

# Iodine-125 radiation inhibits epithelial-mesenchymal transition in lung cancer cells by blocking TGF- $\beta$ 1/Smad3/Snai1 signaling

F. Song<sup>1#</sup>, J. Che<sup>1#</sup>, H. Li<sup>2</sup>, G. Zhu<sup>1</sup>, M. Huang<sup>2</sup>, D. Xu<sup>3\*</sup>

<sup>1</sup>Department of Minimally Invasive Intervention, The Third Affiliated Hospital of Kunming Medical University, Yunnan Cancer Hospital, Peking University Cancer Hospital Yunnan, Kunming, 650118, China

<sup>2</sup>Department of Hepatobiliary Surgery, The Third Affiliated Hospital of Kunming Medical University, Yunnan Cancer Hospital, Peking University Cancer Hospital Yunnan, Kunming, 650118, China

<sup>3</sup>Department of Medical Laboratory, Pingbian County People's Hospital, Pingbian 661200, Yunnan, China

## ABSTRACT

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#### \*Corresponding author:

Dan Xu, M.D.,

E-mail: 632533054@qq.com

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#Co-first authors contributed equally to this work.

**Background:** Iodine-125 (<sup>125</sup>I) brachytherapy is an effective strategy for treating human tumors. The current study aimed to discover the mechanisms underlying the therapeutic action of <sup>125</sup>I radiation in lung cancer, with a focus on its impact on the epithelial-mesenchymal transition (EMT). **Materials and Methods:** A549 cells, a human lung adenocarcinoma cell line, were treated with transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) and/or <sup>125</sup>I (control, TGF- $\beta$ 1, <sup>125</sup>I, and TGF- $\beta$ 1 + <sup>125</sup>I groups) to evaluate the effects of <sup>125</sup>I on TGF- $\beta$ 1-induced EMT. After treatment, the viability of A549 cells was detected using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The expression of E-cadherin, N-cadherin, Vimentin, Smad3, and Snai1 markers and pathway molecules was measured. **Results:** <sup>125</sup>I radiation inhibited the viability of A549 cells, both with and without TGF- $\beta$ 1 treatment. TGF- $\beta$ 1 intervention promoted the EMT of A549 cells, as demonstrated by the morphological transition from a polygonal shape to a spindle shape, reduced E-cadherin levels, and elevated Vimentin and N-cadherin expression. Notably, TGF- $\beta$ 1-activated EMT was significantly weakened by <sup>125</sup>I radiation. Moreover, <sup>125</sup>I radiation reversed TGF- $\beta$ 1-induced upregulation of Smad3 and Snai1 in A549 cells. **Conclusion:** <sup>125</sup>I radiation suppresses the EMT by blocking TGF- $\beta$ 1/Smad3/Snai1 signaling, contributing to the treatment of lung cancer.

## INTRODUCTION

Lung cancer is a common and fatal malignancy worldwide <sup>(1,2)</sup>. According to global cancer statistics, in 2022, there were 2,480,301 newly diagnosed cases and 1,817,172 deaths, cases in 2022, making lung cancer the leading cause of both cancer incidence and mortality worldwide <sup>(3)</sup>. Smoking is the main cause of 80-90% of lung cancer cases, with other factors including radon or fume exposure, toxic occupational environment, and microbial infection, among others <sup>(4,5)</sup>. Similar to other types of cancer, surgery, chemotherapy, and radiotherapy are traditional therapeutic strategies for lung cancer in clinical practice <sup>(6)</sup>. The development of immunotherapy and molecular targeted therapy has great advantages for improving the outcomes of patients with lung cancer <sup>(7)</sup>. However, the outcome of lung cancer remains poor, particularly because of late diagnosis, metastasis, and drug resistance <sup>(8,9)</sup>. Therefore, more effective therapeutic strategies are required for lung cancer.

Brachytherapy is a type of radiotherapy that puts radioactive sources within or close to the tumor parenchyma, allowing more concentrated radiotherapy while sparing surrounding normal tissues <sup>(10)</sup>. Evidence has shown that brachytherapy is effective and safe for tumors located at various sites, such as the lungs, liver, colon, pancreas, prostate, breast, and endometrium <sup>(11,12)</sup>. In brachytherapy, radioactive sources contain Cobalt-60, iridium-192, ruthenium-106, palladium-103, and astatine-211 <sup>(13,14)</sup>, among which iodine-125 (<sup>125</sup>I) is the most common one <sup>(15-17)</sup>. <sup>125</sup>I brachytherapy is widely used to treat diverse types of tumors <sup>(16,18-20)</sup>, including lung cancer <sup>(21)</sup>. A biocentric analysis showed that <sup>125</sup>I brachytherapy was more effective in elevating the survival rate within six months without progression (76.3% vs. 51.5%, P=0.002) than external beam radiotherapy in patients with non-small cell lung cancer (NSCLC) accompanied by brain metastasis <sup>(22)</sup>. <sup>125</sup>I brachytherapy improves clinical outcomes and reduces the possibility of myelosuppression in patients when compared with chemotherapy <sup>(23)</sup>.

Another meta-analysis involving eight studies found that  $^{125}\text{I}$  brachytherapy improved the efficacy of transarterial chemical infusion without inducing severe adverse events in patients with advanced lung cancer (24). However, the therapeutic mechanisms of  $^{125}\text{I}$  brachytherapy in lung cancer have not been fully elucidated.

Epithelial-mesenchymal transition (EMT), a process involving cell morphological transformation, plays a crucial role not only in embryogenesis and wound healing but also in tumour progression (25, 26). In terms of molecular mechanisms, transcription factors, including SNAI, ZEB, and TWIST, are master regulators of EMT (27). The TGF- $\beta$  pathway is a predominant signalling pathway involved in the regulation of EMT. As a major driver, TGF- $\beta$  can induce EMT via activating Smad/non-Smad and cross-talking with many other signals (28). Recent studies have revealed that many agents exhibit therapeutic potential in lung cancer by blocking TGF- $\beta$ -mediated EMT. For example, salinomycin inhibits cell migration and invasion by suppressing TGF- $\beta$ 1-activated EMT in lung cancer. Cucurbitacin B inhibits TGF- $\beta$ 1-activated EMT in NSCLC, contributing to remission of tumour metastasis in vivo (29). A TGF- $\beta$ 1 inhibitor, Compound 67 (an analogue of chalcones), suppresses cell migration, invasion, and EMT in lung cancer (30).

The above demonstrates that EMT is closely linked to metastasis and recurrence of lung adenocarcinoma and that  $^{125}\text{I}$  radiation exerts superior effects in patients with advanced lung adenocarcinoma. However, there are few studies on the association between radioactive  $^{125}\text{I}$  particles and EMT, as well as the underlying mechanism in the context of lung adenocarcinoma. Hence, we aimed to explore the mechanism of action of  $^{125}\text{I}$  radiation in lung cancer, primarily concerning EMT. Specifically, TGF- $\beta$ 1 was used to induce EMT in human lung adenocarcinoma cells. The effects of  $^{125}\text{I}$  radiation on EMT and TGF- $\beta$ 1/Smad3/Snai1 signaling were mainly explored at the cellular level. This study aims to reveal the mechanism of action of  $^{125}\text{I}$  radiation on EMT related to the TGF- $\beta$ 1/Smad3/Snai1 signaling, laying the foundation for lung cancer therapy.

## MATERIALS AND METHODS

### Cell culturing and treatments

A549 cells (a human lung adenocarcinoma cell line; Procell, Wuhan, China) were maintained in RPMI-1640 medium (Meilun, Xingtai, China) containing 10% foetal bovine serum (FBS; Gibco, Grand Island, NY, USA) at 37 °C with 5% CO<sub>2</sub>.

$^{125}\text{I}$  seeds were obtained from Beike Biotechnology (Beijing, China) and stored on lead clips. The parameters of  $^{125}\text{I}$  seeds are as follows: diameter = 0.8 mm, length = 4.5 mm, effective radiation radius = 17 mm, half-life = 59.43 d, X-ray energy = 27.4-31.5 keV,  $\gamma$  radiation energy = 35.5

keV, and radiation activity = 0.8 mCi. For treatment, A549 cells were categorised into four groups. In the TGF- $\beta$ 1 group, cells received 48 h of treatment with 5 ng/mL TGF- $\beta$ 1, as previously described (31). In the  $^{125}\text{I}$  group, cells were irradiated with 10  $^{125}\text{I}$  seeds at an interval of 1 cm. In the TGF- $\beta$ 1 +  $^{125}\text{I}$  group, cells received both TGF- $\beta$ 1 treatment and  $^{125}\text{I}$  irradiation simultaneously. Untreated cells were used as the control group. After treatment, the morphological transformation of A549 cells was monitored under a microscope (MOTIC, Chengdu, China).

Throughout the experiment, the personnel were equipped with lead-protective clothing. Cells in each group were cultured in a separate incubator and separated with 0.5 mm lead plates. After the experiments, all  $^{125}\text{I}$  seeds were recycled into a lead tank and disposed of according to the guidelines for radioactive waste.

### MTT analysis

The viability of A549 cells in different groups was determined using an MTT assay kit (Sparkjade, Qingdao, China) according to the manufacturer's instructions. Simply, we seeded A549 cells ( $2 \times 10^4$  cells/well) in 96-well plates and cultured for 24 h. Afterwards, cells were stimulated with TGF- $\beta$ 1 and/or  $^{125}\text{I}$  for another 24 or 48 h (the 48<sup>th</sup> and 72<sup>th</sup> hour). After 4 h of incubation with 10  $\mu\text{L}$  MTT working solution, cells were continuously treated with 100  $\mu\text{L}$  dimethyl sulfoxide for 2 h. The optical density was measured at 570 nm and was eventually read by a microplate reader (Hiwell Diatek, Wuxi, China).

### qRT-PCR

Cells were lysed in TRIzol reagent (Vicbio Biotechnology Co., Ltd., Beijing, China) on ice to separate RNA samples, and the isolated RNAs were immediately reverse-transcribed into cDNAs using a cDNA synthesis kit (Servicebio, Wuhan, China). Using a SYBR Green qPCR Master Mix (Servicebio, Wuhan, China), qRT-PCR was run on a PCRAMplifier (#CFX96 Touch Deep Well, Bio-Rad, CA, USA). Utilising the 2- $\Delta\Delta\text{Ct}$  method (internal control: GAPDH), we calculated the relative expression of specific mRNAs. The primer sequences are listed in table 1.

**Table 1.** The used primers in this study.

Name	Gene symbol	Gene ID	Sequences (5'-3')
E-cadherin	CDH1	999	Forward primer: TGGACCGAGA-GAGTTTCCT
			Reverse primer: TTAGCCTCGTTCTCAGGCAC
Vimentin	VIM	7431	Forward primer: GGAC-CAGCTAACCAACGACA
			Reverse primer: AAGGTCAA-GACGTGCCAGAG
N-cadherin	CDH2	1000	Forward primer: GAGGCTTCTGGTGAATCGC
			Reverse primer: AATCTG-CAGGCTCACTGCTC
SMAD3	SMAD3	4088	Forward primer: TCCATGACTGTGGATGGCTTC
			Reverse primer: TTCAGGTT-GCATCCGATGTG
SNAI1	SNAI1	6615	Forward primer: TAGCGAG-TGGTTCTTCTGCG
			Reverse primer: AGGGCTCTG-GAAGGTTAAAC

### Western blot

Cells were lysed in RIPA lysis buffer (Servicebio, Wuhan, China) on ice to isolate protein samples. Equivalent amounts of protein from different groups were used for detection. First, after separation using 10% SDS-PAGE, we transferred the proteins onto PVDF membranes (Millipore Billerica, MA, USA). Subsequently, the membrane was blocked with 5% BSA for 30 min at 37 °C, followed by co-incubation with the following primary antibodies (anti-β-actin, Proteintech, Wuhan, China; anti-E-cadherin, -Vimentin, -N-cadherin, -Smad3, and -Snai1, Abcam, Cambridge, UK) for 12 h at 4 °C. Afterwards, co-incubation with secondary antibody was carried out for 1 h (HRP-labelled IgG, Servicebio, Wuhan, China) at 25 °C. Finally, the membranes were visualised using an efficient chemiluminescence kit (Servicebio, Wuhan, China) and quantified using a Gel Imaging System (Tanon, China).

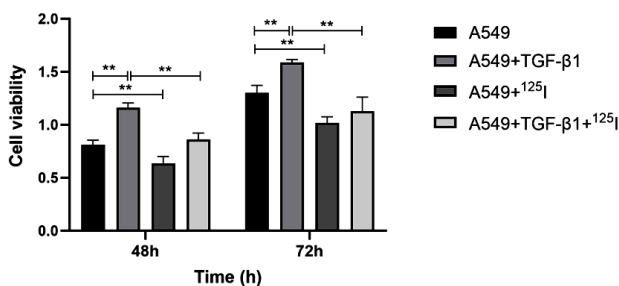
### Statistical analysis

Quantitative data were displayed as mean ± standard deviation and were analyzed using GraphPad Prism v7.0 (San Diego, CA, USA). One-way ANOVA and Tukey's test were used to compare data across the four groups. Statistical significance was set at P<0.05.

## RESULTS

### Radiation from <sup>125</sup>I inhibits the viability of A549 cells

The viability of the A549 cells in response to <sup>125</sup>I radiation was analyzed. At both 48 and 72 h post-treatment, a significantly higher viability was observed in TGF-β1-stimulated A549 cells in comparison with non-stimulated A549 cells (P<0.01). <sup>125</sup>I radiation decreased the viability of A549 cells, regardless of TGF-β1 stimulation, with significant levels (P<0.01) (figure 1).



**Figure 1.** The viability of A549 cells in different groups was measured by MTT assay. A549 cells were treated with TGF-β1 and/or <sup>125</sup>I. \*\*P < 0.01.

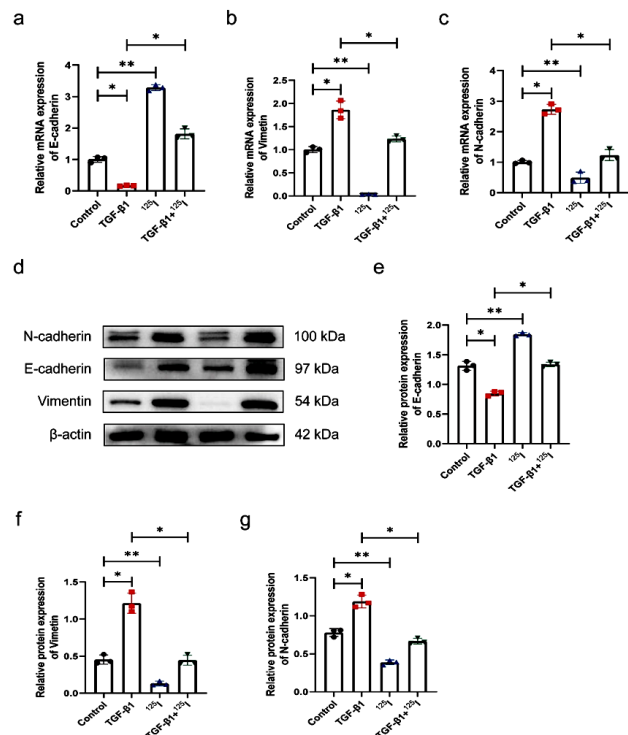
### Radiation from <sup>125</sup>I inhibits the EMT of A549 cells

Three EMT markers were measured to determine the effects of <sup>125</sup>I radiation on EMT. As displayed in

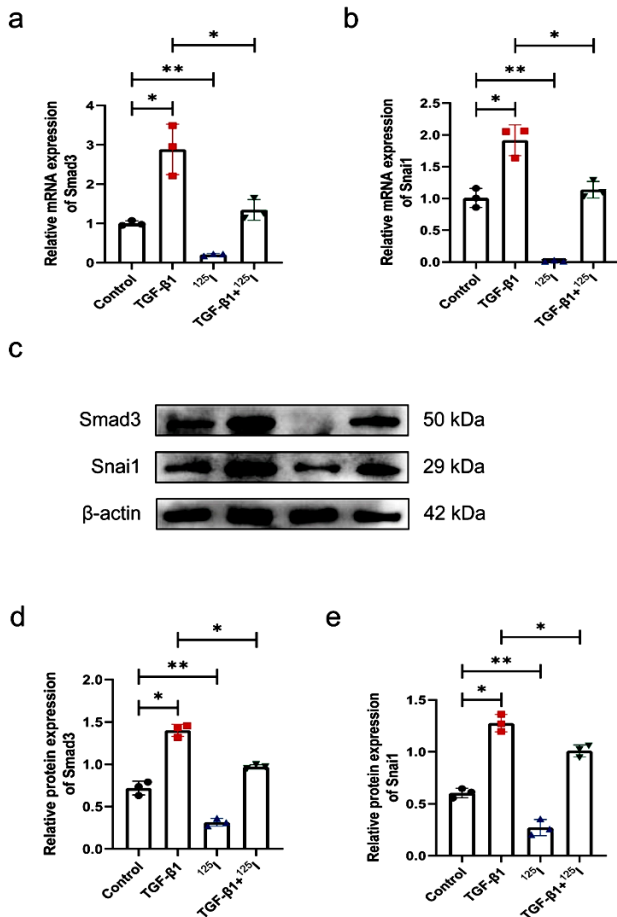
figure 2a, TGF-β1 induced a down-regulation of E-cadherin mRNA expression in A549 cells (P<0.05). On the contrary, mRNA levels of Vimentin and N-cadherin were enhanced in TGF-β1-stimulated A549 cells in comparison with non-stimulated A549 cells (P<0.05) (figure 2b and c). Radiation from <sup>125</sup>I significantly elevated E-cadherin levels while decreasing Vimentin and N-cadherin levels in A549 cells (P<0.01). Additionally, it reversed the effects of TGF-β1 on the regulating of these EMT markers (P<0.05) (figure 2a-c). In accordance with the above observations on mRNA levels, western blotting revealed the same changes in the protein levels of E-cadherin, N-cadherin, and Vimentin in the different groups (P<0.05) (figure 2d-g).

### Radiation from <sup>125</sup>I blocks TGF-β1/Smad3/Snai1 signaling in A549 cells

The mechanism of action of <sup>125</sup>I radiation on Smad3 and Snai1 cells was further evaluated. As a result, the mRNA and protein levels of Smad3 and Snai1 were elevated by TGF-β1 (P < 0.05) but were decreased by <sup>125</sup>I radiation in A549 cells (P<0.01). Notably, the upregulation of Smad3 and Snai1 induced by TGF-β1 was significantly weakened by <sup>125</sup>I radiation (P<0.05) (figure 3a-e).



**Figure 2.** The expression of three EMT markers in A549 cells of different groups. **a**, The mRNA expression of E-cadherin; **b**, The mRNA expression of Vimentin; **c**, The mRNA expression of N-cadherin; **d-g**, The protein expression of E-cadherin, Vimentin, and N-cadherin. \*P < 0.05, \*\*P < 0.01.



**Figure 3.** The expression of Smad3 and Snai1 in A549 cells of different groups. **a**, The mRNA expression of Smad3; **b**, The mRNA expression of Snai1; **c-e**, The protein expression of Smad3 and Snai1, \*P < 0.05, \*\*P < 0.01.

## DISCUSSION

Lung cancer is a common pulmonary tumor associated with high mortality rates worldwide (32). As a minimally invasive radiotherapy, brachytherapy can be used as an alternative therapy for lung cancer at an early stage and as a principal or auxiliary therapy for lung cancer at a locally advanced stage or with metastasis (33). However, knowledge of the mechanisms of action of brachytherapy involving EMT in lung cancer remains limited.

EMT is an important biological process that drives the epithelial-to-mesenchymal phenotype. In addition to embryonic development, wound healing, and organ fibrosis, EMT also plays a prominent role in metastasis and resistance (34,35). On the one hand, EMT endows tumor cells with the abilities of stemness and invasiveness, contributing to distant metastasis and recurrence (36). On the other hand, EMT also enhances the drug efflux pump and anti-apoptotic capacity of tumor cells, contributing to drug resistance (34). Therefore, targeting the EMT is a key focus in cancer treatment. Evidence has determined that A variety of molecules, including

EFEMP2 (37), ALOX12 (38), PTPL1 (39), HRH3 (40), and LINC00891 (41), act as potential therapeutic targets for lung cancer by inhibiting EMT, such as EFEMP2 (37), ALOX12 (38), PTPL1 (39), HRH3 (40), and LINC00891 (41), among others. One review summarized that natural product-derived compounds with the ability to inhibit EMT are beneficial for the treatment of lung cancer (42). E-cadherin, Vimentin and N-cadherin are well-known biomarkers of EMT; E-cadherin is a marker for epithelial cells, whereas the other two are markers for mesenchymal cells (43). As a typical epithelial cell marker of EMT, downregulation of E-cadherin can induce EMT in tumor cells and promote their metastasis (44). E-cadherin expression is enhanced in human liver cancer cells after radioactive <sup>125</sup>I treatment (45). Metastasis of cancer cells is highly correlated with vimentin expression in NSCLC (46). Abnormal expression of N-cadherin enhances tumor cell invasion and migration, and N-cadherin-induced MMP-9 is regarded as a core step in tumor invasion and metastasis (47). In TGF-β1-treated cells, <sup>125</sup>I radiation increased E-cadherin levels while reducing Vimentin and N-cadherin levels, indicating inhibition of EMT after <sup>125</sup>I therapy. Similar results were observed in a previous study (48).

TGF-β is a pivotal cytokine that is implicated in the modulation of embryonic development, organogenesis, wound healing, immunomodulation, fibrosis, and carcinogenesis, among others (49). Notably, TGF-β is well-known as an inducer of EMT, and its activation is positively associated with metastasis and chemotherapy resistance in cancer (50). The underlying mechanisms of TGF-β in EMT are complex, and the TGF-β1/Smad3 signal axis is a pivotal one. In cells, the receptor complex of TGF-β1 can lead to the activation of Smad2/3 by inducing C-terminal phosphorylation. The trimers formed by Smad2, 3 and 4 then bind to DNA-binding transcription factors and synergistically regulate the target genes involved in EMT (28). Until now, emerging evidence has determined that TGF-β1/Smad3 signaling is the target of agents with therapeutic potential in cancer. For example, baicalin inhibits EMT-related metastasis in breast cancer by inhibiting TGF-β1/Smad3 signaling (51). Nobiletin inhibits the EMT of NSCLC cells by blocking TGF-β1/Smad3 signaling (52). OPB suppresses EMT in TGF-β1-induced lung cancer cells by regulating Smad3 (53). Snai1 is also a pivotal modulator of EMT and can be activated by Smad3 (54), which induces EMT by directly inhibiting E-cadherin transcription (55). Overexpression of Snai1 downregulates E-cadherin and Plakoglobin, and upregulates Vimentin and Fibronectin to activate EMT (28). Therefore, the TGF-β1/Smad3/Snai1 signaling pathway is an important mechanism by which <sup>125</sup>I radiation inhibits EMT in lung cancer.

Our study demonstrates that the therapeutic action of <sup>125</sup>I radiation in lung cancer is partly

achieved by inhibiting EMT. However, several limitations of this study should be considered. EMT is closely associated with tumor metastasis, and we mainly focused on the effects of <sup>125</sup>I radiation on EMT marker expression, while ignoring its effects on tumor cell migration and invasion. In addition, this was a preliminary study that included only a limited number of in vitro experiments. Further in vivo experiments are required to verify the findings obtained from this study.

## CONCLUSION

In conclusion, TGF- $\beta$ 1 induces the EMT in lung cancer cells, an effect that is reversed by <sup>125</sup>I radiation. This radiation may inhibit EMT by blocking the TGF- $\beta$ 1/Smad3/Snai1 signaling pathway.

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