Original Article
IL-17 induces EMT via Stat3 in lung adenocarcinoma

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Abstract: Epithelial-mesenchymal transition (EMT) plays a vital role in lung inflammatory diseases, including lung cancer. However, the role and mechanism of action of the proinflammatory cytokine IL-17 in EMT in lung adenocarcinoma remain unresolved. In our study, we discovered that the expression of N-cadherin, Vimentin, Snail1, Snail2, and Twist1 was positively correlated with IL-17 expression, while E-cadherin expression was negatively correlated with IL-17 expression in human lung adenocarcinoma tissues. Moreover, we confirmed that IL-17 promoted EMT in A549 and Lewis lung carcinoma (LLC) cells in vitro by upregulating N-cadherin, Vimentin, Snail1, Snail2, and Twist1 expression and downregulating E-cadherin expression. Stat3 was activated in IL-17-treated A549 and LLC cells, and Stat3 inhibition or siRNA knockdown notably reduced IL-17-induced EMT in A549 and LLC cells. Thus, IL-17 promotes EMT in lung adenocarcinoma via Stat3 signaling; these observations suggest that targeting IL-17 and EMT are potential novel therapeutic strategies for lung cancer.

Keywords: IL-17, Stat3, Snail1, Snail2, Twist1, lung adenocarcinoma

Introduction

Lung cancer is the leading cause of cancer death worldwide [1-3]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers, and adenocarcinoma is the most common subtype of NSCLC. Outcomes for lung cancer patients remain poor despite substantial advancements in treatment. Currently, the 5-year survival rate for lung cancer patients is approximately 15% [4]. This low survival rate is predominantly attributed to the metastatic tendencies and resistance to various treatments (radiotherapy, chemotherapy, targeted therapy) exhibited by lung cancer. Because lung cancer is often diagnosed at advanced stages and fails to respond to therapy [5], novel strategies that focus on minimizing lung cancer metastasis are urgently needed.

Tumor metastasis is a complex process in which tumor cells from the primary site spread to distant sites. Epithelial-mesenchymal transition (EMT) is a key step in local invasion and distant metastasis and plays an important role in the resistance of lung cancer to targeted treatment [6, 7]. Accumulating data have revealed that cytokines, chemokines, growth factors, and inflammatory mediators derived from both neoplastic and non-neoplastic cells within the tumor microenvironment communicate with oncogene signaling, such as Stat3 signaling, to promote EMT during tumor invasion and metastasis in the context of lung cancer [8, 9].

IL-17 is a newly identified pro-inflammatory cytokine that is primarily produced by activated CD4+ T helper cells (TH17 cells) [10]. Recently, IL-17-producing cells and IL-17/IL-17RA signaling have been widely investigated in the context of human solid tumors [11], including lung cancer [12-14]. Recent reports have indicated that IL-17 promotes EMT profiles in lung inflammatory diseases, such as obliterative bronchiolitis [15], severe asthma [16], pulmonary fibrosis [17], and COPD [18, 19], and stimulates EMT in multiple myeloma [20]. Additionally, studies
IL-17 induces EMT in lung adenocarcinoma

Table 1. Sequence of primers used for qRT-PCR amplification

<table>
<thead>
<tr>
<th>Gene</th>
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<th>Mouse</th>
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<tr>
<td>IL-17</td>
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<td>AGAGCGGAGACTGCGGAGAC</td>
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<td>CAGGCAAGCAGGCTCACC</td>
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<td>SNAI 1</td>
<td>TGCCCTCAAGATGCAATCC</td>
<td>CGCTGTCGTCGATCAAGG</td>
</tr>
<tr>
<td>SNAI 2</td>
<td>AGACCTCTGTTGGCCTAGAAG</td>
<td>CAGGCCAGTCTTGAGGGG</td>
</tr>
<tr>
<td>TWIST 1</td>
<td>GGATCCTGAGCTCTAGG</td>
<td>TCTGGAGAAGCTGAGGTG</td>
</tr>
<tr>
<td>GAPDH</td>
<td>GTCCGAAGCAGCAGGATTGG</td>
<td>GGAAGATGTTGAGGATTGC</td>
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</table>

have demonstrated that IL-17 facilitates lung cancer progression by, for example, promoting proliferation, angiogenesis [21-23], immune evasion, and metastasis [24, 25].

Recent discoveries have revealed complex interplay between Stat3 signaling and IL-17-producing cells. Stat3 favors the differentiation and expansion of TH17 cells to produce IL-17, which further triggers Stat3 activation to further promote tumor progression in inflammatory tumor microenvironments [11], such as in lung cancer [24, 26]. Although Stat3 is involved in IL-17-induced angiogenesis in many types of cancer, including hepatocellular carcinoma [27] and lung cancer [24], no data have been published on the role of Stat3 in IL-17-modulated EMT in cancers such as lung cancer.

In our study, we explored (i) the relationship between IL-17 and EMT profiles (EMT markers: E-cadherin, N-cadherin and Vimentin; EMT transcription factors (TFs): SnaI1, SnaI2, Twist1) in tumor tissues from lung adenocarcinoma patients; (ii) the effects of IL-17 on the wound healing and migration of lung adenocarcinoma cells as well as on EMT profiles in vitro; and (iii) the effects of Stat3 knockdown on IL-17-induced EMT profiles in A549 and LLC cells in vitro. These data improve the understanding of the communication between IL-17 and EMT and provide new insights for targeting both inflammation and EMT in lung cancer treatment.

Materials and methods

Clinical samples

Tumor and corresponding peritumoral tissues were obtained from 35 lung adenocarcinoma patients as described previously [28].

Cell lines

The A549 human lung adenocarcinoma cell line (ATCC #CCL-185) and the Lewis lung carcinoma (LLC) cell line (ATCC #CRL-1642) were purchased from ATCC (Manassas, VA, USA) and cultured according to the provided guidelines. Recombinant human and mouse IL-17 were obtained from PeproTech (Rocky Hill, NJ). The Stat3 inhibitor (WP1066) was acquired from Santa Cruz Biotechnology.

Wound healing assay

A549 and LLC cells (3×10^5 cells/well) were seeded in six-well plates and incubated overnight. After cells had reached 80-90% confluence, the culture medium was removed, and a denuded area of constant width was created by mechanical scraping with a sterile 200-μl pipette tip. Cell debris was removed, and the monolayer was washed three times with serum-free medium. The cells were cultured for an additional 24 h, and wound closure was monitored and photographed under a microscope. Results are expressed as migration indices.

Cell migration assays

Migratory profiles were evaluated using Costar 24-well plates containing polycarbonate filter inserts with 8-mm pores. A549 and LLCs (3×10^5 cells/well) were added to the upper inserts and resuspended in serum-free medium; 500 μl of medium containing 10% FBS with or without IL-17 and/or WP1066 were added to the corresponding lower chambers. After 24 h, non-migrating cells were removed, and the
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underside of the insert was stained with crystal violet. Cells that had migrated into the lower chamber medium were collected and counted. Migration was calculated in terms of total cells on the lower membrane surface.

**RNA interference**

The Stat3 and control siRNAs (human STAT3-siRNA, sc-29493; mouse Stat3-siRNA, sc-29494; human and mouse control-siRNA, sc-siRNA, sc-37007) were obtained from Santa Cruz Biotechnology. siRNAs were transfected into A549 and LLC cells with the siRNA Reagent System (sc-29528, Santa Cruz Biotechnology) at a final concentration of 80 nm for 48 h according to the manufacturer’s protocol.

**Quantitative real-time PCR**

A549 and LLC cells (3×10⁵ cells/well) were seeded in 12-well plates and incubated overnight. For inhibitory assays, the cells were stimulated with human or mouse IL-17 (100 ng/ml) in the presence of the Stat3 inhibitor (30 μM) or medium for an additional 6 h. For RNA interference experiments, A549 and LLC cells (1×10⁶ cells/well) were transfected with siRNA for 48 h and then treated with human or mouse IL-17 (100 ng/ml), respectively, for an additional 6 h. Then, total RNA was extracted. Reverse transcription and real-time quantitative PCR (qRT-PCR) were performed as previously described [26], and the mRNA levels of target genes were normalized to those of Gapdh. The primer sequences used for PCR are presented in Table 1.

**Western blotting**

A549 and LLC cells (1×10⁶ cells/well) were seeded in six-well plates and incubated overnight. Cell lysates were separated by SDS-PAGE and transferred onto PVDF membranes (Millipore, Billerica, MA, USA). The membranes were blocked in 5% BSA containing 0.05% Tween-20 and probed with the appropriate primary antibodies overnight at 4°C. The membranes were washed three times for 10 min each and incubated with horseradish peroxidase-conjugated secondary antibodies for 1 h at room temperature. Membranes were then washed as above and visualized by enhanced chemiluminescence. All the antibodies were purchased from CST (P-Stat3: #9138; Stat3: #14801; EMT antibody sampler kit: #9782; Gapdh: #5174) except for anti-human and anti-mouse N-Cadherin (13769-1-AP, 13769-2-AP, and 13769-7-AP).
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Correlation between IL-17 and EMT markers in human lung adenocarcinoma tissues

IL-17 and EMT have been reported to promote lung cancer metastasis; thus, we explored the relationship between IL-17 and EMT marker expression in human lung adenocarcinoma tissues using qRT-PCR. Interestingly, our results clearly demonstrated that IL-17 expression was positively correlated with N-cadherin, Vimentin, Snail1, Snail2, and Twist1 expression and negatively correlated with E-cadherin expression in human lung adenocarcinoma tissues (Figure 1A-F), suggesting that IL-17 may participate in EMT in human lung adenocarcinoma.

Statistics

The data are presented as the mean ± SEM. T-tests for independent events were used to evaluate the significance of differences. Data in different groups were compared by Kruskal-Wallis one-way analysis of variance. Correlations were used to analyze the relationships in human lung cancer tissue. Statistical analyses were conducted using SPSS statistical software, version 16.0 (Chicago, IL); two-tailed results with p<0.05 were regarded as significant.

Results

IL-17 and EMT in lung adenocarcinoma

Our in vitro western blotting results indicated that IL-17 treatment led to a significant increase in Stat3 phosphorylation at different time points and concentrations in A549 cells (Figure 2A). Moreover, Stat3 was also activated in LLC cells by 100 ng/ml IL-17 at 6 h (Figure 2B). For subsequent experiments, 100 ng/ml IL-17 was utilized.

Stat3 inhibitor is required for IL-17-mediated wound healing in A549 and LLC cells in vitro

To evaluate the effect and mechanism of action of IL-17 in A549 and LLC cells in vitro, wound healing assays were performed. IL-17 markedly and persistently promoted A549 and LLC cell wound closure at several time points (Figure 3A-C). Furthermore, we noted that the Stat3 inhibitor significantly abrogated IL-17-induced A549 and LLC wound healing (Figure 3A-C).

Stat3 inhibitor is required for IL-17-mediated A549 and LLC cell migration in vitro

The metastatic properties of IL-17-treated A549 and LLC cells were further validated by migration assays. As expected, the two cell lines displayed greater migratory activity after IL-17 treatment compared with control medium (Figure 4A-D). Moreover, the Stat3 inhibitor decreased the IL-17-induced migration of the two cell lines (Figure 4A-D).

Stat3 knockdown decreases IL-17-induced EMT in A549 and LLC cells in vitro

To further determine whether IL-17 enhances EMT properties in A549 and LLC cells, we used qRT-PCR and western blotting to assess EMT markers after treatment with or without IL-17. Our data indicated that E-cadherin mRNA expression was decreased and that N-cadherin, Vimentin, Snail1, Snail2 and Twist1 mRNA expression levels were increased in IL-17-
IL-17 induces EMT in lung adenocarcinoma treated A549 and LLC cells relative to control cells (Figure 5A). These findings were further confirmed by western blotting (Figure 5B), demonstrating that IL-17 enhanced EMT in A549 and LLC cells in vitro.

Subsequently, to determine if Stat3 knockdown is involved in IL-17-induced EMT on lung adenocarcinoma, the cells were pretreated with a Stat3 inhibitor (WP1066) or Stat3 siRNA before IL-17 stimulation and EMT profiles were determined by western blotting.

Importantly, our findings indicated that the Stat3 inhibitor significantly suppressed the IL-17-induced EMT profile in A549 and LLC cells at the mRNA and protein levels (Figure 5A, 5B). Furthermore, after transfection with Stat3 siRNA for 48 h, the cells displayed an effective Stat3 knockdown (~90%) and markedly reduced Stat3 activation by qRT-PCR and western blotting (Figure 6A, 6B). Next, Stat3 siRNA had a similar effect in the two cell lines; it considerably weakened the IL-17-mediated EMT profile compared to control siRNA (Figure 7A, 7B). In summary, Stat3 was involved in the IL-17-mediated EMT profile in lung adenocarcinoma in vitro.

Discussion

Previous lung cancer studies, including ours, have demonstrated that high expression of IL-17 and/or IL-17RA signaling correlate with TNM stage [24, 28] and poor prognosis [22] in NSCLC patients and promote metastasis by enhancing angiogenesis [21].

Figure 3. Stat3 inhibitor reduced IL-17-induced wound healing by A549 and LLCs. A549 and LLCs were incubated with medium alone, IL-17, or IL-17 plus the Stat3 inhibitor for 24 h (IL-17, 100 ng/ml; inhibitor, 30 μM). Microscopic photography was performed at several time points (0, 6, 12, 24 h) after wound generation on a confluent monolayer of A549 and LLCs (magnification, ×200). A and C. Graphs show the wound closure over time by A549 cells. B and C. Graphs show the wound closure over time by LLCs. Data are presented as the mean ± SEM of three independent experiments. The comparisons were evaluated by Kruskal-Wallis one-way analysis of variance on ranks. * and #, IL-17 compared with medium and the Stat3 inhibitor, respectively. * and #, p < 0.05; ** and ###, p < 0.001.
IL-17 induces EMT in lung adenocarcinoma and lymphangiogenesis [22]. Our results are the first to clearly show that EMT marker expression levels were positively correlated with IL-17 expression in lung adenocarcinoma patient tissues. IL-17 also triggers EMT profiles in multiple myeloma and lung inflammatory diseases. A prior study indicated that IL-17 promotes EMT by repressing E-cadherin and inducing Vimentin, Snail and Slug in multiple myeloma [20]. In addition, several previous studies have shown that IL-17 induces EMT in airway epithelial cells, 16HBE cells, and alveolar epithelial cells via TGF-β-dependent and/or TGF-β-independent mechanisms in obliterative bronchiolitis [15], severe asthma [16], and pulmonary fibrosis [17]. Importantly, lung inflammatory diseases and COPD [18, 19], as well as lung cancer [29], share common pathogenic mechanisms,
IL-17 induces EMT in lung adenocarcinoma

A

**A549**

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**Twist1**

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**Twist1**

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B

**Western Blots**

- E-cadherin
- N-cadherin
- Vimentin
- Snail 1
- Snail 2
- Twist1
- Gapdh

*Note: Bars represent mean ± SD. Statistical significance: *p < 0.05, **p < 0.01, ***p < 0.001, #p < 0.05, ##p < 0.01, ###p < 0.001.*
IL-17 induces EMT in lung adenocarcinoma

Our prior discoveries in lung adenocarcinoma patient tissues and previous evidence connecting IL-17 and EMT in other diseases led us to further explore the effects and corresponding mechanism of action of IL-17 on EMT profiles in lung adenocarcinoma in vitro.

As reported previously, IL-17 decreases E-cadherin and increases Vimentin in A549 cells via the NF-κB-mediated upregulation of ZEB1 but not of Snail1, Snail2, or Twist1 [29]. Although NF-κB signaling is required for IL-17-mediated effects in many inflammatory and immune diseases, IL-17 is a weak NF-κB activator [30]. Accumulating evidence suggests that EMT profiles are directly modulated by EMT TFs (Snail family, Twist1) or indirectly modulated by the Stat3 pathway in many malignancies [9, 31-33], including lung cancer [6, 34, 35]. Stat3 signaling is a common mechanism through which IL-17 mediates tumor progression [24, 27, 29], including that of lung cancer [24]. Interestingly, we found that Stat3 was activated by IL-17 and that Stat3 knockdown significantly suppressed IL-17-mediated A549 and LLC wound healing and migration; these results were somewhat similar to those of a previous study implicating Stat3 in IL-17-mediated A549 migration [24].

Next, we further explored whether Stat3 is also involved in IL-17-induced EMT in vitro and revealed that Stat3 knockdown notably inhibited the IL-17-mediated increases in N-cadherin, Vimentin and EMT TFs (Snail1, Snail2, Twist1) and reversed the IL-17-induced decrease in E-cadherin expression in A549 and LLC cells. Compared with the work by Gu et al. [29], our data innovatively showed that IL-17 exerted a similar effect in the mouse lung adenocarcinoma cell line, LLC. Moreover, we confirmed these results in A549 cells and showed that IL-17 also induced N-cadherin in A549 cells. Thus, we concluded that IL-17 promotes EMT in lung adenocarcinoma via Stat3 signaling.

It is well established that inflammatory cytokines drive the excessive activation of Stat3 signaling to facilitate EMT in many types of cancer [9], including lung cancer [36]. For example,
IL-17 induces EMT in lung adenocarcinoma

A

**A549**

- E-cadherin
- N-cadherin
- Vimentin

**LLCs**

- E-cadherin
- N-cadherin
- Vimentin

B

- SNAIL 1
- SNAIL 2
- TWIST 1

**E-cadherin**

**N-cadherin**

**Vimentin**

**SNAIL 1**

**SNAIL 2**

**TWIST 1**

**GAPDH**

A549 LLCs
it has been frequently reported that Stat3 is required for IL-6-induced EMT in lung cancer [31, 37-39]. As described previously, the IL-6/Stat3 axis favors the differentiation of TH17 cells to produce IL-17, which further triggers these cells to promote tumor progression in the inflammatory microenvironment [11], such as is present for lung cancer [24, 26]. In turn, IL-17 facilitates the progression of many types of cancer [24, 27, 29], including lung cancer [24], via Stat3 signaling. All these data may imply that EMT represents one outcome of the interplay between IL-17-producing cells and IL-6/Stat3 signaling in lung cancer, but this remains to be fully elucidated.

In conclusion, Stat3 is activated as part of an inflammatory repair process that promotes EMT in both COPD and lung cancer [9, 18, 19, 40]. In addition, IL-17 signaling frequently induces EMT in both lung inflammatory diseases and lung cancer. Therefore, targeting IL-17 and EMT may represent a potential strategy for preventing early molecular events in lung inflammatory diseases to decrease or delay the development of lung cancer. Our investigation sheds new light on inflammation and EMT in lung cancer and thereby contributes to possibilities for preventing lung tumorigenesis at earlier stages.

Acknowledgements

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Disclosure of conflict of interest

None.

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