Research status and controversy on non-small cell lung cancer stem cells

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2025;34(4):633–640

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Funding sources
The Shandong Province Natural Science Foundation (General Program, grant No. ZR2022MH204).

Conflict of interest
None declared

Acknowledgements
The authors would like to thank Dr. Fenggang Xian for his advice.

Received on December 9, 2023
Reviewed on March 23, 2024
Accepted on April 11, 2024

Published online on November 18, 2024

Abstract

Lung cancer is a major cause of cancer-related deaths worldwide. It can be divided into 2 main types, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Most patients with NSCLC are diagnosed at an advanced stage, and current treatments have limited success. Moreover, relapsing tumors that often appear after surgical or drug treatment are particularly difficult to treat. The existence of cancer stem cells (CSCs) has been proposed as a key factor contributing to the development of resistance to therapy, recurrence and metastasis. Targeting CSCs is a potential strategy for eradicating tumors. However, due to the tumor-type specificity and cellular plasticity, the real clinical application of lung cancer stem cells (LCSCs) has not been realized. This review details the existing phenotypic markers of LCSCs and the limitations of their identification and summarizes the roles of the tumor microenvironment (TME) and epithelial–mesenchymal transition (EMT) in the existence and maintenance of LCSCs, as well as the contribution and controversy of cellular plasticity theory on LCSCs. It is expected that future research on LCSCs can solve the present problems, and approaches targeting LCSCs may be applied in the clinic as soon as possible.

Key words: non-small cell lung cancer, cancer stem cells, epithelial–mesenchymal transition, tumor microenvironment, cellular plasticity

Cite as
Jin Wang J, Chen Y, Wang C, Ren K. Research status and controversy on non-small cell lung cancer stem cells. *Adv Clin Exp Med*. 2025;34(4):633–640. doi:10.17219/acem/187053

DOI
10.17219/acem/187053

Introduction

Lung cancer is a major cause of cancer-related deaths worldwide.[1] It is a heterogeneous disease that can be divided into 2 distinct pathological types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for approx. 80–85% of all lung cancer types.[2–4] After diagnosis, approx. 75% of patients with NSCLC have advanced diseases (stage III–IV), and the survival rate is low despite the oncological treatment of late-stage lung cancer seeing significant advances in recent years. The UK's Office for National Statistics reported that patients diagnosed with stage IV lung cancer had a 1-year survival rate of just 15–19%.[5]

In addition, relapsing tumors that often appear after surgical or drug treatment are more difficult to treat.[6] For example, platinum-based chemotherapy was most common for advanced NSCLC, but a generation of drug-resistant tumors has proven to be a major barrier to chemotherapy efficacy.[7–9] Although tyrosine kinase inhibitors have demonstrated significant responses in patients with advanced adenocarcinoma in recent years, almost all patients have developed drug resistance after 2–3 years of treatment.[10,11]

Until now, the cancer stem cells (CSCs) hypothesis has been posited to be the underlying cause of relapse, metastasis and therapeutic resistance.[12,13] On the one hand, CSCs can generate new stem cells and daughter cells that differentiate and continuously proliferate to form tumor parenchyma. Conversely, CSCs display high expression of the adenosine-triphosphate-binding cassette G2 (ABCG2), which contributes to pumping out chemotherapeutic drugs,[14–16] leading to chemoresistance. Therefore, targeting CSCs means potential tumor eradication, and several strategies have been used in the clinical treatment of hematological malignancies and several solid tumors.[17–19]

However, the CSCs theory has faced 2 major barriers. First, a universal CSC marker is lacking.[20] The specific markers to purify CSCs are still unclear because the cell surface markers used to identify CSCs vary among tumor types. Second, the mechanism by which CSCs cause the failure of therapies and the relapse is not fully understood.[16,21–23] One likely explanation for the above controversy surrounding CSCs characterization is cellular plasticity,[24–26] which refers to the reversible transition between a variety of cellular states, including stem cells (SCs)/non-stem cells (non-SCs), asymmetric divisions (ADs)/symmetric divisions (SDs), quiescence/proliferation, epithelial–mesenchymal transition (EMT)/mesenchymal-to-epithelial transition (MET), and drug sensitivity/drug resistance. Increasing evidence supports that CSCs represent a dynamic cellular state, in which the acquisition of stem-like traits is necessary for resistance and the promotion of tumor progression.[27,28] Additionally, the tumor microenvironment (TME) plays an integral role in tumor progression and metastasis and is believed to support the cellular fate of CSCs.[19,29] Thus, it is crucial to better understand the behavior of CSCs based on their microenvironment. This understanding will aid in the development of more effective therapeutic strategies targeting CSCs.

We searched PubMed online database relevant literature until July 21, 2023, using the following search terms; "lung cancer stem cell" OR "lung cancer stemness" AND "cellular plasticity" OR "tumor microenvironment" OR "TME" OR "epithelial–mesenchymal transition" OR "EMT". Moreover, we reviewed citations from retrieved articles to search for additional relevant studies. The retrieved studies were manually screened to assess their appropriateness for inclusion. Here, we introduced the characteristics of lung cancer stem cells (LCSCs), including their specific recognition, the interaction between LCSCs and TME, the role of EMT in acquiring stem-like phenotype, and the relationship between cellular plasticity and LCSCs. Our purpose was to summarize the existing research controversy in the LCSCs theory and to provide further direction for the study of LCSCs.

Objectives

We aimed to list the common phenotypic markers of LCSCs and summarize their limitations, reveal the relationship between LCSCs and TME and EMT, and to determine the role of cellular plasticity theory in the generation and transformation of LCSCs.

Lung cancer stem cells

Several studies have suggested that CSCs are associated with tumor heterogeneity and growth, leading to relapse and therapeutic resistance at any stage of cancer progression. The gold standard for assessing the oncogenic potential of CSCs is their ability to form transplantable tumors in immunodeficient mice. This approach has successfully confirmed the existence of CSCs in various tumor types, including brain, breast, lung, and hematological malignancies.[30–32]

The first observation of LCSCs was published in 1982,[33] and subsequent growing evidence has confirmed that putative LCSCs can be isolated from various cell lines and tumor specimens. Lung cancer stem cells share similar properties to CSCs in other tumors: They have been associated with higher recurrence rates, radioresistance[34] and chemoresistance.[35–37] Lung cancer stem cells can form stem cell spheres[38] and express stem-like phenotypes, including CD133, ABCG2 and ALDH1, among others.[39] In short, there is overwhelming evidence that stem cells exist in lung cancers.

Studies have identified CD133, CD44, CXCR4, CD166, EpCAM, CD90, and CD44 as common stemness-associated markers in lung cancers. In both NSCLC and SCLC cell lines, CD133-positive cells may generate long-term tumor spheres and differentiate into CD133-negative cells. Studies

performed in vivo have shown that 1×10^4 CD133-positive cells could generate tumors in immunodeficient mice. Additionally, $CD133^+$ cells were found to be chemoresistant and expressed high levels of ABCG2 and other common stem cell markers, such as Oct4 or Nanog.[32] Similarly, CD44-positive cells exhibited stemness properties in NSCLC cell lines.[40] $CD90^+$ CSCs were also isolated from lung cancer cell lines A549 and H446,[41] while cells positive for CXCR4, a chemokine receptor on the surface of hematopoietic stem cells (HSCs), can form tumor spheres in vitro and exhibited self-renewal capacity and radio-resistance in NSCLC.[42] Finally, $CD166^+/CD44^+$ and $CD166^+/EpCAM^+$ lung cancer cells displayed multipotent characteristics of stem cells that can differentiate into adipogenic and osteogenic cells and express stem cell transcription factors such as Sox2 and Oct4.[43]

The ALDH activity has also been shown to be associated with stemness traits in lung cancer cell lines. It had been reported that ALDH1-positive cells from NSCLC displayed the ability of self-renewal, proliferation potential and in vivo carcinogenicity. Moreover, these ALDH1-positive cells also expressed CD133 and produced resistance after treatment with commonly used chemotherapy drugs.[44] Earlier research has also demonstrated that the putative CSCs in lung cancer were able to express Oct4, Sox2, Nanog, and other core transcription factors responsible for regulating self-renewal and differentiation in embryonic stem cells, as well as CSCs.[45,46]

However, it must be acknowledged that the expression of stem cell markers mainly depends on the source of CSCs isolation (such as primary tumors vs patient-derived xenograft tumors vs cell lines), as sometimes cell suspension culture may also cause a variety of cell surface markers. Although surface markers such as CD133 and CD44 have been successfully used to isolate CSCs, their expression is not exclusively linked to the CSC phenotype and is prone to environmental alteration.[47] Conflicting data have arisen in some settings due to the use of different markers and isolation methods, highlighting the challenges of isolating a pure CSC population.[48] For instance, CD133 was not detected at all in many lung cancer cases,[49,50] while the expression of CD44 and ALDH display particularly strong associations with squamous cell carcinoma (SCC).[51,52] In addition, the combined effect of these stem markers on LCSCs is not completely clear. While it has been shown that the expression of CD133 partially overlapped with that of ALDH protein in NSCLC cell lines,[53] there is no convincing evidence to confirm that the enrichment for 1 CSC marker also enriches the others. As these markers possibly play separate roles and represent different subgroups,[54] more powerful markers need to be identified to isolate pure CSCs in lung cancer.

Furthermore, it is being questioned whether these surface markers can accurately target CSCs. For example, CD133-negative cells in lung cancer cell lines may also cause the formation of tumors, just like CD133-positive cells.[55] Similar results have been observed in the ALDH or SP-negative cells.[56,57] Overall, the accuracy of currently known markers in identifying CSC populations remains uncertain, as these markers can only identify tumor gene subpopulations to varying degrees. More specific markers may be discovered in future work, and we all look forward to the emergence of real targeting markers for these cells.

Lung cancer stem cells and tumor microenvironment

There is increasing evidence that tumor biology is determined not only by the cancer cells, but also by the surrounding stromal cells and structures, known as the TME. This consists of multiple cell types that are embedded in the extracellular matrix (ECM), including immune cells, endothelial cells and cancer-associated fibroblasts (CAFs). It is now known that TME plays a vital role in the regulation of EMT and the acquisition of stem cell phenotypes.[58,59] Moreover, it has been reported that the cytokine network established by CSCs and TME supports the upkeep of existing CSCs and promotes the generation of new CSCs. This process ultimately facilitates tumor survival, propagation and relapse.[60]

One of the cellular components in the TME, CAFs, plays a critical role in promoting both the differentiation of CSCs and the dedifferentiation of non-CSCs. Cancer-associated fibroblasts increase both CD133 and CD44 expression, increase the proportion of $CD133^+$ and $CD44^+$ CSCs cells, and enhance the ability of metastasis and chemotherapy resistance during tumor progression. In addition, fibroblasts have a promoting effect as feeder cells on culturing LCSCs.[61,62] It has been reported that the activation of the IGF1R signaling pathway in the presence of CAFs expressing IGF2 can induce the expression of Nanog and promote cancer stemness in NSCLC cells.[63] Additional research revealed that a unique subpopulation of CAFs in human NSCLC tissues expresses both CD10 and a receptor G-protein coupled receptor 77 (GPR-77), promoting the stemness properties and inducing chemoresistance by activating the NF-κB pathway and secreting intelerleukin 6 (IL-6) and IL-8.[64] These findings all demonstrate that CAFs serve as a supportive niche for cancer stemness in NSCLC.

Mesenchymal stem cells (MSCs) are another important cellular component in the TME, but their precise role in tumor progression is still under debate. Research suggests that the specific effect of MSCs on tumors is dependent on the source of MSCs and tumor types.[65,66] One study found that MSCs increase the stemness of lung cancer cells by secreting factors that activate JAK2/STAT3 pathways.[67] Another report displayed that MSCs at the primary tumor site promote the proliferation and infiltration of the malignant cells, while the metastatic site MSCs facilitate cell re-seeding.[68,69] Non-small cell lung cancer adjacent MSCs were found to induce the expression of stem-related genes

and facilitate the formation of spheroids when tumor cells were co-incubated with them.[70]

The TME also includes chronic inflammation that promotes tumor proliferation and metastasis through immunosuppression and evasion from immune surveillance. Cancer cells and CSCs create an inflammatory niche by secreting chemokines and cytokines to recruit tumor-associate macrophages (TAMs), tumor-associated neutrophils (TANs) and myeloid-derived suppressor cells (MDSCs).[71] In TME, TAMs are the predominant subpopulation of immune cells, which include 2 subtypes: the classically activated M1 subtype and the alternatively activated M2 subtype. M1 macrophages may cause tumor cells to undergo lysis, promote antigen presentation and activate Th1-type cell-mediated immune responses; they mainly exert their antitumor effects by enhancing the tumor-killing ability of immune cells. In contrast, M2 macrophages may secrete immunosuppressive cytokines and promote tumor growth and metastasis.[72] During the malignant progression in NSCLC, TAMs can also differentiate into either a tumor-inhibitory (M1) or tumor-promoting (M2) phenotype based on the influence of various stimuli.[73,74] Tumor-associated macrophages can also activate both pro-inflammatory and anti-inflammatory pathways, which can directly inhibit or promote the cytotoxic effects of natural killer (NK) cells and $CD8^+$ T lymph cells. Additionally, TAMs can trigger Th1 immune responses and induce cytotoxic functions directed toward malignant cells by producing toxic mediators.[75] In a recent publication, a correlation study was conducted between tumor-infiltrating lymphocytes (TILs) and CSCs in tumor tissues from 12 patients with NSCLC. This research found a moderate-to-high positive linear and rank correlation between $ALDH^+$ CSCs and $CD3^+$ or $CD8^+$ TILs. However, there was no correlation between $ALDH^+$ CSCs and $CD4^+$ cells.[76] Another group demonstrated that there is no correlation between $CD8^+$ TILs and CD133 CSCs in surgical samples taken from 172 NSCLC patients.[77] The variation observed in these studies could be attributed to several aspects, such as the utilization of different stem-like markers (ALDH vs CD133), and the involvement of NSCLC in various stages (primary tumors vs metastasis). It has been reported that $CD8^+$ T cells are crucial cytotoxic effectors in many kinds of tumors, including NSCLC. At the same time, $ALDH^+$ CSCs have the potential to induce the loss of their antitumor activity through the exhaustion of $CD8^+$ T cells that lost antitumor activity, or immunosuppressive $CD8^+$ regulatory T cells (Tregs).[78] Furthermore, A549 cells overexpressing Oct4 were found to express higher levels of macrophage colony-stimulating factor (M-CSF), which contributed to enhanced tumor migration and increased the number of M2 macrophages. This data suggests that lung cancer cells that express Oct4 promote the polarization of M2 macrophages by upregulating the secretion of M-CSF.[79]

In addition, the TME has the highest concentrations of extracellular ATP (eATP), which is mainly produced from necrotic or lytic tumor cells and stromal cells.[80–84] Recent studies suggest that eATP can induce and regulate transcription, translation and metabolic levels of CSCs through STC1, which interacts with ATP synthesized by mitochondria.[85] Notably, the role of eATP in regulating CSCs is an area of active research and remains poorly understood.

Taken together, to better understand the emergency and maintenance of LCSCs, it is crucial to focus on the TME, which can be called the CSC niche and regulates CSCs through intercellular communication or changes in the secreted milieu. Importantly, we should know that the CSC niche is different in a variety of tumor types, which means the makeup of the CSC niche can vary significantly between tumor types, even within the same subtype of cancer. Thus, more research is needed to fully understand the complex interplay between the CSCs niche and CSCs themselves.

Lung cancer stem cells and epithelial–mesenchymal transition

A key process of invasion and metastasis, EMT, has been reported to be associated with the existence of CSCs. Epithelial–mesenchymal transition can promote epithelial cells to acquire invasive and migratory properties and become CSC-like cells. Moreover, it has also been observed that CSCs can undergo EMT[86] during radiotherapy and chemotherapy,[87,88] in a hypoxic environment,[89] or in the process of long-term exposure to $PM_{2.5}$.[90,91] Lung cancer cells can also show EMT and CSC characteristics from signaling that induces EMT, such as TGF-β, Wnt, NF-kB, ERK/MAPK, and Notch pathways, which can promote stemness characteristics of solid tumors.[92–94] It has been shown that the induction of EMT by TGFβ-1 may increase stemness in primary lung cancer cells.[95] Moreover, when 8 different lung cancer cell lines were treated by TGFβ1, it was found that TGFβ1 signaling can not only induce EMT but also stimulate the modulation of $CD133^+$ CSCs. However, the responses to TGFβ1 treatment are heterogeneous across the lung cancer cell lines. Some cell lines readily switch to a stem cell state, while others remain unresponsive. This may be caused by the ratio of expression of CDH1 (E-cadherin) to Snail2,[96] both downstream effectors of TGFβ1 signaling. Further study revealed that TGF-β signaling induces stemness through the activation of Slug and CD87 by promoter demethylation.[94] Moreover, tumor necrosis factor receptor superfamily member 19 (TNFRSF19) can inhibit TGFβ downstream signal factors Smad2/3 through binding with TGFβ receptor I, thus modulating stemness properties and chemotherapy resistance to gefitinib.[97] Moreover, TGFβ1 may promote cancer sphere-forming capacity, stemness traits

and chemoresistance through the expression of CXCR7.[98] In addition, other factors such as microRNAs miR-181b-5p, miR-99a, long non-coding RNAs (lncRNAs), and RNA demethylase ALKBH5 have also been revealed to modulate EMT concomitantly with the changes of stemness features in lung cancer.[99–102] Conversely, CSCs also display some degree of EMT regulation. For example, Oct4/Nanog may regulate drug resistance and EMT change through Wnt/β-catenin signaling activation.[103] Additionally, CD133 may induce CXCR4-mediated EMT in NSCLC.[104] The above studies have demonstrated the close correlation between EMT and CSCs in lung cancers, although the crosstalk mechanism between EMT and CSCs remains elusive.

Lung cancer stem cells and cellular plasticity

In general, cellular plasticity refers to the capability of a cell to change its differentiation levels or hierarchy. It can also be defined as a cell's ability to accept a new identity when faced with changes to its environment. Cellular plasticity is not limited to stem cells, as even progenitor cells, daughter cells, transient cells, and differentiation-committed cells have been found to possess this capacity. This implies that daughter cells and even fully differentiated cells can re-enter the niche to take the place of stem cells that have been lost. We now call this course neutral competition.[105,106]

Previous investigations believed that plasticity is largely only related to CSCs because it was widely suggested that plasticity is limited to non-CSCs.[31] However, recent research has demonstrated that non-CSCs can also supplement the CSC pool through cell plasticity in certain environmental niches, although this phenomenon is not observed in all tumor types.[107–109] These findings highlight that CSCs are not a fixed entity in malignant tumors, but rather a state controlled by temporal and spatial characteristics.[110] It has been revealed that transformation is also common between both CSCs and non-CSCs in lung adenocarcinoma.[54] One study demonstrated that lung cancer cells grown under standard culture conditions exhibited multidrug resistance when cultured as floating tumor spheres. However, upon re-incubation under standard culture conditions, the cells rapidly reattached and lost the acquired resistance.[111] One study revealed that dedifferentiation of lung non-CSCs into CSCs may be induced by the transcription factor HOXA5 that is mediated by oxidative stress.[112] A hybrid epithelial/mesenchymal phenotype could, therefore, identify tumors with a greater ability to "sense" microenvironment signals, and for this reason, lung cancer cells displaying both EMT traits may retain a high level of plasticity and could be highly reactive to convert to a stem-like state.[96] Marjanovic et al. prospectively isolated mixed program cells during lung adenocarcinoma evolution from human patient-derived xenografts.[113] These cells were defined as being in a high-plasticity cell state (HPCS). They found that the HPCS cells possess functions of both normal stem cells and CSCs, such as increased proliferation and differentiation potential. However, the *HPCS* gene expression was largely different from the common signatures in both normal stem cells and CSCs.[105,114] Consequently, further research is required to elucidate the relationship between CSCs and HPCS.

Limitations

There is a large amount of literature on LCSCs. Unfortunately, we only summarized part of it, and the clinical application was not covered in this paper. This review catalogued the findings of pertinent research and highlighted discrepancies or deficiencies. However, the underlying mechanism remained underexplored, necessitating a more comprehensive investigation in the subsequent study.

Conclusions

In recent years, there has been a great deal of interest in the use of CSCs as a targeted antitumor strategy. Here, we concentrated on the characteristics of LCSCs, including the existing stemness phenotypes, the relationship and interaction between EMT, TME and LCSCs, as well as the role of cell plasticity theory in CSCs. As discussed, the clinical application of LCSCs will not be possible in the near future due to the present research controversy on LCSCs. On the one hand, accurate recognition of these cells requires the discovery of more specific phenotypic markers. On the other, the acquisition and maintenance of CSCs not only depend on the plasticity potential of cancer cells but also have a close relationship with the microenvironmental tumor niche. Thus, gaining a better understanding of the molecular mechanisms in CSC biology and cancer heterogeneity may help us find more effective and innovative treatment strategies.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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