Published in final edited form as:
Cancer Lett. 2013 September 10; 338(1): 89–93. doi:10.1016/j.canlet.2012.08.014.

Lung cancer stem cells: progress and prospects

Amber Lundin[a,b] and **Barbara Driscoll**[a]

[a]Developmental Biology & Regenerative Medicine Program, Department of Surgery, Children's Hospital Los Angeles, University of Southern California, Los Angeles, California 90027, United States

[b]California Institute of Regenerative Medicine Bridges to Stem Cell Research, Biotechnology Program, Pasadena City College, Pasadena, California 91106, United States

Abstract

Epithelial stem cells are critical for tissue generation during development and for repair following injury. In both gestational and postnatal stages, the highly branched and compartmentalized organization of the lung is maintained by multiple, resident stem/progenitor cell populations that are responsible for the homeostatic maintenance and injury repair of pulmonary epithelium. Though lung epithelial injury in the absence of oncogenic mutation is more commonly expressed as chronic lung disease, lung cancer is the most common form of death worldwide and poses a highly significant risk to human health. Cancer is defined by the cell of origin, responsible for initiating the disease. The Cancer Stem Cell Hypothesis proposes that cancer stem cells, identified by stem-like properties of self-renewal and generation of differentiated progeny, are responsible for propagating growth and spread of the disease. In lung cancer, it is hypothesized that cancer stem cells derive from several possible cell sources. The stem cell-like resistance to injury and proliferative potentials of bronchioalveolar stem cells (BASCs) and alveolar epithelial type II cells (AEC2), as well as cells that express the cancer stem cell marker glycoprotein prominin-1 (CD133) or markers for side populations make them potential reservoirs of lung cancer stem cells. The abnormal activation of pathways that normally regulate embryonic lung development, as well as adult tissue maintenance and injury repair, including the Wnt, Hedgehog (Hh) and Notch pathways, has also been identified in lung tumor cells. It is postulated that therapies for lung cancer that specifically target stem cell signaling pathways utilized by lung cancer stem cells could be beneficial in combating this disease.

Keywords

lung cancer; cancer stem cells; epithelial stem cells

1. Introduction

Stem cells, which are critical for the generation and regeneration of all tissues, are defined by their undifferentiated phenotype. Stem cells divide both symmetrically and asymmetrically, with the mode of propagation dependent on cell type, differentiation status,

Conflicts of Interest
None declared.

niche context and requirements of the tissue dependent on the stem cell pool in question. Symmetrical division, as occurs in the intestinal crypts, produces identical daughter cells that supply the pool needed to generate the rapidly turned over tissue of the gut epithelium [1,2,3]. In the distal embryonic lung, the distribution of molecules that specify polarity, including the Notch-binding protein Numb, appears to drive the stem cell decision to divide symmetrically or asymmetrically [4]. Asymmetric division is the method by which stem cells generate both undifferentiated and differentiated offspring during development and in multiple, differentiated tissues. The stem cell ability to self-renew in order to produce an adequate supply of cells that are identical to the cell of origin and to each other allows them to be conserved for future use in tissue repair [2,5,6]. The stem cell ability to differentiate into specialized cells when exposed to certain experimental and physiological conditions defines their role in tissue regeneration [5,6,7].

In adult organisms, tissue specific stem cells are found throughout the body. The ability to differentiate into a variety of cell types as needed allows the replenishment of damaged or aged cells that is required to withstand normal wear and tear [5,6,7,8]. Each stem cell division involves a decision to self-renew or differentiate. The transcription factors Oct4, Sox2 and Nanog regulate factors that inhibit differentiation and promote self-renewal [5]. Stem cell self-renewal and differentiation are regulated by multiple protein signaling pathways. Pathways of note include the WNT, Hedgehog (Hh), and Notch signaling cascades [8,9]. These signaling pathways are essential in development during embryogenesis and in the regulation of stem-cell function in adult organs. Stem cells play a critical role in the homeostatic maintenance of functional epithelium. Within adult organs, stem cell activity is specific to discrete compartments of functioning organs. This is particularly true in the highly branched and specialized structures that make up the lung.

2. Lung Development: Role of Lung Stem Cells in Function and Homeostasis

The embryonic lung develops from a small stem cell population originating from the laryngotracheal groove, leading to the morphogenesis of the intricate branched structure of the bronchial and alveolar epithelium [10]. Following birth, the lung alveolar epithelium plays a vital role in gas exchange. Lung function is supported by the combined efforts of the highly vascularized, extraordinarily large surface area within alveoli that facilitate gas exchange via alveolar epithelial type 1 cells (AEC1), the specialized alveolar epithelial type 2 cells (AEC2) that produce the surfactant that regulates surface tension and the balance of other tissues, both rigid and elastic, that along with the chest infrastructure create the forces necessary to inhale and exhale. Specialized cells within the large proximal airways, the distal airways and alveoli are responsible for the repair of damaged epithelial tissue within these lung compartments. When compared to an organ that features rapid turnover, such as the gastrointestinal tract, lung exhibits a much slower rate of cell replacement and many fewer actively dividing cells can be identified under normal conditions. After damage has been inflicted on the alveolar lung epithelium, which is especially vulnerable to injury, cell populations responsible for maintenance and repair increase their rate of proliferation to restore homeostasis [11,12].

It is hypothesized that the slower cell turnover rate within the lung decreases the likelihood of producing mutations that are essential to the formation of malignancies [13,14,15]. More common manifestations of lung epithelial cell injury are chronic lung diseases in which the lung is repeatedly damaged over time, such as chronic obstructive pulmonary disease (COPD) or obliterative bronchitis (OB). Both diseases lead to changes in the lung cellular environment, including changes in immune cell number and function, which leads to release of inflammatory cytokines. The damage produced by repeated inflammation has a

significant impact on the resident cell populations responsible for the regulation and repair of epithelium [11,12,16,17,18]. It is hypothesized that homeostatic repair, and the necessary increase in mitosis required for restoration of homeostatic conditions within the lung, will increase the probability of carcinogenic mutations occurring within cell populations. These mutations can therefore accumulate to the point where carcinogenic changes occur and lung cancer develops [14,16,19].

3. Lung Cancer: Environmental and Genetic Influences

Despite the slow rate of distal lung epithelial cell turnover and the propensity for human lung tissue to scar rather than regenerate, lung cancers are prevalent, most probably due to the self-inflicted insults of smoking and passive insults due to atmospheric toxins and carcinogens. The correlation between inflammation and carcinogenesis has been substantiated by a number of studies. Cigarette smoking is known to produce an inflammatory response within the lung. The carcinogens found in cigarette smoke have a significant effect on the resident cell population and the microenvironment of the lung epithelium. The chemicals and reactive oxygen species (ROS) generated by cigarette smoke, especially of the side stream (secondary) variety, inflict damage on the lung through DNA damage, the impairment of the normal cellular function of epithelial cells and alterations in gene expression, which, individually and combined, can result in an inflammatory response. The cytokines activated during inflammatory episodes can remain within the lung and are considered the proximate, underlying cause of chronic pulmonary inflammation which, in combination with specific mutations in specific types of proliferation-competent initiating cells, has been implicated in the development of lung cancers [20,21,22,23,24].

Lung cancer is the most common cause of cancer-related death worldwide, responsible for approximately 1 million deaths per year [16,19,25]. Lung cancers are classified into histological categories based on the initiating cell type. The two main groups are small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC), accounting for approximately 18% and 80% of occurrence respectively. SCLC is the more aggressive and potentially lethal form of the disease, while NSCLC is much more common and metastasizes at a slower rate [14,16,19,25,26]. The 5-year survival rate in the U.S. is approximately 15% for NSCLC and less than 5% for SCLC. Within the NSCLC classification, there are three sub categories: adenocarcinoma (AC), squamous cell carcinoma (SCC), and Large cell lung carcinomas (LCLC) [16,19,26], which appear to be mainly epithelial (bronchial, airway or alveolar) in origin. In contrast, the cells that make up the most common types of SCLC exhibit dense, neurosecretory granules, indicating a very different type of cell involved in the initiation for this tumor, namely the airway neuroendocrine cells. In addition to tumors of the lung that arise from lung cells, the highly vascularized lung is also a preferential site for metastatic growth of tumor cells of extra-pulmonary origin, including, but not limited to, breast cancers and melanomas.

Within the main categories of lung cancer there are a large number of tumor sub-types now recognized. In addition, individual lung tumors can be highly heterogeneous, in that the tumor mass can be made up of cells along a continuum of undifferentiated to well differentiated phenotypes. The lung can also give rise to heterogeneous tumors that show less variation in differentiation status but are made up of mixtures of cell types. These observations make it difficult to conceive of a limited number and type of initiating cells, but instead indicate more complex tumor initiating events, where a tumor-promoting environment activates multiple cell types or, alternatively, in which initiating cells with a broad potential for differentiation are activated. The highly compartmentalized nature of the lung, in which specialized cell populations can be found distributed amongst proximal and distal structures, as well as airway and alveolar parenchyma and the distinctive progenitor

populations that maintain these tissues, may contribute to the heterogeneity observed in lung cancers.

4. Cancer and Cancer Stem Cells

Cancer is described as a disease of unregulated proliferation of abnormal cells eventually leading to the invasion of surrounding tissues. Cancer is identified by its origin, or the type of cell that first suffered oncogenic mutation. As the disease progresses, uncontrolled cellular growth produces lesions comprised of abnormal tissues called tumors. Tumors are comprised of a heterogeneous population of cells [27,28]. Among this varied cell population are tumor forming cells, which possess stem cell like properties and behaviors. What separates these cells from the remaining tumor cells is that only these tumor initiating cells contribute to tumor growth and are able to form additional tumors. Since the characteristics of these tumor cells are similar to those of stem cells, these cells have been termed cancer stem cells (CSCs). Cancer stem cells are capable of unrestricted self-renewal and multipotent differentiation [27,28,29]. The American Association of Cancer Research has stated that the definition of a cancer stem cell is “a cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor.” [30]

Results of comparisons of normal tissue stem cells to cancer stem cells have shown that the behaviors of metastatic cancer cells are similar in many ways to the behaviors of somatic stem cells. Due to these similarities, it has been proposed that cancer stem cells, in fact, arise from stem cells [6,31,32]. The Cancer Stem Cell Hypothesis suggests that cancer cells arise from stem cells, progenitor cells, or differentiated cells that have been reprogrammed to a less differentiated state, all of which have then been transformed by mutations. This transformed cell is capable of self-renewal, can differentiate into a variety of cells, and is therefore capable of fueling the continuous growth and spread of the disease [6,33,34].

5. Evidence for Lung Cancer Stem Cells

Because of the highly compartmentalized nature of the lung, multiple epithelial cell types, from the trachea to the distal airways, have been designated putative lung progenitors due to their stem/progenitor cell-like responses to injury. Studies that have delved into the behaviors and characteristics of these populations have identified limited, local progenitors that can repopulate injured tissue following experimental injury [12,35,36,37]. In addition, AEC2 have been characterized as a limited, epithelial progenitor for the alveolus, in that they have been hypothesized to be the progenitor of AEC1, the cell responsible for gas exchange in the alveolus [38]. More recently, a novel, less differentiated cell located in the bronchioalveolar duct junction called the bronchioalveolar stem cell (BASC) has been hypothesized to act as an injury-responsive, limited progenitor for the distal airway-alveolar epithelium [12,13,39,40]. BASCs were first identified by their response to oncogenic K-ras overexpression. The rapid expansion of BASCs due to constitutive K-ras signaling led to studies which defined BASC involvement in lung cancer tumorigenesis [41,42]. K-ras is an oncogenic protein that promotes proliferation. Investigators found that long term activation of K-ras expression in BASCs led to tumors composed of cells that expressed both Clara cell and AEC2 markers, that is, Clara cell secretory protein (CCSP) and surfactant protein C (SP-C) respectively. Although the identity of BASCs as a progenitor for AEC2 and, more particularly, airway cells is still controversial [43], several studies have shown that cancer cells carrying the distinctive combination of markers present in BASCs can be isolated from lung tumors. The appearance of these double positive tumorigenic cells suggested that BASCs could be responsible for adenocarcinoma formation [11,14,26,41,42].

More recent investigations have provided evidence for additional, possible cells of origin for adenocarcinomas. One study used K-ras activation in three distal lung epithelial cell types: BASCs, Clara cells and AEC2, resulting in hyperproliferation of all three cell types. Further stimulation produced adenocarcinomas within the alveoli that contained cells positive for SP-C expression only, indicating that AEC2 can produce tumors upon K-ras induction. However, in this same study, K-ras activation failed to produce tumors within the bronchioalveolar duct junction. These results expand the pool of potential stem/progenitor-like distal lung initiating cell types and challenge the concept that mutated BASCs could play a singular, cancer stem cell-like role in the initiation of adenocarcinomas [44].

6. Lung Cancer Stem Cells as a Reservoir for Disease and Metastasis

In addition to being highly responsive to proliferative stimuli, BASCs and a subset of AEC2 are also resistant to damage and injury and continue to proliferate within the epithelium during repair following lung damage [39,45,46,47,48,49,50,51,52]. This is an additional, critical characteristic for both normal tissue and cancer stem cells. In the case of lung cancer, cells that are resistant to injury could serve as a stem cell-like reservoir for generating additional tumors. In addition to BASC and AEC2, recent work has shown that both SCLC and NSCLC contain cells that express the glycoprotein prominin-1 (CD133), a cancer stem cell marker, which is essential for tumor cell propagation and metastasis [14,18,19,51,53]. The proliferative capacity of CD133-positive cells is still undetermined. However, it is hypothesized that these cells could serve as a reservoir for generating more cancer cells that are capable of tumorigenesis, leading to metastasis [18,49,51,53,54].

Numerous mechanisms have been demonstrated in specific cell types that can promote the stem cell-like ability to resist injury. Studies indicate that CSC resistance to apoptosis may be due to the upregulation of the ATP binding cassette transporters (ABCG2) and dysfunction of the p53 tumor suppressor gene. ABCG2, also referred to as the breast cancer resistance protein (BCRP), is an important drug resistance transporter within the ATP binding cassette. Since many of the commonly used chemotherapy drugs are known to bind to the transporter, ABCG2 is suggested as being directly involved in CSC drug resistance. The loss of function of the p53 gene, which induces programmed cell death in response to DNA corruption, could also be responsible for the tumorigenicity and the proliferation potential of CSCs. Studies have found a overexpression of ABCG2 and the mutation of p53 leading to loss or missexpression within both primary tumors and in several carcinoma cell lines, as well as in CD133+ cells, though investigations into the specific mechanisms responsible for the injury-resistant phenotype are still ongoing [55,56,57,58,59].

CSC populations are commonly isolated and enriched using cell surface markers such CD133. However, a cell population found within tumors and present within human carcinoma cell lines has also been identified due to its ability to expel Hoechst dyes, which, during the definitive fluorescence-activated cell sorting (FACS) protocols originally used to differentiate hematopoietic stem cells populations, produces a Hoechst negative population. Hoechst negative cells comprise what is referred to as side population (SP) cells [60,61,62]. Using SP assays that focus on the overexpression of certain cell surface pumps which exclude Hoechst dye 33342, SP cells have been isolated from a number of tissues in addition to the hematopoietic compartment, including from lung tissue and from a variety of tumors. It has been observed that SP cells posses minimal self-renewal and differentiation capabilities in vitro. However, in studies where pure SP and non-SP cell populations were isolated using Hoechst 33342 staining followed by FACS, and cells from both populations were cultured for 6 weeks and then reanalyzed, investigators noted that the SP cell population was multipotent, capable of producing both SP and non-SP cells. In contrast, the non-SP cell population was found to be incapable of generating multiple cell types [62,63].

In addition, SP cells isolated from human SCLC and NSCLC cell lines were capable of forming tumor spheres in vitro and/or had an higher tumorigenicity in vivo, indicating that CSCs could be present within the side population. These stem cell-like characteristics and the oncogenic capabilities observed suggest that SPs could also be an additional source of lung cancer stem cells [61,62,63].

7. Lung Cancer Stem Cells as Therapeutic Targets

Identifying CSCs within lung tumors provides a focus for a wide range of possible treatments and therapies that specifically target stem-like cells. Several possible therapeutic targets unique to these cells include the repair or correction of dysfunctional signaling cascades, including altered Wnt, Hedgehog, and Notch pathways [53]. These signaling pathways play vital roles in lung development and in the regulation of stem cell self-renewal and may play a role in the initiation of tumorigenesis when mutated, by causing dysregulation of the process of stem cell renewal and directed and appropriate differentiation.

The canonical and non-canonical Wnt signaling pathways play vital roles in embryogenesis and homeostatic maintenance of adult tissues. Wnt proteins are critical for the regulation of differentiation, self-renewal, and cellular migration of stem cells [9,53,64,65]. Investigators have identified nineteen different Wnt proteins that perform specific roles in mammalian tissue development and maintenance, including several that are specific to the lung. Further investigation has led to the hypothesis that the Wnt signaling cascade also plays a significant role in oncogenic transformation of lung cancer stem cells [9,53,66,67], as multiple studies have shown a dysfunction in Wnt pathway regulation within certain cancers. In NSCLC, the expression of Wnt1 and Wnt2 are upregulated within lung tumors. Wnt1 and Wnt2 are considered proto-oncogenes but are also critical for cell differentiation and development during embryogenesis. In contrast, investigators have discovered that Wnt-7a, a possible tumor suppressor, is downregulated in these same cells, providing the growth advantage that is a hallmark of cancer cells [9,66,67,68].

Like the Wnt pathways, Hedgehog (Hh) signaling is vital to development during embryogenesis and maintenance of adult tissues. It has been demonstrated that Hedgehog signaling plays a critical part in the initiation of inflammation associated with both tissue repair and oncogenesis [53,68,69]. A key role for the Hh signaling cascade is the regulation of stem cell fate, which determines whether a cell undergoes differentiation or self-renewal. The normal function of Hh has led investigators to propose that dysfunctional Hh signaling is responsible for cell malignancy. Multiple studies have been conducted to examine the expression of target genes Patched (Ptch) and Gli1 within the Hh pathway [70,71], as well as the expression of the Hh ligand Sonic Hedgehog (Shh) [70,71,72]. Data from these studies indicate that Hh signaling is not activated in normal lung tissues, but is increased in tumor specimens, indicating abnormal Hh activation or Shh overexpression. In several studies, while evidence of complete Hh activation was not present in all lung tumors, as indicated by the lack of Ptch and Gli1 expression, Shh overexpression was found to be present in most of the tumor samples, indicating that the Shh ligand may be a useful indicator when screening for abnormalities within the lung [69,70,71,72,73].

Like Wnt and Hh signaling, the function of the Notch receptors are critical to embryogenesis and adult tissue maintenance, in that they are responsible for cell self-renewal and the regulation of cell to cell communication [68,74,75]. Investigators have suggested that dysfunction of the Notch signaling network through mutations at various receptors can induce certain forms of carcinoma. Studies have indicated that a form of squamous cell carcinoma in the lung may result from a gain-of-function mutation of the Notch1 receptor.

Notch, when functioning properly, is hypothesized to play a role in tumor suppression, indicating that oncogenesis will increase with Notch dysfunction [76,77]. In loss of function studies it was observed in vivo that inactivation of the Notch network via Notch1 knockdown led to lung tumor development in mice. These data show a specific role for Notch1 signaling in lung cancer development. Interestingly, inactivation of other Notch receptor combinations induced tumors in organs other than lung [68,76,77].

A summary of the dysregulation of the embryonic/repair repair pathways Wnt, Hedgehog and Notch that have been described in the two main lung tumor types can be found in Table 1. This summary shows that studies to date have found that all three pathways can be disrupted in NSCLC, while Hedgehog and Notch signaling are most commonly disrupted in SCLC. These data may reflect some commonality in lung tumor types, with changes in Hedgehog and Notch signaling observed in the more ubiquitous NSCLC, while disruption of Wnt signaling is an added change observed mainly in the more lethal SCLC. Studies on the efficacy of specifically targeting these pathways in lung tumors is ongoing.

8. Conclusions

Ongoing analysis of the initiation and propagation of tumors by cancer stem cells, which are hypothesized to derive from resident, local epithelial progenitor cell populations, has provided new insight into the progression of this disease. The stem cell-like resistance to injury and proliferative potentials of cancer initiating cells appears to contribute to cancer growth and resistance to treatment. Under normal conditions the lung exhibits a low rate of cellular turnover, but exposure to conditions produced by chronic inflammation, resulting from either environmental toxins or injury, can have a significant impact on the microenvironment of the lung epithelium, thus promoting carcinogenesis. Lung cancer is the most common cause of cancer-related death worldwide, so identification of the cells of origin is essential for the ongoing pursuit of effective treatments.

Further research into the validity of BASCs, lung CD133+ cells, lung side population cells and/or AEC2 cells as stem/progenitor-like sources of lung carcinogenesis is needed to properly identify these population as lung tumor cells of origin. Identification of a common cell or limited population of cells of origin may provide information regarding the mechanisms responsible for the development and spread of lung cancers. The specificity of dysfunction in components of the Wnt, Hh and Notch pathways, which are critical for correct lung development, in lung tumor cells has led investigators to pursue targeted therapies, an approach that could prove beneficial for addressing lung cancers that arise from stem-like cells.

Acknowledgments

This work was partially supported by NIH grant R01 HL 065352 to B.D. and a CIRM Bridges to Stem Cell Research Intern stipend to A.L.

References

1. Dingli D, Traulsen A, Michor F. (A)symmetric stem cell replication and cancer. PLoS Comput Biol. 2007; 3:e53. [PubMed: 17367205]
2. Morrison SJ, Kimble J. Asymmetric and symmetric stem-cell divisions in development and cancer. Nature. 2006; 441:1068–1074. [PubMed: 16810241]
3. Snippert HJ, van der Flier LG, Sato T, van Es JH, van den Born M, Kroon-Veenboer C, Barker N, Klein AM, van Rheenen J, Simons BD, Clevers H. Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. Cell. 2010; 143:134–144. [PubMed: 20887898]

4. El-Hashash AH, Warburton D. Cell polarity and spindle orientation in the distal epithelium of embryonic lung. Dev Dyn. 2011; 240:441–445. [PubMed: 21246661]
5. He S, Nakada D, Morrison SJ. Mechanisms of stem cell self-renewal. Annu Rev Cell Dev Biol. 2009; 25:377–406. [PubMed: 19575646]
6. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001; 414:105–111. [PubMed: 11689955]
7. Nimmo RA, Slack FJ. An elegant miRror: microRNAs in stem cells, developmental timing and cancer. Chromosoma. 2009; 118:405–418. [PubMed: 19340450]
8. Pardal R, Clarke MF, Morrison SJ. Applying the principles of stem-cell biology to cancer. Nature Reviews. 2003; 3:895–902.
9. Van Scoyk M, Randall J, Sergew A, Williams LM, Tennis M, Winn RA. Wnt signaling pathway and lung disease. Translational Research. 2008; 151:175–180. [PubMed: 18355764]
10. Warburton D, Berberich M, Driscoll B. Stem/progenitor cells in lung morphogenesis, repair and regeneration. Curr Top Dev Biol. 2004; 64:1–16. [PubMed: 15563941]
11. Kim CF, Jackson EL, Woolfenden AE, Lawrence S, Babar I, Vogel S, Crowley D, Bronson RT, Jacks T. Identification of bronchioalveolar stem cells in normal lung and lung cancer. Cell. 2005; 121:823–835. [PubMed: 15960971]
12. Reynolds SD, Malkinson AM. Clara cell: progenitor for the bronchiolar epithelium. Int J Biochem Cell Biol. 2010; 42:1–4. [PubMed: 19747565]
13. Griffiths MJ, Bonnet D, Janes SM. Stem cells of the Alveolar epithelium. Lancet. 2005; 366:249–260. [PubMed: 16023517]
14. Peacock CD, Watkins DN. Cancer stem cells and the ontogeny of lung cancer. J Clin Oncol. 2008; 26:2883–2889. [PubMed: 18539968]
15. Yagui-Beltran A, He B, Jablons DM. The role of cancer stem cells in neoplasia of the lung: past, present and future. Clin Transl Oncol. 2008; 10:719–725. [PubMed: 19015068]
16. MacKinnon AC, Kopatz J, Sethi T. The molecular and cellular biology of lung cancer: identifying novel therapeutic strategies. Br Med Bull. 2010; 95:47–61. [PubMed: 20643690]
17. Snyder JC, Teisanu RM, Stripp BR. Endogenous lung stem cells and contribution to disease. J Pathol. 2009; 217:254–264. [PubMed: 19039828]
18. Sullivan JP, Minna JD, Shay JW. Evidence for self-renewing lung cancer stem cells and their implications in tumor initiation, progression, and targeted therapy. Cancer Metastasis Rev. 2010; 29:61–72. [PubMed: 20094757]
19. Dong J, Kislinger T, Jurisica I, Wigle DA. Lung cancer developmental networks gone awry? Cancer Biol Ther. 2009; 8:312–318. [PubMed: 19202349]
20. Peebles KA, Lee JM, Mao JT, Hazra S, Reckamp KL, Krysan K, Dohadwala M, Heinrich EL, Walser TC, Cui X, Baratelli FE, Garon E, Sharma S, Dubinett SM. Inflammation and lung carcinogenesis: applying findings in prevention and treatment. Expert Rev Anticancer Ther. 2007; 7:1405–1421. [PubMed: 17944566]
21. Walser T, Cui X, Yanagawa J, Lee JM, Heinrich E, Lee G, Sharma S, Dubinett SM. Smoking and lung cancer: the role of inflammation. Proc Am Thorac Soc. 2008; 5:811–815. [PubMed: 19017734]
22. Kundu JK, Surh YJ. Inflammation: gearing the journey to cancer. Mutat Res. 2008; 659:15–30. [PubMed: 18485806]
23. Kundu JK, Surh YJ. Emerging avenues linking inflammation and cancer. Free Radic Biol Med. 2012; 52:2013–2037. [PubMed: 22391222]
24. Gonda TA, Tu S, Wang TC. Chronic inflammation, the tumor microenvironment and carcinogenesis. Cell Cycle. 2009; 8:2005–2013. [PubMed: 19550141]
25. Yagui-Beltran A, Jablons DM. A translational approach to lung cancer research. Ann Thorac Cardiovasc Surg. 2009; 15:213–220. [PubMed: 19763051]
26. Sutherland KD, Berns A. Cell of origin of lung cancer. Mol Oncol. 2010; 4:397–403. [PubMed: 20594926]
27. Rahman M, Deleyrolle L, Vedam-Mai V, Azari H, Abd-El-Barr M, Reynolds BA. The cancer stem cell hypothesis: failures and pitfalls. Neurosurgery. 2011; 68:531–545. [PubMed: 21135745]

28. Tysnes BB, Bjerkvig R. Cancer initiation and progression: involvement of stem cells and the microenvironment. BBA-Rev Cancer. 2007; 1775:283–297.
29. Guo W, Lasky JL 3rd, Wu H. Cancer stem cells. Pediatr Res. 2006; 59:59R–64R.
30. Girouard SD, Murphy GF. Melanoma stem cells: not rare, but well done. Laboratory Investigation. 2011; 91:647–664. [PubMed: 21445060]
31. Buzzeo MP, Scott EW, Cogle CR. The hunt for cancer-initiating cells: a history stemming from leukemia. Leukemia. 2007; 21:1619–1627. [PubMed: 17541397]
32. Glinsky GV. “Stemness” genomics law governs clinical behavior of human cancer: implications for design making in disease management. J Clin Oncol. 2008; 26:2846–2853. [PubMed: 18539963]
33. Clarke MF, Fuller M. Stem cells and cancer: Two faces of Eve. Cell. 2006; 124:1111–1115. [PubMed: 16564000]
34. Fang D, Nguyen TK, Leishear K, Finko R, Kulp AN, Hotz S, Van Belle PA, Xu X, Elder DE, Herlyn M. A tumorigenic subpopulation with stem cell properties in melanomas. Cancer Res. 2005; 65:9328–9337. [PubMed: 16230395]
35. Rock JR, Onaitis MW, Rawlins EL, Lu Y, Clark CP, Xue Y, Randell SH, Hogan BL. Basal cells as stem cells of the mouse trachea and human airway epithelium. Proc Natl Acad Sci USA. 2009; 106:12771–12775. [PubMed: 19625615]
36. Hong KU, Reynolds SD, Watkins S, Fuchs E, Stripp BR. Basal cells are a multipotent progenitor capable of renewing the bronchial epithelium. Am J Pathol. 2004; 164:577–588. [PubMed: 14742263]
37. Liu X, Driskell RR, Engelhardt JF. Stem cells in the lung. Methods Enzymol. 2006; 419:285–321. [PubMed: 17141060]
38. Evans MJ, Cabral LJ, Stephens RJ, Freeman G. Renewal of alveolar epithelium in the rat following exposure to NO2. Am J Pathol. 1973; 70:175–198. [PubMed: 4566990]
39. Jackson SR, Lee J, Reddy R, Williams GN, Kikuchi A, Freiberg Y, Warburton D, Driscoll B. Partial pneumonectomy of telomerase null mice carrying shortened telomeres initiates cell growth arrest resulting in a limited compensatory growth response. Am J Physiol Lung Cell Mol Physiol. 2011; 300:L898–L909. [PubMed: 21460122]
40. Kim C. Paving the road for lung stem cell biology: bronchioalveolar stem cells and other putative distal lung stem cells. Am J Physiol Lung Cell Mol Physiol. 2007; 293:L1092–L1098. [PubMed: 17693488]
41. Berns A. Stem cells for lung cancer? Cell. 2005; 121:811–813. [PubMed: 15960966]
42. Kratz JR, Yagui-Beltran A, Jablons DM. Cancer stem cells in lung tumorigenesis. Ann Thorac Surg. 2010; 89:S2090–S2095. [PubMed: 20493987]
43. Rawlins EL, Okubo T, Xue Y, Brass DM, Auten RL, Hasegawa H, Wang F, Hogan BL. The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. Cell Stem Cell. 2009; 4:525–534. [PubMed: 19497281]
44. Xu X, Rock JR, Lu Y, Futtner C, Schwab B, Guinney J, Hogan BL, Onaitis MW. Evidence for type II cells as cells of origin of K-Ras-induced distal lung adenocarcinoma. Proc Natl Acad Sci U S A. 2012; 109:4910–4915. [PubMed: 22411819]
45. Reddy R, Buckley S, Doerken M, Barsky L, Weinberg K, Anderson KD, Warburton D, Driscoll B. Isolation of a putative progenitor subpopulation of alveolar epithelial type 2 cells. Am J Physiol Lung Cell Mol Physiol. 2004; 286:L658–L667. [PubMed: 12922980]
46. Lee J, Reddy R, Barsky L, Weinberg K, Driscoll B. Contribution of proliferation and DNA damage repair to alveolar epithelial type 2 cell recovery from hyperoxia. Am J Physiol Lung Cell Mol Physiol. 2006; 290:L685–L694. [PubMed: 16299057]
47. Alison MR. Stem cells and cancer in the aerodigestive tract. Eur J Cancer. 2009; 45:175–185. [PubMed: 19775616]
48. Chapman HA. Epitheilial-Mesenchymal interactions in pulmonary fibrosis. Annu Rev Physiol. 2011; 73:413–435. [PubMed: 21054168]
49. Chen YC, Hsu HS, Chen YW, Tsai TH, How CK, Wang CY, Hung SC, Chang YL, Tsai ML, Lee YY, Ku HH, Chiou SH. Oct-4 expression maintained cancer stem-like properties in lung cancer-derived CD133-positive cells. PLoS ONE. 2008; 3:e2637. [PubMed: 18612434]

50. Giangreco A, Groot KR, Janes SM. Lung cancer and lung stem cells strange bedfellows? Am J Respir Crit Care Med. 2007; 175:547–553. [PubMed: 17158280]
51. Gomperts BN, Spira A, Massion PP, Walser TC, Wistuba II, Minna JD, Dubinett SM. Evolving concepts in lung carcinogenesis. Semin Respir Crit Care Med. 2011; 32:32–43. [PubMed: 21500122]
52. Sullivan JP, Minna JD. Tumor oncogenotypes and lung cancer stem cell identity. Cell Stem Cell. 2010; 7:2–4. [PubMed: 20621039]
53. Alison MR, Le Brenne AC, Islam S. Stem cells and lung cancer: future therapeutic targets? Expert Opin Biol Ther. 2009; 9:1127–1141. [PubMed: 19653862]
54. Adcock IM, Caramori G, Barnes PJ. Chronic obstructive pulmonary disease and lung cancer: new molecular insights. Respiration. 2011; 81:265–284. [PubMed: 21430413]
55. Mimeault M, Hauke R, Mehta PP, Batra SK. Recent advances in cancer stem/progenitor cell research: therapeutic implications for overcoming resistance to the most aggressive cancers. J Cell Mol Med. 2007; 11:981–1011. [PubMed: 17979879]
56. Spike BT, Wahl GM. p53, stem cells, and reprogramming: tumor suppression beyond guarding the genome. Genes Cancer. 2011; 2:404–419. [PubMed: 21779509]
57. Ding XW, Wu JH, Jiang CP. ABCG2: a potential marker of stem cells and novel target in stem cell and cancer therapy. Life Sci. 2010; 86:631–637. [PubMed: 20159023]
58. Bertolini G, Roz L, Perego P, Tortoreto M, Fontanella E, Gatti L, Pratesi G, Fabbri A, Andriani F, Tinelli S, Roz E, Caserini R, Lo Vullo S, Camerini T, Mariani L, Delia D, Calabrò E, Pastorino U, Sozzi G. Highly tumorigenic lung cancer CD133+ cells display stem-like features and are spared by cisplatin treatment. Proc Natl Acad Sci U S A. 2009; 106:16281–16286. [PubMed: 19805294]
59. Abbott BL. ABCG2 (BCRP): a cytoprotectant in normal and malignant stem cells. Clin Adv Hematol Oncol. 2006; 4:63–72. [PubMed: 16562373]
60. Das B, Tsuchida R, Malkin D, Koren G, Baruchel S, Yeger H. Hypoxia enhances tumor stemness by increasing the invasive and tumorigenic side population fraction. Stem Cells. 2008; 26:1818–1830. [PubMed: 18467664]
61. Salcido CD, Larochelle A, Taylor BJ, Dunbar CE, Varticovski L. Molecular characterisation of side population cells with cancer stem cell-like characteristics in small-cell lung cancer. Br J Cancer. 2010; 102:1636–1644. [PubMed: 20424609]
62. Shi Y, Fu X, Hua Y, Han Y, Lu Y, Wang J. The side population in human lung cancer cell line NCI-H460 is enriched in stem-like cancer cells. PLoS One. 2012; 7:e33358. [PubMed: 22428030]
63. Hirschmann-Jax C, Foster AE, Wulf GG, Nuchtern JG, Jax TW, Gobel U, Goodell MA, Brenner MK. A distinct “side population” of cells with high drug efflux capacity in human tumor cells. Proc Natl Acad Sci U S A. 2004; 101:14228–14233. [PubMed: 15381773]
64. Camilli TC, Weeraratna AT. Striking the target in Wnt-y conditions: intervening in Wnt signaling during cancer progression. Biochem Pharmacol. 2010; 80:702–711. [PubMed: 20211149]
65. Gehrke I, Gandhirajan RK, Kreuzer KA. Targeting the Wnt/β-catenin/TCF/Lef1 axis in solid and haematological cancers: multiplicity of therapeutic options. Eur J Cancer. 2009; 45:2759–2767. [PubMed: 19729298]
66. He B, Barg RN, You L, Xu Z, Reguart N, Mikami I, Batra S, Rosell R, Jablons DM. Wnt signaling in stem cells and non-small-cell lung cancer. Clin Lung Cancer. 2005; 7(1):54–60. [PubMed: 16098245]
67. Mazieres J, He B, You L, Xu Z, Jablons DM. Wnt signaling in lung cancer. Cancer Lett. 2005; 222:1–10. [PubMed: 15837535]
68. García Campelo MR, Alonso Curbera G, Aparicio Gallego G, Grande Pulido E, Antón Aparicio LM. Stem cell and lung cancer development: blaming the Wnt, Hh and Notch signalling pathway. Clin Transl Oncol. 2011; 13:77–83. [PubMed: 21324794]
69. Katoh Y, Katoh M. Hedgehog signaling pathway and gastrointestinal stem cell signaling network (Review). Int J Mol Med. 2006; 18:1019–1023. [PubMed: 17089004]
70. Chi S, Huang S, Li C, Zhang X, He N, Bhutani MS, Jones D, Castro CY, Logrono R, Haque A, Zwischenberger J, Tyring SK, Zhang H, Xie J. Activation of the hedgehog pathway in a subset of lung cancers. Cancer Lett. 2006; 244:53–60. [PubMed: 16446029]

71. Watkins DN, Berman DM, Baylin SB. Hedgehog signaling: progenitor phenotype in small-cell lung cancer. Cell Cycle. 2003; 2:196–198. [PubMed: 12734424]

72. Daniel VC, Peacock CD, Watkins DN. Developmental signalling pathways in lung cancer. Respirology. 2006; 11:234–240. [PubMed: 16635080]

73. Gupta S, Takebe N, Lorusso P. Targeting the Hedgehog pathway in cancer. Ther Adv Med Oncol. 2010; 2:237–250. [PubMed: 21789137]

74. Dang TP. Notch, apoptosis and cancer. Adv Exp Med Biol. 2012; 727:199–209. [PubMed: 22399349]

75. Xu K, Moghal N, Egan SE. Notch signaling in lung development and disease. Adv Exp Med Biol. 2012; 727:89–98. [PubMed: 22399341]

76. Carlson ME, O'Connor MS, Hsu M, Conboy IM. Notch signaling pathway and tissue engineering. Front Biosci. 2007; 12:5143–5156. [PubMed: 17569636]

77. South AP, Cho RJ, Aster JC. The double-edged sword of Notch signaling in cancer. Semin Cell Dev Biol. 201210.1016/j.semcbd.2012.01.017

Table 1

Alterations in expression of components of embryonic stem cell pathways in lung tumors

	Wnt[9,66-68]	**Hh**[70-72]	**NOTCH**[68,72,76,77]
SCLC	-	↑Shh ↑Ptch ↑Gli1	↑hASH1
NSCLC	↑Wnt1 ↑Wnt2 ↓Wnt7a ↑Dvl3	↑Shh	↑HES1 ↑NOTCH1 ↑NOTCH2