

# Tobacco Smoke Plays an Important Role in Initiation and Development of Lung Cancer by Promoting the Characteristics of Cancer Stem Cells

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**Abstract:** Lung cancer is one of the most common causes of cancer-related deaths worldwide. Tobacco smoke is the single greatest risk factor of lung cancer. Although enormous progress in understanding the molecular mechanisms by which tobacco smoke leading to lung cancer has been made, the molecular pathogenesis remains largely unclear. Cancer stem cells have been implicated in cancer initiation, development, and drug resistance. In this review, we reviewed the relationship between tobacco smoke and lung cancer, the key role of cancer stem cells in lung cancer and other tumors. More importantly, we elucidate the mechanism of tobacco smoke promoting lung cancer from the perspective of the characteristics of cancer stem cells induced by tobacco smoke.

**Keywords:** lung cancer, tobacco smoke, cancer stem cells, mechanism

## Introduction

Lung cancer is one of the most common causes of cancer-related deaths worldwide.<sup>1</sup> About 1.8 million people are diagnosed with lung cancer and about 1.6 million people die as a result of lung cancer annually.<sup>2</sup> Tobacco smoke is the single greatest risk factor of lung cancer.<sup>3,4</sup> Studies have shown that 75–90% of lung cancers are related to the use of tobacco smoke.<sup>4</sup> Although enormous progress in understanding the molecular mechanisms by which tobacco smoke leading to lung cancer has been made, the molecular pathogenesis remains largely unclear. In this review, we attempt to elucidate the mechanism of tobacco smoke promoting lung cancer from the perspective of the characteristics of cancer stem cells promoted by tobacco smoke.

## Tobacco Smoke is Highly Correlated with the Initiation and Development of Lung Cancer

Tobacco smoke is a complex chemical mixture, containing several thousand compounds, including at least 60 known carcinogens.<sup>5,6</sup> Studies found that tobacco smoke was related to the incidence of lung cancer, and then the relationship between tobacco smoke and lung cancer has been widely studied since 1950s.<sup>5</sup> It is reported that there are an estimated 1.1 billion smokers globally, 1.8 million deaths from lung cancer each year, and about 80–90% of those deaths are attributable to tobacco smoke exposure.<sup>6,7</sup> More and more evidences show that tobacco smoke promote the occurrence and development of lung cancer.<sup>6–10</sup> It is reported

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that smokers have up to a 30-fold higher risk of developing lung cancer than non-smokers.<sup>6,7</sup> Tobacco smoke is a tumor initiator and a tumor promoter.<sup>9</sup> Conversion of tobacco smoke compounds to reactive forms results in gene mutation, DNA damage, abnormal DNA methylation, formation of DNA adducts, pulmonary inflammation, oxidative stress, abnormal proliferation, abnormal differentiation, Epithelial-Mesenchymal Transition (EMT) and so on.<sup>7-9,11</sup>

Enormous progress in understanding the molecular mechanisms by which tobacco smoke leading to lung cancer has been made; however, the molecular pathogenesis remains largely unclear. More and more studies have found that cancer stem cells (CSCs) play key roles in cancer initiation, development and relapse.<sup>12</sup> Herein, this article focuses on tobacco smoke affecting CSCs, thereby promoting the occurrence and development of lung cancer.

## Cancer Stem Cells Play a Key Role in Tumorigenesis and Development

It is believed that CSCs are responsible for cancer initiation and local or metastatic recurrence. It may be because the inherent self-renewal and tumorigenic properties of these cells provide them with unique capabilities to resist various forms of anti-cancer treatment, disseminate to and colonize distant tissues.<sup>12</sup> CSCs are resistant to conventional chemotherapy and radiation therapy, and can remain dormant for many years before cancer initiation, metastases and relapses.<sup>13</sup> Some previous studies showed that the critical role of CSCs in initiation and development of lung cancer, liver cancer, breast cancer, head and neck squamous cell carcinomas, pancreatic cancer and glioblastoma.<sup>14-19</sup>

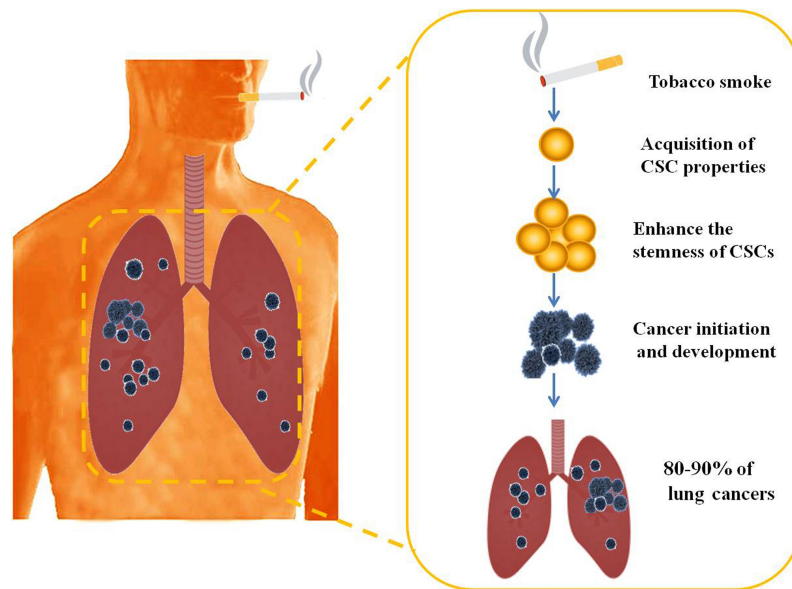
Lung CSCs are considered as the cancer initiating and maintaining cells of lung cancer.<sup>15</sup> Lin et al reported that lung CSCs are responsible for lung cancer initiation and local or metastatic recurrence, the mitochondrial deoxyguanosine kinase is required for CSCs stemness in lung adenocarcinoma.<sup>13</sup> Wang et al investigated that arsenic and BaP co-exposure produce CSC-like cells and promote the occurrence of lung cancer.<sup>20</sup> Hsu et al reported that lung CSCs confer tumorigenesis and resistance to standard treatment in lung cancer, targeting the upregulated glycolysis and its associated downstream pathways may be the novel strategies for eliminating CSCs and the better prognosis of cancer.<sup>21</sup> These studies have shown that lung

CSCs play a very important role in the occurrence, development and treatment of lung cancer.

## Tobacco Smoke Enhance the Stemness of Cancer Stem Cells

Toxicants, such as tobacco smoke, have various enhancement effects on cancer stem cells. Acquisition of CSCs properties induced by tobacco smoke is an early event in the initiation of carcinogenesis. Xie et al reported that long-term tobacco smoke exposure increased the stemness of hepatic CSCs, induced EMT process and IL-33 expression via IL-33/p38.<sup>22</sup> Liang et al found that long time tobacco smoke exposure induced urocytic EMT and acquisition of CSCs properties by activating the Wnt pathway.<sup>23</sup> Tobacco smoke is a major risk factor for pancreatic cancer and exposure to tobacco smoke activates stem cell features of pancreatic cancer cells via PAF1.<sup>24</sup> Qian et al found that tobacco smoke effectively promoted renal CSCs stemness via Sonic Hedgehog pathway by enhancing self-renewal ability, increasing the expression of CSCs markers and elevating CD133<sup>+</sup> cell population.<sup>25</sup> It is reported that nicotine is effective in the occurrence, the development and metastasis of breast cancer by inducing enrichment of side population cells with CSCs-like properties.<sup>26,27</sup> Exposure to chewing tobacco smoke increased cell proliferation, invasive ability and anchorage independent growth. Datta et al proposed that chronic exposure of esophageal epithelial cells to tobacco smoke leads to CSCs-like phenotype.<sup>28</sup> In summary, tobacco smoke enhanced the self-renewal ability, stemness, and induce the generation of CSCs-like cells, which promoted the occurrence and development of liver cancer, kidney cancer, breast cancer, etc.

More importantly, it is believed that tobacco smoke is effective in the occurrence, the development and metastasis of lung cancer by enhancing the stemness of lung CSCs (Figure 1). Schaal et al demonstrated that nicotine can induce the expression of Sox2 and Oct4, which are indispensable for self-renewal and maintenance of CSCs properties in non-small cell lung adenocarcinoma cells.<sup>29</sup> Xie et al suggested that long-term tobacco smoke exposure enhancing self-renewal ability, increasing the expression of CSCs markers and tumorigenic ability of human bronchial epithelial cells, the IL-6/ $\Delta$ Np63 $\alpha$ /Notch axis and Wnt/ $\beta$ -catenin pathway play an important role in this process.<sup>30,31</sup> Mouse models with initial and advanced forms of lung cancer were developed using tobacco



**Figure 1** Tobacco smoke is effective in the occurrence and development of lung cancer by enhancing the stemness of lung CSCs.

smoke carcinogen, the number of OCT4-positive cells increases as lung cancer progresses and play important role in lung cancer progresses.<sup>32</sup> Experiments by Liu et al have shown that long-term tobacco smoke exposure promote formation of CSCs, EMT process and malignant transformation.<sup>33</sup> Wang et al demonstrated that epigenetic silencing of miR-218 is involved in the acquisition of CSC-like properties and malignant transformation of human bronchial epithelial cells induced by long-term tobacco smoke exposure.<sup>34</sup> Tobacco smoke could induce the generation of lung CSCs and enhance the self-renewal ability and stemness of lung CSCs, which plays a key role in the occurrence and development of lung cancer. These findings may have important significance in the prevention, diagnosis and treatment of lung cancer.

## Summary and the Future Challenges

Based on the above research, we found that tobacco smoke promotes the acquisition of CSCs characteristics and enhanced CSCs properties, then play an important role in the process of lung cancer initiation, development, metastasis, etc. However, there are still many unknown need to study and explore, and many improvement and challenges in the future research.

Excellent and highly recognized cell and animal models need development and establishment. Based on these excellent models, we can use new techniques to study the exact role and molecular mechanism of tobacco smoke-

induced CSCs in the initiation, development of lung cancer. Then, these data will provide theoretical basis for targeted therapy and precise treatment.

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## Disclosure

Ling Lu and Qiaoyan Liang shared equal contribution and are co-first authors for this study. All authors of this study declare no conflicts of interest for this work.

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