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Cancer Stem Cells (CSCs) in Lung Cancer

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1. Introduction

The cancer stem cell model for tumor progression is the first model of its type to suggest that only one subpopulation of cancer cells is capable of proliferating indefinitely. These cells resemble normal stem cells in their capacity for self-renewal and multi-potential differentiation, and can both initiate and maintain tumors. The prevailing names for these cells are “cancer stem cells (CSCs)” and “cancer initiating cells (CICs).” The CSC model implies a hierarchical organization within the tumor in which a limited number of CSCs represents the apex of the hierarchy. CSCs are chemo-resistant, radio-resistant, and quiescent, and have been shown to cause both metastasis and relapse.

CSCs were first described in patients with acute myeloid leukemia (AML) by Dick et al. (Lapidot et al., 1994). As to be expected from leukemia stem cells, these CSCs exhibited the properties of self-renewal, proliferation and multipotency. The frequency of these leukemia-initiating cells in the peripheral blood of those AML patients was one engraftment unit in 250,000 cells. Dick et al. identified the leukemia-initiating cells as CD34⁺CD38⁻.

In the years since, CSCs have been identified in cancers of the breast (Al-Hajj et al., 2003), brain (Singh et al., 2003) and prostate, pancreas and lung (Eramo et al., 2008). In this chapter we review CSCs in lung cancer.

2. Overview of CSCs in lung cancer

2.1 Concept of CSCs

Two major models have been described for tumor propagation: the clonal evolution model, which involves a stochastic component, and the CSC model, which is defined as hierarchical. According to the clonal evolution model, a neoplasm arises from a single cell of origin, whereupon an acquired genetic variability within the original clone allows a sequential selection to more aggressive clones, thereby allowing the tumor to progress. According to the CSC model, tumor cells are heterogeneous, and only the CSC subset has the ability to proliferate extensively and form new tumors (Wicha et al., 2006). Yet neither model alone can adequately explain the complex biology of tumor progression, resistance, and metastasis. Fig. 1 describes a new CSC hypothesis model that encompasses both the CSC hierarchical and clonal evolution components, a model in which pre-existing CSCs can transform into secondary CSCs (Takebe & Ivy, 2003).

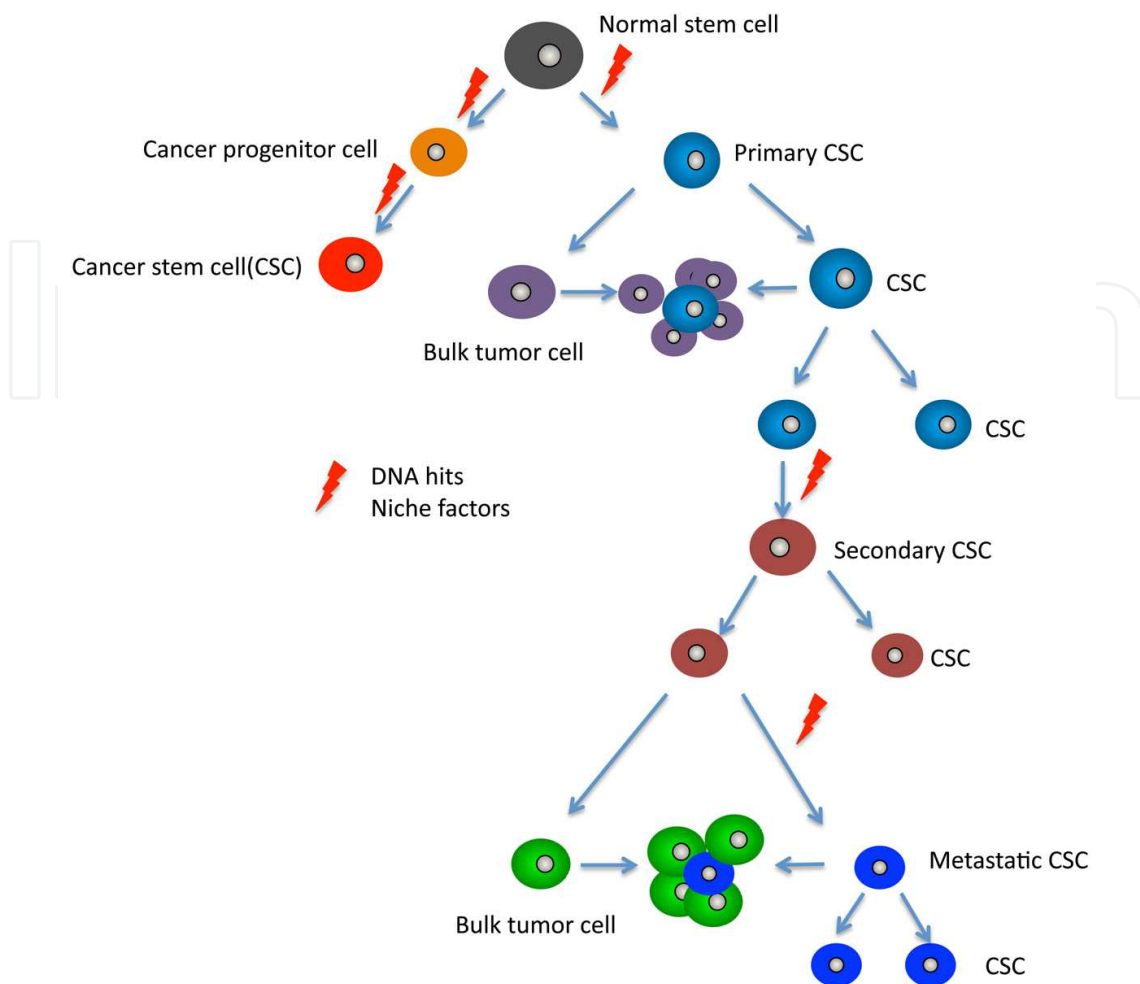


Fig. 1. CSC development.

A combination of DNA hits and niche microenvironmental factors can transform normal stem cells into primary CSCs or more differentiated cancer progenitor cells. Primary tumors are formed mostly from bulk tumor cells together with a small percentage of CSCs. The accumulation of additional DNA hits plus an altered niche microenvironment may drive primary CSCs to evolve into a genetically distinct population of secondary CSCs. Metastatic CSCs have the potential to proliferate and form metastatic tumors at distant sites composed mostly of bulk tumor cells together with a minority of metastatic CSCs (Takebe & Ivy, 2003).

2.2 Origins of CSCs

It remains uncertain whether CSCs originate from normal (somatic) stem cells that acquire oncogenic mutations or from non-stem cells of more differentiated forms that dedifferentiate and acquire stem-cell-like properties through mutation and reprogramming. CSCs can convert into differentiated cells, (Fig. 2) and evidence has suggested that these differentiated cells can acquire stem-cell-like properties via exogenous circumstances (including the niche), with plasticity. (Fig. 2) Cancer stem cells, for example, might be supplied from cancer cells of a non-metastatic epithelial form through a process referred to as “epithelial-mesenchymal transition” (EMT). Besides tissue stem cells, bone marrow-derived cells (BMDCs) may also represent a potential source of malignancy (Fig. 2). Houghton et al.

showed that chronic infection of C57BL/6 mice with *Helicobacter*, a known carcinogen, repopulated the stomach with BMDCs (Houghton et al., 2004). Not long after, these cells progressed through metaplasia and dysplasia to intraepithelial cancer. These findings have broad implications for the multistep model of cancer progression, as they suggest that epithelial cancers can originate from bone-marrow-derived sources. The BMDCs may also be the precursors to CSCs in lung cancer.

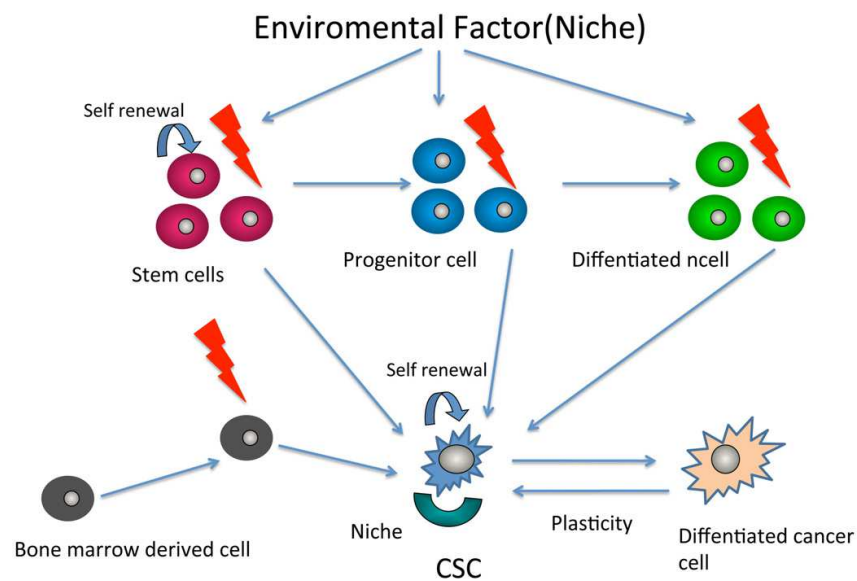


Fig. 2. Origins of CSCs

2.3 How CSCs can be identified?

Cancer stem cells are difficult to isolate in solid cancers, though several possible methodologies for attempting isolation are available. The process can be attempted with a surface marker (CD44 or CD133), or with non-adherent cells cultured in a specific condition (sphere-forming), or with side population (SP) cells identified by efflux of dye and an intracellular enzyme activity (aldehyde dehydrogenase, ALDH). As yet, there is no apparent consensus about the 'best marker' by which to identify CSCs. The gold standard assay *in vivo*, the assessment that isolates what most closely fits the definition of CSCs, may be serial transplantation in animal models.

2.3.1 Surface marker

CD44 or CD133 have served as CSC markers in many solid cancers. In a lung cancer study by Eramo et al., some tumors contained a rare population of CD133⁺ cancer stem-like cells that could both self-renew and generate an unlimited progeny of non-tumorigenic cells (Eramo et al., 2008). Eramo's group found that the tumorigenic cells in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) consisted of rare populations of undifferentiated cells expressing CD133, an antigen present in the cell membrane of normal and cancer-primitive cells of the hematopoietic, neural, endothelial and epithelial lineages. In their cultures, lung cancer CD133⁺ cells were able to grow indefinitely as 'tumor spheres.' Meanwhile, Bertolini et al. independently reported similar findings using CD133⁺ cells isolated from 60 samples of human lung cancer (Bertolini et al., 2009). In their experiments, a CD133⁺ population was increased in primary NSCLC compared with normal lung tissue.

Importantly, the expression of CD133 in tumors was linked to shorter progression-free survival of NSCLC patients treated with platinum-based regimens. The proliferative potential, invasiveness, and chemoresistance of CD133⁺ cells isolated from human lung tumors are reported to depend on the expression of Oct-4 (Chen et al., 2008), a protein important in embryonic stem cell development. Lung cancer CD133⁺ cells have higher Oct-4 expression, can self-renew, and robustly resist both chemotherapy agents and radiotherapy. Leung et al. found that stem cell-like properties are enriched in CD44⁺ subpopulations of some lung cancer cell lines, while most cancer cell lines showed no significant CD133 expression (Leung et al., 2010).

Urokinase plasminogen activator (uPA) and its receptor (uPAR/CD87) are major regulators of extracellular matrix degradation. Both take part in cell migration and invasion under physiological and pathological conditions. uPAR/CD87 was identified as one of the candidate CSC markers in SCLC (Gutova et al., 2007). uPAR⁺ cells exhibited multi-drug resistance, high clonogenic activity, and co-expression of the putative cancer stem cell markers CD44 and MDR1 in all of the SCLC cell lines examined.

2.3.2 Sphere formation in culture

Primary cancer cells can be propagated in spheroid cultures (Reynolds & Weiss, 1992), and doing so may allow extensive CSC characterization *in vitro*. The cells are grown *in vitro* as tumor spheres under nonadherent conditions using a serum-free medium supplemented with growth factors. Once cultured by this technique, they exhibit high clonogenic potential and readily renew themselves, generate differentiated progeny, and generate tumors *in vivo* (Singh et al., 2003; Ricci-Vitiani et al., 2007). From the major subtypes of lung cancer, 'tumor spheres' were found to possess CSC properties, both *in vitro* (expression of the CSC marker CD133, unlimited proliferative potential, extended abilities to self-renew and differentiate) and *in vivo* (high tumorigenic potential, capacity to recapitulate tumor heterogeneity and mimic the histology of the specific tumor subtype from which CSCs were derived). Lung cancer 'spheres' are also extremely resistant to most conventional drugs currently used to treat lung cancer patients. This spheroid culture method serves adequately in isolating CSCs from clinical samples.

2.3.3 Side population (SP) on flow cytometry

SP cells are a subpopulation of cells rich in stem-cell-like characteristics. This subpopulation was first identified by flow-cytometer-based cell sorting defined by Hoechst 33342 dye exclusion (Goodell et al., 1996). Hoechst low cells are described as side population (SP) cells by virtue of their typical profiles in Hoechst red versus Hoechst blue bivariate fluorescent-activated cell sorting dot plots. This test is based on ABCG2 transporter, the second member of the G subfamily of ATP binding cassette (ABC) transporters. ABCG2 is one of the most important multidrug-resistance transporters, and its substrates include Hoechst 33342 (Ding et al., 1996). SP cells were isolated from several solid cancers and certified to have stemness. Regarding the lung, SP cells isolated from six lung cancer cell lines exhibited higher invasiveness, higher resistance to chemotherapeutic drugs, and higher tumorigenicity *in vivo* compared with non-SP cells (Ho et al., 2007). Most of the SP fraction appeared to be in the G(0) quiescent state. Several SCLC cell lines examined by Salcido et al. contained a consistent SP fraction comprising <1% of the bulk population. SP cells had higher proliferative capacity *in vitro*, were able to efficiently self-renew, and exhibited

reduced cell surface expression of differentiation markers. These cells also over-expressed many genes associated with cancer stem cells, drug resistance, and angiogenesis (Salcido et al., 2010).

2.3.4 ALDH activity

Aldehyde dehydrogenase (ALDH) is a detoxifying enzyme known for its role in the oxidation of intracellular aldehydes and for its contribution to the oxidation of retinol to retinoic acid in early stem cell differentiation (Jiang et al., 2009). Class 1 of the ALDH family (ALDH1) is the predominant ALDH isoform in mammals, and ALDH1 activity might serve as a common marker for both normal and malignant stem cell populations. Jiang et al. used the Aldefluor assay and fluorescence-activated cell sorting (FACS) analysis to isolate ALDH1-positive cells from human lung cancer cell lines. The ALDH1-positive cancer cells they isolated exhibited several of the important CSC properties: self-renewal, differentiation, multidrug resistance and expression of stem cell marker *in vitro*; tumor initiation and occurrence of a heterogeneous population of cancer cells *in vivo*. Jiang et al. also found that relatively high ALDH1 protein levels were positively associated with the stage and grade of the tumors, and inversely related to patient survival.

2.3.5 Surface marker may vary even when the cells originate from the same tumor subtype

The marked heterogeneity within CSC sub-populations underlines the need to find more specific single markers or to define new marker combinations for the prospective isolation of CSCs in solid tumors. CD133 is generally considered a stem cell marker, but CD133⁻ tumors also contain cells with CSC activity. Independent studies have shown that CD133⁻ glioblastoma cells can establish tumors in recipient mice with efficiencies comparable to those of CD133⁺ cells (Beier et al., 2007). In a study by Meng et al., CD133⁺ and CD133⁻ subpopulations in lung cancer cells exhibited similar levels of colony formation, self-renewal, proliferation, differentiation, and invasion, as well as similar resistance to chemotherapy drugs (Meng et al., 2009). As such, these CD133⁺ and CD133⁻ subpopulations can be assumed to have contained similar numbers of cancer stem cells. In some cases, CD133 is undetectable among lung cancer samples. In a study by Tirino et al., for example, CD133⁺ was found in only 72% of 89 fresh specimens (Tirino et al., 2009). As to be expected from heterogeneous populations, the CSC phenotype is less than uniform, even when the cells originate from the same tumor subtype. Primary tumors with different genotypes at just one locus can have tumor-propagating cell populations with distinct markers. Fig. 3 (Curtis et al., 2010)

Transgenic mice carrying mutant Kras (left), mutant Kras with p53 deficiency (center), and mutant EGFR (right) all develop lung adenocarcinomas that harbor similar proportions of cells expressing the mouse stem cell marker Sca-1 (blue cells). The tumor-propagating capacity of Sca-1⁺ and Sca-1⁻ cells from each primary tumor genotype was tested by implanting small numbers of sorted cells into the lungs of recipient mice. When isolated from primary Kras tumors, both Sca-1⁺ and Sca-1⁻ cells generated secondary tumors that recapitulated the Sca-1 cell heterogeneity found in the primary tumor (left). Yet in tumors with the mutant Kras and p53 deficiency, Sca-1⁺ cells were better able to form secondary tumors (represented as larger tumors) than Sca-1⁻ cells (center). Further, the secondary tumors derived from Sca-1⁺ cells harbored Sca-1⁺ cells in a proportion comparable to the

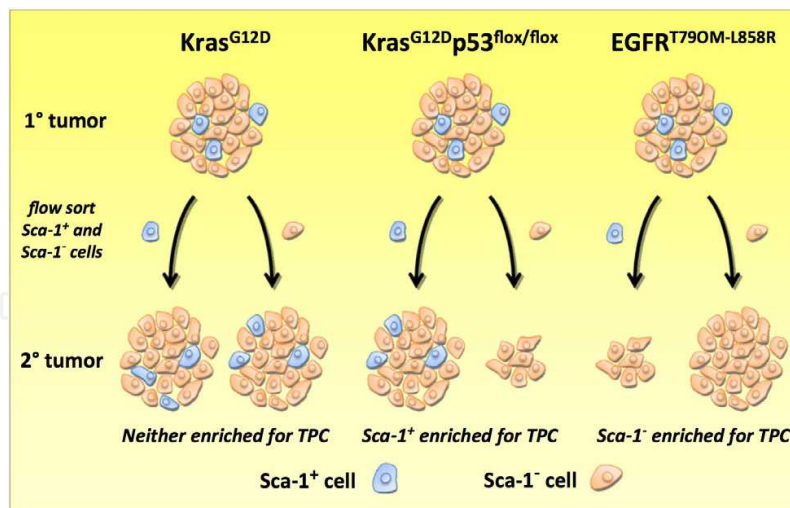


Fig. 3. Tumor Propagating Capacity of Sca-1+ Lung Cancer Cells

primary tumor, whereas the few small tumors derived from Sca-1⁻ cells had no detectable Sca-1⁺ population. These data suggest that the Sca-1⁺ cells in this tumor genotype are enriched in lung cancer stem cells. The opposite appears to be true in mutant EGFR adenocarcinomas, in which Sca-1⁻ cells exhibited a greater capacity for generating secondary tumors (right). The distribution of Sca-1⁺ cells in secondary mutant EGFR tumors remains undetermined. Adapted with permission from Sullivan JP, Minna JD. Tumor oncogenotypes and lung cancer stem cell identity. *Cell Stem Cell*. 2010 Jul 2;7(1):2-4.

2.4 Serial transplantation is the gold standard to validate CSCs

Serial transplantation in animal models has been the gold standard to certify stemness, but animal models fail to mimic the human tumor microenvironment as closely as desired. This can be overcome, however, by orthotopic transplantation of candidate cancer-initiating cells back into their normal microenvironment. When working with putative lung cancer-initiating cells, this can be achieved by intratracheal delivery into the lung cavity using a methodology employed for the delivery of an adeno-Cre virus in sporadic murine models of human lung cancer (Meuwissen et al., 2001, 2003). In serial transplantation in animal models, the presence of residual immune effector cells in recipient mice may influence the efficiency of human cell engraftment in NOD/SCID mice. Shultz et al. showed that NOD-*scid* IL2R γ null (NSG) mice engrafted with human hemopoietic stem cells generate a 6-fold higher percentage of human CD45⁺ cells in host bone marrow compared to similarly treated NOD-*scid* mice (Shultz et al., 2005).

2.5 How do we overcome obstacles of researching CSCs?

It would be impossible to extensively investigate CSCs without expanding the cell populations *in vitro*. Given the low frequency of lung CSCs within primary tumor tissues, we have difficulty in finding agents which can kill CSCs with strong selective toxicity. There are two methods to surmount this obstacle.

2.5.1 Sphere formation is the best way to obtain CSCs from patients

This experimental strategy is the best approach so far developed to obtain the unlimited expansion of a tumorigenic lung cancer cell population from primary patients. As such, it

serves as a powerful enabler for extensive studies on these cells. Yet CSC spheres are difficult to establish from epithelial tumors, particularly in the case of lung cancer. Indeed, only a few specialized laboratories in the world are able to use CSC spheroids from primary tumors. And as another potential limiting factor, CSCs constitute 5 - 30% of the cells in an average tumor sphere (Eramo et al., 2008).

2.5.2 Inducing CSCs by EMT

Another potential solution is the generation of 'induced' CSCs (iCSC). The induction of an epithelial-mesenchymal transition (EMT) in normal or neoplastic mammary epithelial cell populations has been shown to enrich the cells with stem-like properties. Gupta et al. demonstrated that normal and cancer cell populations experimentally induced into an EMT also exhibited an increased resistance to chemotherapy drug treatment. When cancer cell populations are induced to pass through an EMT, the proportion of CSCs could increase (Gupta et al., 2009).

2.6 Lung stem cells and lung cancer stem cells

The lung is a complex organ made up of regionally and functionally distinct cell phenotypes. A diverse class of lung stem cells drives the development and turnover of these populations. The epithelium of the adult airways consists of three distinct compartments arranged along a proximal-distal axis. One factor impeding efforts to demonstrate the existence of adult lung stem cells has been the slow turnover rates in the adult epithelium. Yet in spite of this factor, findings from new studies on pollutant- and pathogen-induced injuries leading to massive lung cell proliferation suggest that adult stem cells are present in each of the epithelial compartments. These different tumor subclasses may arise from distinct cells of origin localized within a defined regional compartment/microenvironment. (Fig. 4)

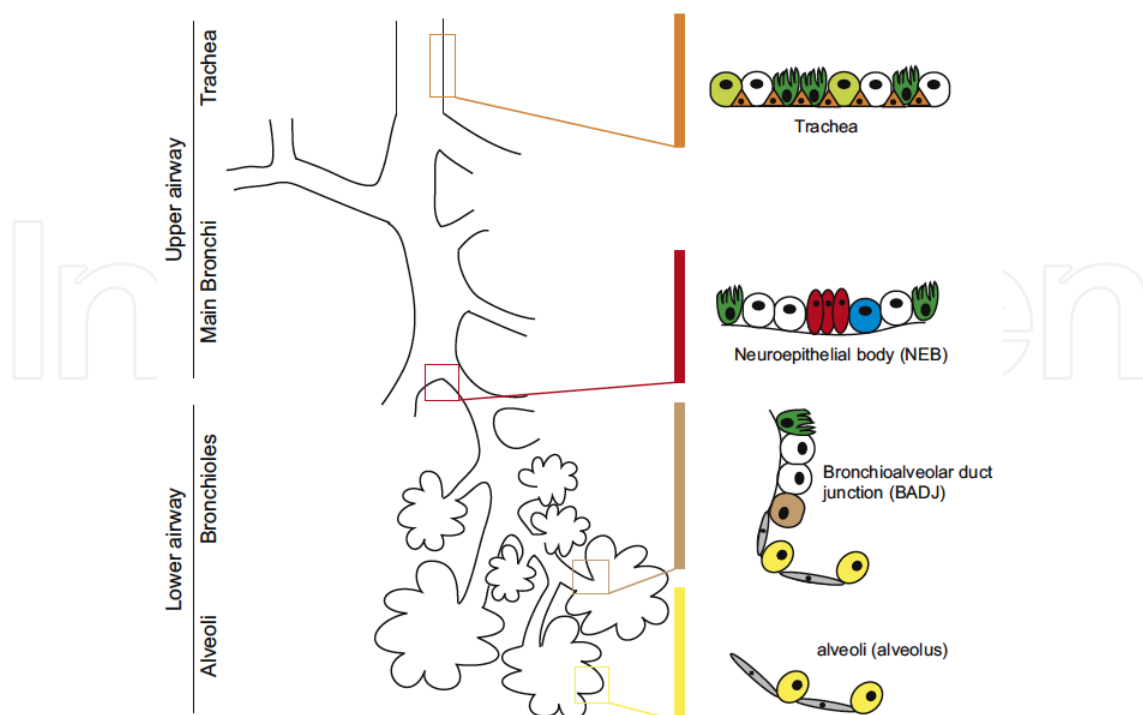


Fig. 4. Airway stem cell microenvironments and associated human carcinomas.

A schematic diagram of the mouse lung highlighting the spatially distinct cellular environments shown to harbour airway stem/progenitor cells. Candidate epithelial niches (depicted on the right hand side) have been identified and found to exist in spatially defined regions: the tracheal submucosal gland ducts, neuroendocrine bodies (NEB) of the bronchi/bronchioles, and the bronchioalveolar duct junction (BADJ). Adapted with permission from Sutherland KD, Berns A. Cell of origin of lung cancer. *Mol Oncol*. 2010 Oct;4(5):398.

2.6.1 Adenocarcinoma

The distal airways are composed of respiratory bronchioles and alveoli lined with cuboidal epithelium. The bronchioalveolar duct junction (BADJ) has been identified as a microenvironment harboring airway stem cells (Giangreco et al., 2002). With regard to tumorigenicity, Jackson et al. reported that lung tumors were suggested to initiate by oncogenic K-Ras activation appeared to be derived from targeted cells located in the BAD (Fig. 5A) (Jackson et al., 2001). Kim et al. have isolated bronchioalveolar stem cells (BASCs), a regional pulmonary stem cell population, in BADJ, and have identified the candidate origins of CSCs in lung adenocarcinomas (Kim et al., 2005). The BASCs in their experiments resisted bronchiolar and alveolar damage and proliferated during epithelial cell renewal *in vivo*. The BASCs also exhibited self-renewal capability and multipotent properties in clonal assays, and expanded in response to oncogenic K-ras in culture and developed to the lung tumor precursors *in vivo*.

2.6.2 Squamous carcinoma

The histopathology and gene expression patterns of mouse lung SCC-like lesions frequently resemble those of tracheal basal cell progenitors. This presents the appealing prospect that these are the target cells of origin in this subclass of lung cancer (Fig. 5C). Keratin (K) 5/14-expressing basal cells are located at the submucosal gland duct junctions or intracartilaginous boundaries and are capable of self-renewal, proliferation, and multipotency (Borthwick et al., 2001; Hong et al., 2004a, 2004b; Rawlins et al., 2008; Rock et al., 2009). As such, K 5/14-expressing cells are the putative major airway stem cells. But the clear relationship between basal progenitors and lung SCC has not been established yet.

2.6.3 Small cell carcinoma

The specific cell population that gives rise, upon genetic alteration, to SCLC remains to be identified. Human and mouse SCLC predominately localize to the midlevel bronchioles and typically express a range of neuroendocrine markers, including calcitonin-gene related peptide (CGRP) and other neuropeptides normally expressed within pulmonary neuroendocrine cells (PNECs) (Meuwissen et al., 2003). Some investigators have hypothesized, based on these observations, that a rare population of PNECs are the progenitors of SCLC. (Fig. 5B) In the mouse lung, microenvironments found in close proximity to neuroepithelial bodies (NEB) have been shown to maintain putative stem cell populations containing both PNECs and variant CCSP-expressing (vCE) cells (Reynolds et al., 2000a). These may be the CSCs of small cell carcinoma.

2.6.4 Human lung stem cells

Kajstura et al. recently identified a set of potential stem cells in the human lung (Kajstura et al., 2011). These cells were self renewing, clonogenic and multipotent *in vitro*. And when

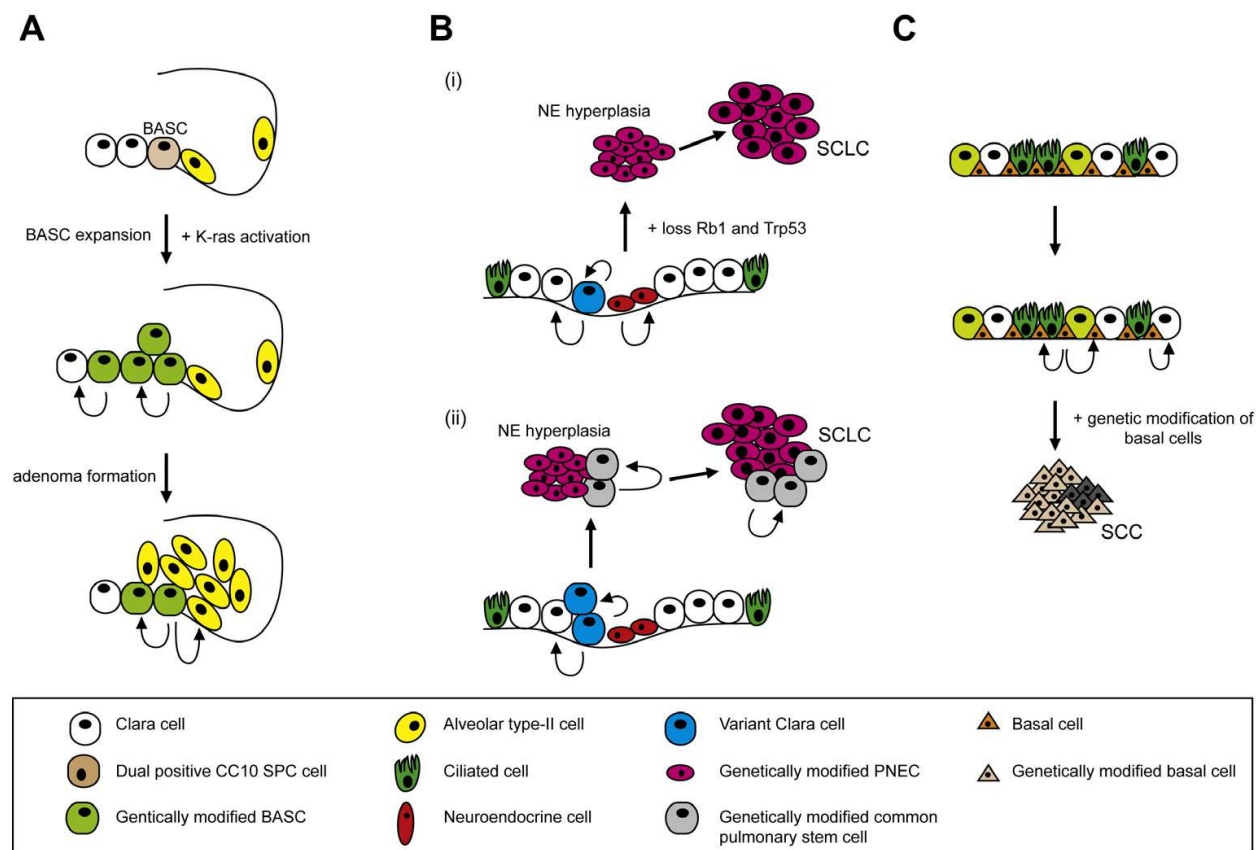


Fig. 5. Schematic overview of the putative role of normal tissue stem/progenitor cells in lung cancer.

(A) BADC contains a rare cell population that expresses both Clara-specific and alveolar-specific markers. These cells are BASCs. K-Ras activation enhances the proliferation of BASCs. (B) Two hypotheses on the origin of lung NE tumors. NEBs in the epithelial lining of the bronchi harbor PNECs associated with vCEs. The first hypothesis proposes that (i) NE tumors arise from these PNECs. The second hypothesis proposes (ii) that NE hyperplasia and SCLC arise from a less-differentiated progenitor-like cell (for example vCE). (C) Given the basal-like phenotype of SCC, one could hypothesize that squamous cell tumors arise from these basal stem cells. Adapted with permission from Sutherland KD, Berns A. Cell of origin of lung cancer. *Mol Oncol.* 2010 Oct;4(5):397-403.

injected into a mouse model of lung injury, they regenerated bronchioles, alveoli, smooth muscle, pulmonary vessels and many other lung components. The experiments were performed using c-kit as a stem cell marker. These results are exciting, though rigorous validation will be required. CSCs of the human lung with the potential to differentiate into NSCLCs and SCLCs may originate from not only regional lung stem cells, but also multipotent stem cells.

2.6.5 Analysis of important molecules and pathways of CSCs in the mouse model

Several papers have reported analyses of important molecules related with CSCs in mouse models.

2.6.5.1 Bmi1

Bmi1 is requisite for K-ras-induced tumorigenesis in the mouse model (Dovey et al., 2008). Loss of Bmi1 in K-ras transgenic mice decreased the prevalence and progression of lung tumors and impaired BADC stem cell proliferation and self-renewal *in vivo* and *in vitro*.

2.6.5.2 PI3K/PTEN/Akt

The phosphoinositide 3-kinases (PI3K)/phosphatase and tensin homolog (PTEN)/protein kinase B (Akt) pathway is requisite for normal stem cell function. The tumor suppressor PTEN encodes a lipid phosphatase that negatively regulates the PI3K /Akt cell survival pathway. In NSCLC, loss of PTEN protein expression occurs frequently (Marsit et al., 2005).

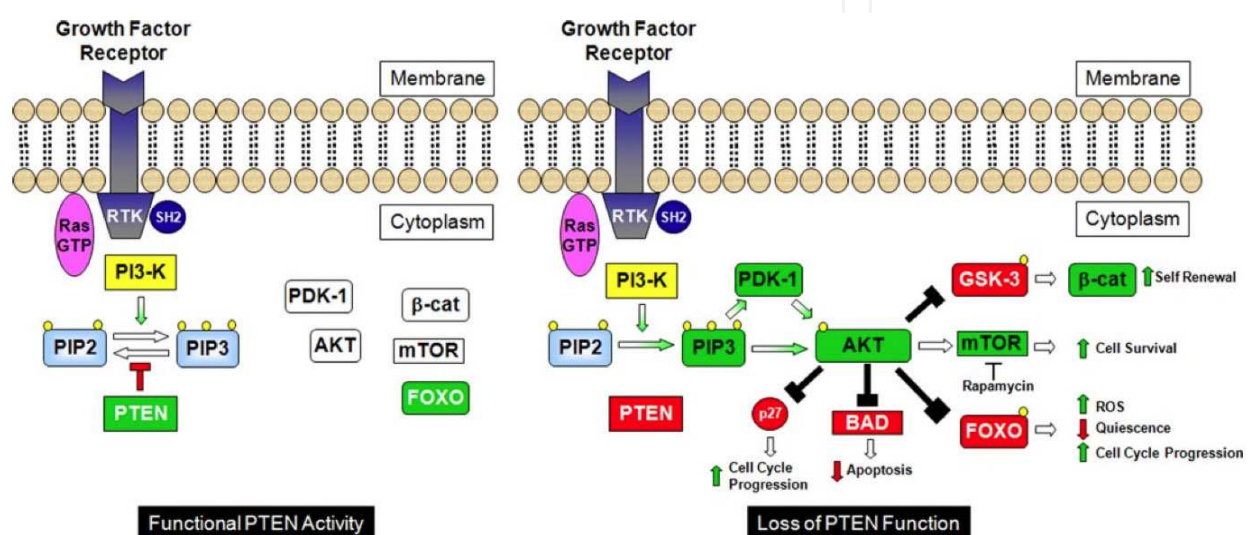


Fig. 6. Loss of PTEN function results in accumulation of PIP3, which activates a cascade of signaling molecules.

AKT activation inhibits pro-apoptotic factors and stimulates cell cycle progression. The loss of PTEN function leads to increased cell survival and proliferation. RTK, receptor tyrosine kinase. Adapted with permission from Hill R, Wu H. PTEN, stem cells, and cancer stem cells. *J Biol Chem.* 2009 May 1;284(18):11755-9.

Recent work has linked the PI3K/PTEN/Akt pathway to lung cancer stem cells and to the suppression of K-ras mutations. (Fig. 6) Spontaneous lung adenocarcinomas develop in transgenic mice with an inducible loss of PTEN expression in bronchioalveolar cells (Yanagi et al., 2007). Interestingly, a loss of PTEN expression resulted in K-ras mutations in 33% of mice and developed spontaneous adenocarcinomas. A loss of PTEN expression and PI3K activation may elicit increases in BADC stem cells, side-population (SP) cells, and the frequency of K-ras mutations, and thereby initiate the development of lung adenocarcinoma over time.

2.6.5.3 Hedgehog

The Hedgehog (Hh) signaling pathway acts as an important regulator of stem cell fates during embryonic development and has been linked to SCLC (Watkins et al., 2003a, 2003b). The observation that intraepithelial Hh signaling is increased after naphthalene-induced airway injury suggests that progenitor cells activate Hh signaling in response to injury. Increased Hh signaling is also observed in the lungs of PTEN-deficient mice that develop

spontaneous lung adenocarcinomas in conjunction with BADC stem cell expansion, and thus may play a causal role in this process (Yanagi et al., 2007).

2.6.5.4 Wnt

The Wnt developmental pathway is another critical regulator of embryonic lung stem cells (Reynolds et al., 2008; Zhang et al., 2008). In adult mice, conditional deletion of p38⁺, a known downstream target of noncanonical Wnt signaling (Ma & Wang, 2007), leads to an expansion of CCSP⁺SP-C⁺ stem cells, hyperproliferation, and increased sensitization to K-ras-induced tumorigenesis (Ventura et al., 2007).

2.7 Therapeutic strategy against CSCs

CSCs are thought to be responsible for disease relapse or metastasis, and also for resistance to radiation or conventional chemotherapy. CSCs showed increased quiescence *in vivo* and *in vitro*, which suggests that they may respond poorly to conventional treatments designed to mainly kill the proliferating cells or terminally differentiated cells forming the bulk of tumors (Guan et al., 2003). Several therapies against CSCs have been considered, but none have been fully developed for lung cancer CSCs. The remainder of this chapter will discuss strategies for targeting CSCs in various organs.

2.7.1 Targeting the key molecule (stem cell marker), key gene & key signaling pathways

Given that CSCs share many of the same features as normal stem cells, there is a potential risk of killing normal stem cells while targeting CSCs. It thus becomes important to further characterize the similarities and differences between these two types of stem cells. New therapeutic approaches to selectively target CSC-specific markers, genes, and pathways are needed.

2.7.1.1 Antibody-based treatment against surface markers

One recently introduced therapeutic approach for human AML employs an activating mAb directed to the adhesion molecule CD44, a known CSC marker of AML (Jin et al., 2006). The *in vivo* administration of this Ab to NOD/SCID mice transplanted with human AML markedly reduced leukemic repopulation. Mechanistically, CD44-specific Ab treatment induced differentiation to a more mature cancer cell progeny that were unable to establish robust leukemia upon xenotransplantation. For solid tumors, CD13, a CSC marker of hepatocellular carcinoma, is expected to become a target of CSC therapy (Haraguchi et al., 2010).

2.7.1.2 Inhibition of essential pathways in the CSCs function

The eventual goal is to generate targeted therapeutics that inhibit essential pathways in the CSC fraction. It will probably be complicated to target these pathways, as the same pathways are also pivotal in normal stem cell function. The Wnt pathway, hedgehog pathway, and notch pathway are all reportedly essential for maintaining stemness. The blocking of these pathways thus holds promise as a therapeutic approach. Many reports and target drugs have been published and developed in pursuit of such a therapy, but only few of these reports have touched upon lung cancer CSCs. The hedgehog pathway may play an important role in lung CSCs, as the pharmacological inhibition of this pathway reduced the growth of lung tumor cells in xenograft models (Watkins et al., 2003a). Suppression of the

Notch pathway by treatment with either a γ -secretase inhibitor or stable expression of shRNA against NOTCH3 significantly decreased ALDH⁺ lung cancer cells, and commensurate reductions in tumor cell proliferation and clonogenicity were observed (Sullivan et al., 2010). Notch signaling thus appears to take part in lung cancer stem cell maintenance.

2.7.1.3 Blocking of the stemness gene

CD133⁺ cells in lung cancer exhibit higher Oct-4 expression. Oct-4 plays a crucial role in maintaining the self-renewing, cancer stem-like, and chemoradioresistant properties of CD133⁺ cells. Knock-down of Oct-4 expression can significantly inhibit the abilities of tumor invasion and colony formation, increase apoptotic activities, and enhance the treatment effect of chemoradiotherapy (Chen et al., 2008). The downregulation of transcription factor SOX in lung CSCs reportedly suppresses growth and metastasis (Xiang et al., 2011), and the blocking of the SCF/c-kit signaling pathway inhibits CSC proliferation and survival after chemotherapy exposure in human lung cancer cell lines (Levina et al., 2010). Cisplatin treatment eliminated most of the tumor cells, but unlike the blocking of c-kit, it was unsuccessful in eliminating CSCs. A combination treatment with cisplatin and c-kit blocking prevented the growth of both tumor cell subpopulations.

2.7.2 Regulation of micro RNA

Micro RNAs can affect the signaling pathways that influence stem cell self-renewal. A lack of let-7 is required for self renewal *in vitro* and for tumorigenicity *in vivo*. In other words, an overexpression of let-7a reduces self renewal and proliferative capacity and converts highly malignant and metastasizing CSCs into less malignant cells (Yu et al., 2007).

2.7.3 Induction of differentiation of CSCs

Differentiation therapy aims at converting tumorigenic CSCs in their non-tumorigenic progeny. Treatment with bone morphogenic protein 4 (BMP4) reduced the tumor-initiating cell pool in a glioma model and markedly slowed down tumor growth *in vivo* without toxic side effects (Piccirillo et al., 2006).

2.7.4 Altering the CSCs' environment (niche)

The stem cell niche plays an important role in maintaining CSCs and apparently enhances the therapy resistance of CSCs by sheltering the cells from diverse insults (Folkins et al., 2007). Perivascular, hypoxic, premetastatic and stromal myofibroblast niches have all been reported. The perivascular niche in brain tumors has been shown to contribute directly to the generation of CSCs and tumor growth. Anti-angiogenic therapy using vascular endothelial growth factor inhibitors not only depleted tumor vascularization, but also ablated CSCs in the xenograft (Calabrese et al., 2007). While some stem cells are perivascular, others may occupy hypoxic niches and be regulated by O₂ gradients (Parmar et al., 2007). However, the underlying mechanisms are still unclear. O₂ availability may have a direct role in stem cell regulation through the HIF-1 α modulation of Wnt/ β -catenin signaling (Mazumdar et al., 2010). These niches are expected to become targets of CSC therapy. In experiments with colon adenocarcinomas, Vermeulen et al. found that hepatocyte growth factor and other myofibroblast-secreted factors activate CSC clonogenicity (Vermeulen et al., 2010). More significantly, myofibroblast-secreted factors

restored the CSC phenotype in more differentiated tumor cells both *in vitro* and *in vivo*. Vermeulen's group therefore propose that the stemness of colon cancer cells is in part orchestrated by the microenvironment.

2.7.5 Activation of reactive oxygen species (ROS)

CSCs have the ability to keep ROS levels low. Subsets of CSCs in some tumors contain lower ROS levels and enhanced ROS defenses compared to their non-tumorigenic progeny. This may contribute to tumor radioresistance. Overcoming low ROS levels within CSCs may be a useful method for improving local and systemic oncologic therapies (Diehn et al., 2009). Haraguchi et al. found that CD13 is a marker for semiquiescent CSCs in human liver cancer cell lines and clinical samples. Mechanistically, CD13 reduced ROS-induced DNA damage after genotoxic chemo/radiation stress and protected cells from apoptosis. In mouse xenograft models, a combination of a CD13 inhibitor and the genotoxic chemotherapeutic fluorouracil (5-FU) drastically reduced tumor volume compared with either agent alone. Thus, the combination of a CD13 inhibitor with a ROS-inducing chemo/radiation therapy may improve the treatment of liver cancer (Haraguchi et al., 2010). CD44 is an adhesion molecule expressed in cancer stem-like cells in gastric cancer. Ishimoto et al. showed that a CD44 variant (CD44v) interacts with xCT, a glutamate-cystine transporter, and controls the intracellular level of reduced glutathione (GSH) (Ishimoto et al., 2011). Human gastrointestinal cancer cells with strong CD44 expression showed an enhanced capacity for GSH synthesis and defense against ROS. Ablation of CD44 induced a loss of xCT from the cell surface and suppressed tumor growth in a transgenic mouse model of gastric cancer. The activation of ROS may be viable as another target therapy for CSCs.

2.7.6 Overcoming of chemoresistance and radioresistance in CSCs

Reversing chemoresistance in CSC populations can be achieved through a specific blockade of multidrug resistance ABC transporters (Frank et al., 2005). Enhanced drug efflux mediated by ABCB1 P-glycoprotein and related ATP-binding cassette transporters is one of several mechanisms of multidrug resistance thought to impair chemotherapeutic success in human cancers. In CD133⁺ CSC in malignant melanoma, ABCB5, a novel human ABC transporter, mediates melanoma resistance to the chemotherapeutic agent doxorubicin, and this effect is reversible by both mAb-mediated inhibition of ABCB5-dependent drug efflux. In addition, ABCB5 gene silencing substantially increases the sensitivity of human melanoma cells to the anticancer chemotherapeutics 5-fluorouracil (5-FU) and camptothecin (Huang et al., 2004). CSC-targeted therapeutic approaches might also include strategies directed at reversal of radioresistance. Bao et al. reported that CD133⁺ human glioma CSCs contributed to tumor radioresistance by preferentially activating the DNA damage checkpoint response and enhancing the DNA repair capacity (Bao et al., 2006). An inhibition of the Chk1 and Chk2 checkpoint kinases reversed the radioresistance of CD133⁺ glioma CSCs in their experiments.

2.7.7 Suppressing EMT and inducing MET

EMT in carcinoma seems to be associated with the acquisition of a CSC phenotype endowed with a more invasive and metastatic phenotype. As such, a new drug to suppress EMT is expected as a target therapy for CSCs. Metastatic progression might involve the dissemination of CSCs at tumor margins that have undergone EMT. Thus, the

mesenchymal-epithelial transition (MET) seems to hold promise as a therapy. Gupta et al. identified small molecules (salinomycin) that specifically inhibit cancer stem cell proliferation through the induction of MET (Gupta et al., 2009).

3. Conclusion

Though targeted therapies have been developed, we have witnessed only limited improvement in the prognosis of lung cancer patients. Ultimately, patient cure will require the eradication of all cells within a cancer. From this standpoint, combination therapies targeting both CSCs and bulk cancer populations hold promise. In the coming years we must clarify the origin of CSCs, find more specific CSC markers, elucidate the CSC niche, and develop more effective innovative agents against resistant tumorigenic lung CSCs. CSCs may vary in different lung cancers, so personalized CSC therapy may be needed.

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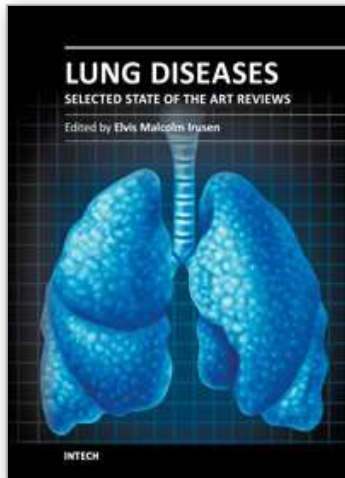
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