roles, CCL20 can directly act on tumor cells to promote proliferation, invasion, and angiogenesis, often through the activation of oncogenic signaling pathways such as PI3K/Akt and NF-κB [12]. Mounting preclinical and translational investigations have established the CCL20–CCR6 signaling axis as a pivotal pathophysiological mediator, which orchestrates malignant progression, immunosuppressive niche remodeling, therapeutic resistance, and fibrotic deterioration across a spectrum of solid tumors, chronic pulmonary disorders and metabolic liver diseases. Despite the encouraging preclinical efficacy and early-phase clinical deployment of CCL20/CCR6-targeted monoclonal antibodies and small-molecule antagonists, unmet needs remain in delineating disease-specific downstream signaling cascades and identifying stratifiable predictive biomarkers to accelerate the clinical translation of CCL20-directed therapeutic strategies [13,14]. Notably, emerging evidence suggests a potential link between CCL20/CCR6 signaling and the maintenance of CSC properties, positioning it as a promising therapeutic target.

A central signaling hub implicated in both CSC biology and the oncogenic actions of various microenvironmental cues is the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway. This pathway is a master regulator of cell growth, survival, metabolism, and is aberrantly activated in a large proportion of NSCLC cases through genetic alterations like *PIK3CA* mutations or PTEN loss [15]. Its hyperactivation drives key malignant phenotypes, including uncontrolled proliferation, evasion of apoptosis, and metastasis [16]. Critically, the PI3K/AKT/mTOR axis is a well-established regulator of stemness in various cancers, influencing CSC self-renewal and drug resistance. In NSCLC, this pathway's activity is closely associated with the maintenance of CSC populations and the EMT program, both of which contribute to aggressive disease and therapy failure [17].

Despite the individual recognition of CCL20's pro-tumorigenic functions and the PI3K/AKT/mTOR pathway's role in CSC regulation, the specific mechanistic link between CCL20 signaling and the activation of this pathway in modulating NSCLC stemness remains poorly defined [18]. It is unknown whether CCL20 exerts its effects on CSC properties through the PI3K/AKT/mTOR axis. This study defines a previously unreported CCL20-driven NSCLC stemness regulatory axis, filling the critical unaddressed gap in existing CCL20/CCR6 NSCLC research. Therefore, this study was designed to investigate the hypothesis that CCL20 promotes stem-

like traits in NSCLC cells by activating the PI3K/AKT/mTOR signaling cascade. By elucidating this connection, we aim to uncover a novel regulatory axis in NSCLC pathogenesis and identify potential therapeutic vulnerabilities for overcoming CSC-mediated therapy resistance.

MATERIALS AND METHODS

Cell Culture

A549 cell line were maintained in Dulbecco's modified Eagle's medium (DMEM, D0822, Gibco, USA) supplemented with 10% fetal bovine serum (FBS, F0392, Gibco, USA), 100 U/ml P/S (P0781, Sigma, USA). The NSCLCSCs preparation. The A549 cells were cultured at 37°C in an atmosphere containing 5% CO_2 until they reached the logarithmic growth phase. At this phase, the cells were collected, washed twice with PBS, and digested into a monolayer suspension using 0.25% trypsin-EDTA (T4049, Sigma, USA). After staining and counting with trypan blue, the cells were seeded at a density of 1×10^5 cells/mL into ultra-low-adhesion culture plates and incubated in serum-free medium (prepared by adding EGF, bFGF, and a penicillin–streptomycin solution to DMEM/F-12 medium, mixing thoroughly, and then filtering to remove bacterial contamination) at 37°C in an atmosphere containing 5% CO_2.

Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR)

Total RNA was extracted using the SV Total RNA Isolation System (Promega) according to the manufacturer's instructions. The procedures for RT-qPCR were performed as described previously, in the presence of 2 μM of specific primers for Oct3/4, Sox2, Nanog (MCE, USA). Oct3/4,

Forward prime: 5'-GACAGGGGGAGGGGAGGAGCTAGG-3',

Reverse primer: 5'-CTTCCCTCCAACCAGTTGCCCCAAAC-3';

Sox2, Forward prime: 5'-GGGAAATGGGAGGGGTGCAAAAGAGG-3';

Reverse primer: 5'-TTGCGTGAGTGTGGATGGGATTGGTG-3';

Klf4, Forward prime: 5'-ACGATCGTGGCCCCGGAAAAGGACC-3';

Reverse primer: 5'-TGATTGTAGTGCTTTCTGGCTGGGCTCC-3';

Nanog, Forward prime: 5'-CAGCCCCGATTCTTCCACCAGTCCC-3';

Reverse primer: 5'-CGGAAGATTCCCAGTCGGGTTCACC-3';

Tube Formation Assay

The cells were seeded at a density of 5×10^5 cells/60 mm dish and incubated at 37 °C with 5% CO_2. When the formation of a 70% confluent monolayer, collected and re-suspended 5×10^5 cells in EBM-2 media and seeded in 12-well plates, coated with growth factors reduced Matrigel for 24h in the presence of a different growth factors, such as human epidermal growth factor (EGF, 5 ng/mL)(HY-P7109, MCE), human vascular endothelial growth factor (VEGF, 0.5 ng/mL)(HY-P77279, MCE), R3-insulin-like growth factor-1 (R3-IGF-1, 20 ng/mL)(HY-W015851, MCE), ascorbic acid (1 μg/ mL), hydrocortisone (0.2 μg/mL), human basic fibroblast growth factor (bFGF, 10 ng/mL)(HY-P5321, MCE), heparin (22.5 μg/ mL) (HY-17567A, MCE) and 2% FBS. Each experiment was performed in triplicate, and the images were captured by using an Olympus IX81 microscope (Olympus, Japan).

CCK8 Assay

After the cells reached the logarithmic growth phase and their density exceeded 80%, they were trypsinized to prepare a cell suspension; 100 μL of this cell suspension (3×10^4 cells/mL) was seeded into each well of a 96-well plate (6 replicates per group). The plates were incubated at 37°C in an incubator with 5% CO_2 for 24 hours; thereafter, the old culture medium was removed. For the experimental groups, 100 μL of complete culture medium containing recombinant human CCL20 (HY-P7262) (concentrations of 0, 25, 50, 100 and 200 ng/mL) was added; for the control group, 100 μL of complete culture medium was added. The plates were then incubated at 37°C in an incubator with 5% CO_2 for an additional 4 hours, after which the old culture medium was removed. Add 100 μL of CCK-8 (K1018, APExBIO, USA) solution (pure CCK-8: complete culture medium = 1:9) to each well, then incubate the wells in a CO_2 incubator for approximately 2 h. Place the treated plates into an ELISA

reader and measure the absorbance value at a wavelength of 450 nm.

Western Blotting

Whole tissue and cell lysates were prepared using 50 mM Tris HCl pH 7.4 and 150 mM NaCl buffer supplemented with protease/phosphatase inhibitor cocktails (Roche) and 1% NP- 40 substitute. Protein concentration was measured using Pierce 660 nm Protein Assay Reagent (Thermofisher). Equal protein amounts were loaded onto Nu PAGE 4- 12% Bis-Tris gels (Invitrogen) and transferred to an activated PVDF membrane (41105339, Millipore, USA). Membranes were blocked in 5% milk in 0.05% TBST and incubated in primary antibody overnight at 4 °C in 3% BSA in TBST. Membranes were washed three times with TBST and incubated with secondary for 1 h at RT. Membranes were washed three times and developed with Immobilon Forte Western HRP substrate (Millipore). Western blots were imaged using the LAS4000 documentation system or Bio- Rad system. The following antibodies were used for WB: p-PI3K (CPA7142, 1:2,000), PI3K (CMA4491, 1:2,000), p-AKT (CMA4142, 1:2,000), AKT (CMA1214, 1:2,000), β-Actin (YA823, 1:1,000).

Statistical Analysis

Each experiment was repeated at least four times. Data points reported in the figures are given as means ± standard deviation (SD). The data were analyzed using GraphPadPrism10.0 and Image-J 1.8.0. Statistical analysis was carried out also using the ANOVA. When indicated, post hoc tests (Bonferroni/Dunn) were also performed. A P-value less than 0.05 were considered to achieve statistical significance.

RESULTS

Validation of Stemness Characteristics in NSCLCSCs

We detected the expression of endogenous stemness markers Oct3/4, Sox2, Nanog, and Klf4 using real-time quantitative PCR (rt-qPCR). These markers play a dominant role in the maintenance of embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), as well as in the self-renewal of viable cells. Using specific primers, we confirmed the expression levels of each endogenous gene and transgene. Compared with untreated non-small cell lung cancer cells, the expression levels of endogenous Oct3/4, Sox2, Nanog, and Klf4 genes were significantly increased (Figure 1A-D). In adherent culture of NSCLC stem cells, most cells underwent differentiation after 3 days, and no cells survived after 1 week (Figure 1E, F). After culturing on Matrigel for 20 hours, the tube formation assay was conducted. Differentiation potential is another characteristic of CSCs, alongside self-renewal. The ability of NSCLCSC to differentiate into endothelial-like cells and form capillary-like tubes on Matrigel was evaluated. These cells formed capillary-like tubes, indicating their pro-angiogenic properties in tumorigenesis. The cells exhibited a high potential for tube formation (Figure 1G).

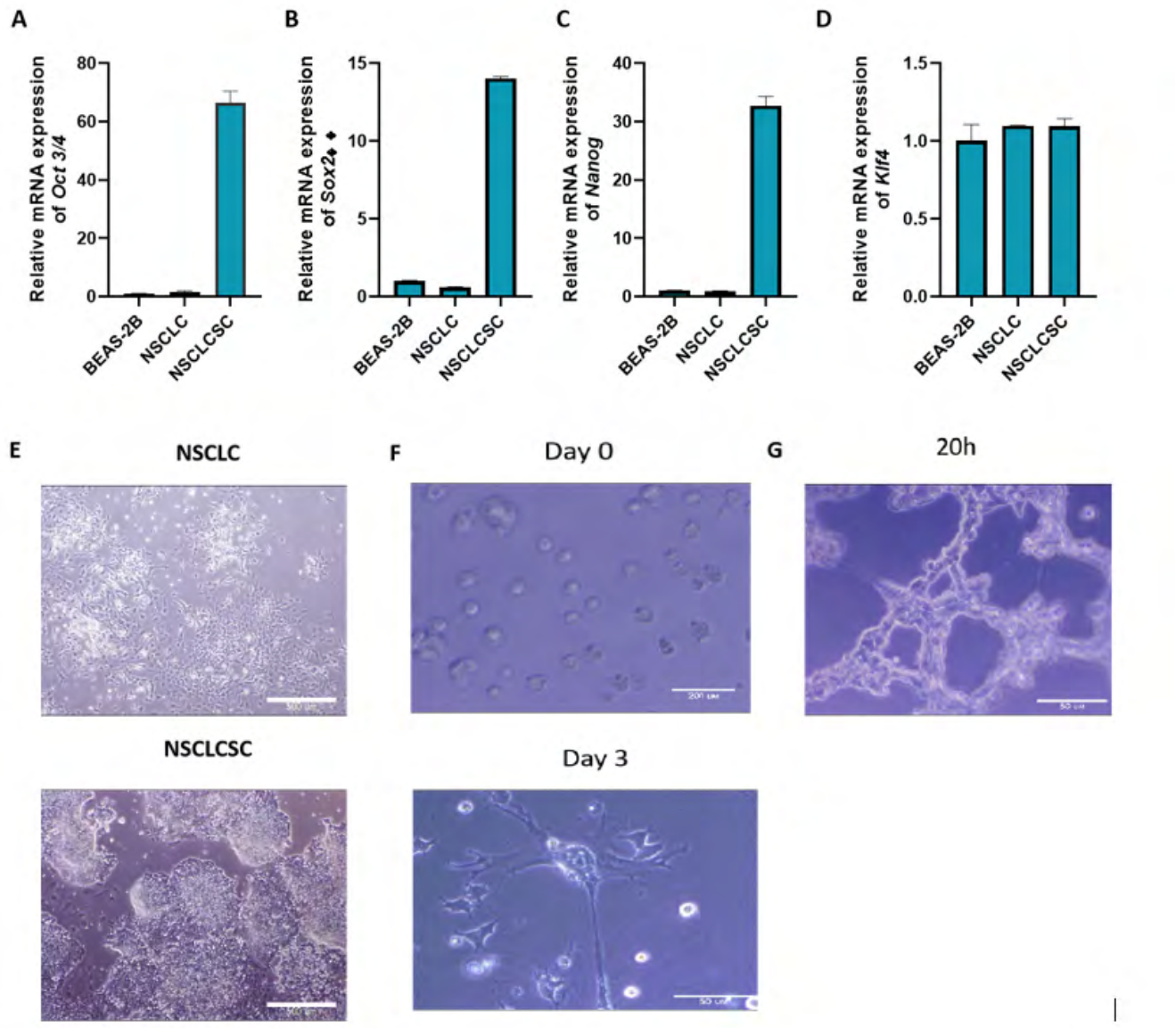

Figure 1: Validation of Stemness Characteristics in NSCLCSCs. (A-D) Total RNA was extracted and real time qPCR analyses targeting expression of endogenous stemness markers Oct3/4, Sox2, Nanog, and Klf4 were performed. (E) Non-small cell lung cancer (NSCLC) cells and NSCLC stem cells cultured for 4 days. (F-G) Cell differentiation capacity and Tube formation assays.

CCL20 Promotes the Stem Cell-Like Characteristics of NSCLCSCs

We treated NSCLCSCs with recombinant human CCL20 at various concentrations for 24 hours, performed CCK-8 assays, and collected RNA and protein samples. The concentration gradient employed was 0 ng/mL, 25 ng/mL, 50 ng/mL, 100 ng/mL, and 200 ng/mL. The results indicated that the cell viability was highest at 100 ng/mL of CCL20, therefore, this concentration was selected as the optimal experimental concentration (Figure 2A). Then we detected the expression of endogenous stemness markers Oct3/4, Sox2, and Nanog using RT-qPCR. Following CCL20 treatment, the expression levels of stemness-related factors in the cells were increased (Figure 2B-2D).

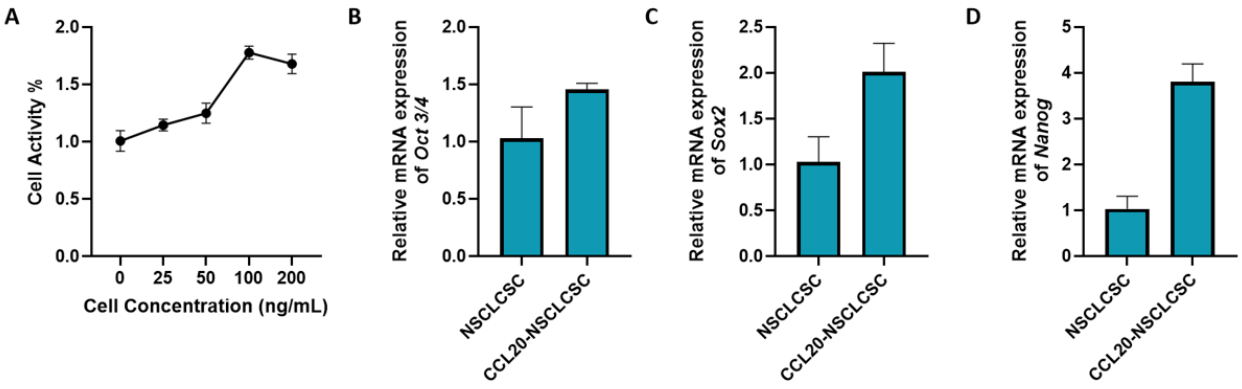

Figure 2: CCL20 promotes the stem cell-like characteristics of NSCLCSCs. (A) Perform CCK8 assays on NSCLC cells treated with recombinant CCL20 at various concentrations. (B-D) Total RNA was extracted and real-time quantitative PCR analyses targeting expression of endogenous stemness markers Oct3/4, Sox2, and Nanog were performed.

CCL20 Activates the PI3K/AKT/mTOR Signaling Pathway

The involvement of PI3K/AKT/mTOR pathway was investigated. NSCLCS cells were pre-treated with PI3K inhibitor prior to CCL20 treatment. The results showed that, after treatment with LY294002 and CCL20, the expression rates were p-PI3K/PI3K (23.5%) and p-Akt/Akt (45%), respectively. The expression rates after treatment with CCL20 alone were p-PI3K/PI3K (86.9%) and p-Akt/Akt (89.9%) (Figure 3). The expression levels of p-PI3K and p-Akt were significantly upregulated following treatment with CCL20, and the expression levels of p-PI3K and p-Akt with the specific **PI3K** inhibitor LY294002 could block the activation.

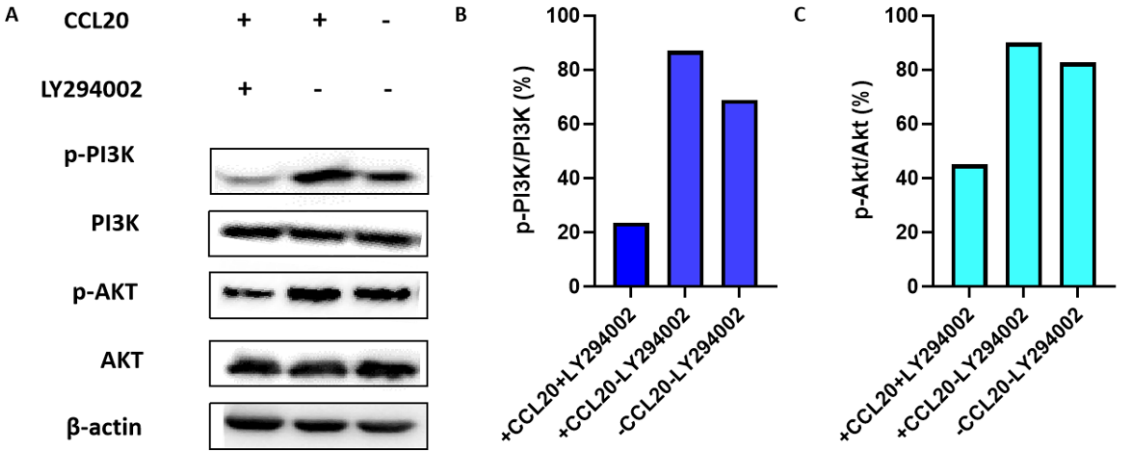

Figure 3. CCL20 activates the PI3K/AKT/mTOR signaling pathway. (A) The protein expression levels of p-PI3K, PI3K, p-Akt and Akt. (B, C) Total RNA was extracted and real-time quantitative PCR analyses targeting expression of endogenous stemness markers Oct3/4, Sox2, and Nanog were performed.

CCL20 Enhances Drug Resistance in NSCLCSCs

To investigate the drug resistance of recombinant human CCL20 protein, we conducted experiments using varying concentrations of cisplatin (P4394, Sigma, USA) and gefitinib (SML1657, Sigma, USA). The drug resistance assay results demonstrated that the IC50 values for Cisplatin (2.947) and Gefitinib (2.783) in the CCL20-treated group were significantly higher than those in the control group ($P<0.05$) (Figure 4).

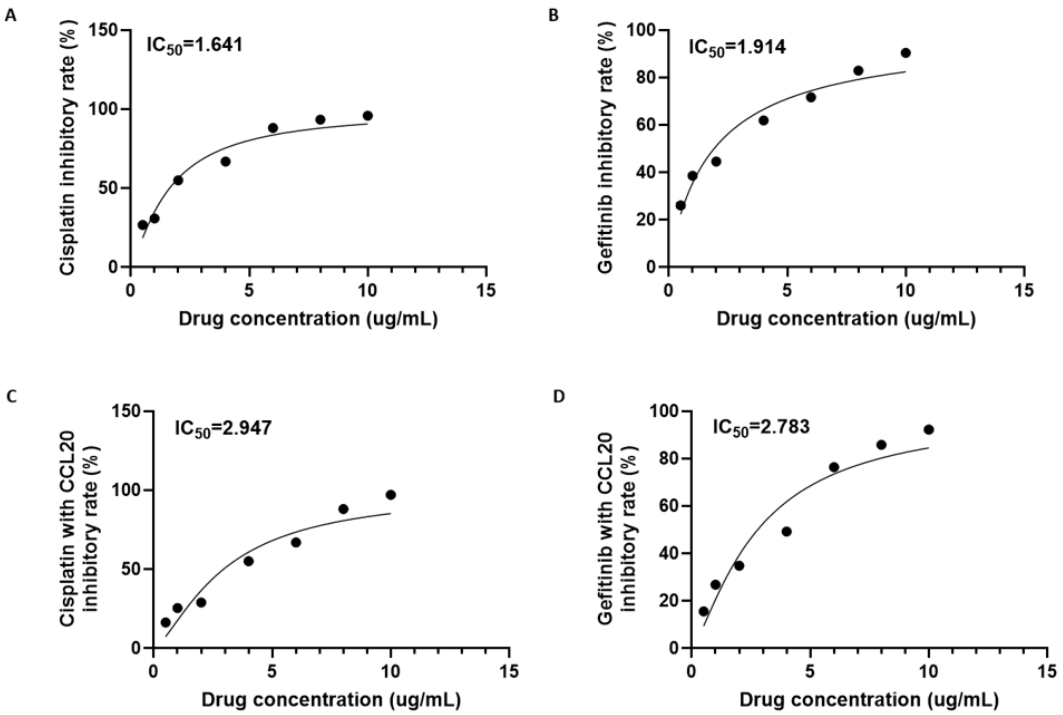

Figure 4. CCL20 enhances drug resistance in NSCLCSCs. (A, B) Perform CCK8 assays on NSCLC cells treated with different concentrations of cisplatin and gefitinib separately. (C, D) The NSCLCSCs after treatment with recombinant CCL20 (100ng/mL) and different concentrations of cisplatin and gefitinib, CCK8 detection was performed.

DISCUSSION

Our findings establish the inflammatory chemokine CCL20 as a potent inducer of stem cell-like properties in NSCLC. Experimental data demonstrate that CCL20 stimulation not only enhances sphere formation and upregulates pluripotency stemness markers (Oct3/4, Sox2, Nanog), but also confers significant resistance to chemotherapeutic agents, including cisplatin and gefitinib. These results position CCL20 as a key driver of the CSC phenotype in NSCLC, a critical mediator of tumor recurrence and therapeutic failure [19,20].

Mechanistically, CCL20's pro-stemness effects are mediated through the PI3K/AKT/mTOR signaling pathway as the essential downstream axis. Pharmacological inhibition of this pathway completely abrogates CCL20-induced stemness, confirming its indispensable role. Notably, this pathway dependency is not unique to NSCLC. In colorectal and breast cancer, CCL20 similarly activates the PI3K/AKT/mTOR cascade to promote stemness and chemoresistance [21,22], suggesting a fundamental oncogenic circuit in epithelial tumors.

Beyond regulating intrinsic stemness, CCL20 is instrumental in facilitating metastasis and sculpting an immunosuppressive tumor microenvironment (TME). In prostate cancer, it drives osteolytic bone metastasis by activating osteoclast differentiation [23]. In head and neck squamous cell carcinoma, CCL20/CCR6 signaling accelerates progression and recruits immunosuppressive regulatory T cells (Tregs) [24]. Coupled with its role in recruiting immunosuppressive myeloid cells in other cancers, CCL20 emerges as a central orchestrator linking tumor cell malignancy to a permissive metastatic and immunosuppressive niche [25,26].

Clinically, CCL20 overexpression correlates strongly with poor prognosis and an immunosuppressive TME in NSCLC [27,28], a regulation governed by epigenetic mechanisms such as histone modifications [29]. Consequently, targeting the CCL20-CCR6 axis or its downstream PI3K/AKT/mTOR pathway presents a promising dual-pronged strategy: eradicating the therapy-resistant CSC pool while reprogramming the immunosuppressive TME, thereby potentially overcoming drug resistance and improving therapeutic outcomes [30-32]. Future studies should

prioritize validating this approach in patient-derived models and exploring synergistic combinations with existing therapies, including immune checkpoint inhibitors [33].

STATEMENTS

Authors Contribution

LZ and JD directed the whole study. JD and LZ designed the experiments. JD and LZ conducted the experiments. JD and YNB analyzed the data. JD, YNB and LZ contributed supplying reagents and materials and supported analysis. JD, YNB and LZ participated in the discussion. LZ directed the research project and wrote the manuscript together with JD. All authors were involved in the final version of the manuscript.

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Availability of Data and Materials

Any information used and/or analyzed during this study is available from the corresponding author on reasonable request.

Consent for Publication

All authors of the manuscript have read and agreed to its content.

Competing Interests

The authors declare that they have no competing interest.

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