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New Therapeutic Strategies in Small Cell Lung Cancer: The Stem Cell Target

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1. Introduction

In 1889, Sir S. Paget introduced the *soil and seed* hypothesis of metastasis to medicine and credited the idea to Fuchs. In Paget´s study, he concluded that the distribution of metastases cannot be due to chance alone and that different tissues provide optimal conditions for the growth of specific cancers. In the *soil and seed* metaphor, the *soil* refers to the secondary site of tumour growth and development and perhaps the chemical signals produced in the microenvironment at the sites of metastasis. The *seed* is the ostensible stem cell or tumour-initiating cell from the primary tumour. These tumour-initiating cells are the tumorigenic force behind tumour initiation, growth, metastasis, drug resistance, and relapse. In a variation of this idea, called the *homing* hypothesis, a secondary signal secreted by cells at the future metastatic sites "calls" the tumour cells to the site and permits them to proliferate in the new environment. In this hypothesis, the *seed* produces cell surface receptors that are able to recognise the site demarcated by the *soil*. Although the mechanisms that define tissue specificity remain obscure, researchers have focused on small messenger molecules as attractants and larger cell surface receptors that guide the tumour-initiating cells. Based on the hypothesis introduced by Paget, other groups have focused on chemokines and their receptors as viable candidates for *soil and seed* signalling and have proposed a "spatial and temporal code" composed of specific combinations of such molecules, while other molecules are responsible for neovascularisation, metastasis, and immunosurveillance avoidance. Lung cancers result from complex genetic and epigenetic changes and are characterised by stepwise malignant progression of cancer cells with an associated accumulation of genetic alterations. This process, referred to as multistep carcinogenesis, develops through the clonal evolution of initiated lung cells. Initiation consists of the acquisition of defined genetic alterations in a small number of genes that confer a proliferative advantage and facilitate progression towards invasive neoplasia. Although many of these genetic changes occur independently of histological type, their frequency and timing of occurrence with respect to cancer progression differ between small cell lung carcinomas (SCLC), which may originate from epithelial cells with neuroendocrine features, and non-SCLCs, which

originate from bronchial, bronchiolar or alveolar epithelial cells. Furthermore, a number of genetic and epigenetic differences have been identified between squamous cell carcinoma (SCC), which arises from bronchial epithelial cells through a squamous metaplasia/dysplasia process, and adenocarcinoma (ADC), which is derived from alveolar or bronchiolar epithelial cells. Hence, lung tumours have been classified according to tumour morphology, but classification is complicated by the fact that a number of different histologic tumour characteristics frequently exist within the same neoplasm. In the 1990s, SCLC accounted for approximately one-quarter of all lung cancers, but a recent Surveillance Epidemiology and End Results (SEER) database analysis found that the incidence has since decreased to approximately 13%. SCLC now accounts for 15% of all newly diagnosed lung cancers and 60% to 70% of patients present with extensive stage (ES) tumours. For patients with limited-stage (LS)-SCLC, standard treatment has consisted of chemotherapy combined with radiotherapy (RT), while chemotherapy alone has been the standard for ES-SCLC patients. Despite a high initial rate of response to chemotherapy, most patients die from rapid recurrence. The median range of survival time after diagnosis for patients with ES-SCLC is 8 to 10 months, and only 5% to 10% of patients survive for as long as 2 years. Although chemotherapy is an essential component in the treatment of SCLC, improvements in survival in the past two decades have primarily been achieved through the appropriate application of radiotherapy. The standard treatment for patients outside of clinical trials is as follows: LS-SCLC patients receive combination chemotherapy, which generally consists of cisplatin and etoposide, with concurrent thoracic radiotherapy; and ES-SCLC patients receive combination chemotherapy (etoposide and cisplatin or carboplatin). The current standard treatment for most cancers involves some combination of chemotherapy, hormonal therapy, radiation treatment, and a growing list of molecularly targeted therapeutics, depending on the tumour characteristics and stage. Following treatment, tumour regression is normally used as an indicator of therapeutic success. To better treat cancer, the new ideas regarding CSCs must be integrated into our strategies for clinical intervention. One approach to inhibit cancer stem cells is to target the proteins that are essential for the growth and maintenance of stem cells, such as the growth regulatory pathways that function in embryonic cells. One pathway, controlled by the Hedgehog (Hh) signalling molecule, contains several genes that function as either tumour suppressor genes or oncogenes. Other pathways that are critical to embryonic development and are potentially important in cancer have also been described, including the Wnt and Notch pathways. These pathways are also subjects of drug development for the treatment of a number of conditions.

2. Development of the airway

The respiratory system is an outgrowth of the ventral wall of the foregut, and the epithelium of the larynx, trachea, bronchi, and alveoli originates in the endoderm. The cartilaginous, muscular, and connective tissue components arise in the mesoderm. In the fourth week of development, the tracheo-oesophageal septum separates the trachea from the foregut, dividing the foregut into the lung bud anteriorly and the oesophagus posteriorly. Lungs are composed of two primary tissue layers, namely epithelium and mesenchyme. Previous investigations have demonstrated that mutual interactions between these two tissues are essential for the sequential events of organogenesis, determination, growth, morphogenesis,

and cytodifferentiation. This mutual interaction is defined as embryonic induction. The morphogenesis and cytodifferentiation of embryonic lung epithelial components are modulated by surrounding mesenchymal components. In embryonic organs that are formed by a process of progressive branching of the epithelium, such as the lung, the mesenchyme plays a determining role in the formation of the characteristic morphology of the organ. Increasing evidence has suggested that the formation of the tracheo-bronchial tree and alveoli results from heterogeneity of the epithelial-mesenchymal interactions along the developing respiratory tract. Genetic data have supported this idea and shown that this heterogeneity is likely the result of activation of distinct networks of signalling molecules along the proximal-distal axis. Among these signals, fibroblast growth factors, retinoids, Sonic hedgehog and transforming growth factors appear to play prominent roles. Variable levels of FGFs, Shh, TGFβ, EGF, retinoid receptors, and other signals that play a role in lung morphogenesis have been reported in the adult lung. Increasing genetic evidence has suggested that the Gli genes play multiple roles during prenatal development, particularly in the lung. All three genes are widely expressed during embryonic development in distinct but sometimes overlapping domains. The extent to which these regulators are expressed during adult life to mediate cellular activities in processes such as post-injury repair and compensatory lung growth is currently unclear. Lung bud initiation has been well-established to be regulated by the Sonic hedgehog (Shh) signalling pathway, by fibroblast growth factor (FGF) receptor signalling, and likely by retinoid-related signalling. Branching morphogenesis is a dichotomous branching process that involves defining the proximal-distal structure of the conducting airway prior to the saccular stage and is dependent on the integrated effects of the conducting airway prior to the saccular stage. Several growth factors have been implicated in branching morphogenesis. Epidermal growth factor (EGF) and transforming growth factor (TGFα) are expressed in embryonic murine lung; both factors influence growth and branching morphogenesis. During early lung branching, the EGF protein is present in bronchial epithelial cells, whereas the EGF mRNA is localised to the mesenchyme; this discordance between the location of the protein and mRNA suggests that EGF is produced by the mesenchyme and acts on the epithelium. EGF receptors (EGFR) have been found in epithelial cells and in the mesenchyme surrounding the branching epithelium of the mouse lung. These data are compatible with the notion that EGF acts in an autocrine and paracrine fashion. Retinoic acid (RA) and glucocorticoid signalling pathways have long been appreciated as major contributors to prenatal and postnatal lung maturation, and some evidence exists for their coordination or antagonism during lung development. Retinoic acid also plays an important role in morphogenesis. RA stimulates lung epithelial branching activity via an epithelial-mesenchymal interaction that, in part, involves the up-regulation of the expression of EGFR, Insulin-like Growth Factors (IGF), basic Fibroblast Growth Factor (bFGF-2), and PDGF.

3. The airway stem cells

For several years, a consensus has been achieved that various types of stem cells exist, differing according to their position within the pulmonary tree, and that the stem cells often form pools that are ready to proliferate in response to injury and effect local repair. The classical subdivision of the airway tree into regions with individual stem cell harbours was

accepted many years ago. Thus, the local repopulating cells of the trachea (basal, mucous secretory), bronchus (basal, mucous secretory), bronchiole (Clara) and alveolus (type II peneumocytes) remain, for the most part, the first reserve of airway stem cells. Stem cell research in the lung has progressed rather slowly due to the anatomical and functional complexities associated with the numerous distinct cell types. This organ must be divided into various anatomical regions when considering multipotent progenitor or stem cells. Evidence has clearly suggested that multipotent progenitors of the conducting airway epithelium and gas-exchange alveolar regions are derived from different populations of stem cells that are anatomically separated in the lung. Stem cell niches in the conducting airways must also be uniquely divided between the proximal and distal regions. Bronchial airways harbour at least two distinct progenitor cell populations. Both basal and non-ciliated secretory cell types of the bronchial airways have been shown to exhibit proliferative capacity. The disparity between bronchial and bronchiolar airways is consistent with a mechanism in which the activity of distinct progenitor cell pools accounts for the regional differences both in lineage specifications during lung development and in the cellular composition of tracheo-bronchial and bronchiolar airways (Table 1).

Tissue	Epithelial stem cell niche	Daughter cells
Lung proximal	Tracheal basal cell	Mucous, ciliated, neuroendocrine
	Tracheal mucus-gland duct cell	Mucous, ciliated, neuroendocrine
	Tracheal secretory cell	Mucous, ciliated, neuroendocrine
	Bronchiolar Clara cell	Mucous, ciliated (Type I/II pneumocyte)
Distal	Alveolar type II pneumocyte	Type I and II pneumocytes (Clara cells),
	Neuroendocrine	PNEC (and Clara cells)

Table 1. Stem or progenitor cell characteristics in the airway

Epithelial cell composition and zone boundaries depend on both the species and the individual animal history. In normal mice, a renewing cell system encompassing a gland-containing, pseudostratified epithelium with Clara cells and few goblet cells is present in the upper trachea. In rats, a similar system, but with more goblet cells and no Clara cells, is present in the entire trachea, whereas this zone in humans penetrates many bronchial generations. Distally, the airway epithelium becomes glandless and cuboidal. This region is dominated by a Clara cell based lineage system before its transformation into a type II cell-based system in the alveoli. Stem cell niches in the airway have been characterised through experiments with rodent models. Stem cells in the proximal mouse trachea reside in the submucous gland duct, whereas those from the bronchi and bronchioles come from a subset of cells expressing a Clara-cell-specific protein located near neuroendocrine bodies and bronchoalveolar-duct junctions.

4. Stem cells and lung cancer

Stem cells give rise to a number of different cell types that can be classified into three groups: fully differentiated cells, transit-amplifying cells, and stem cells. The fully differentiated cells are mitotically inactive cells. These cells are at the end stages of cellular differentiation and will never re-enter the active cell cycle. The transit-amplifying (TA) cells are fast growing cells that are not fully differentiated. TA cells are able to proliferate for several generations, but they eventually terminally differentiate and must be replenished by

the SC. Pluripotency is the ability of a SC to differentiate into the heterogeneous population of cells that comprise a tissue or, in the case of cancer stem cells (CSCs), a tumour. There is growing evidence that some, if not all, tumours are derived from cells with the stem cell properties of self-renewal, multilineage potential, and proliferative capacity. Stem cells are candidates as the "cell of origin" for cancer because they have a pre-existing capacity for self-renewal and unlimited replication. In addition, stem cells are relatively long-lived compared to other cells within tissues. They therefore have a greater opportunity to accumulate the multiple additional mutations that may be required to increase the rate of cell proliferation and produce clinically significant cancers. Recent work has suggested that a subpopulation of cancer cells with stem-cell-like properties may be critical for triggering tumour development. Insights into the function and characteristics of CSCs offer a novel approach to understanding the progression of metastasis. Given that a single cancer cell can drive the formation of a metastatic tumour, CSCs are likely responsible for distant tumourigenesis and primary tumour formation. Thus, research focussed on the role of CSCs in primary lesions has led to discovery that CSCs can drive tumour formation in leukaemia and various solid tumours. While little work has been done to elucidate the role of CSCs in metastasis, properties of CSCs, such as self-renewal and differentiation, make them logical candidates as metastatic colonisers. To facilitate the discussion of CSCs with different metastatic ability, a distinction should be made when referring to two potential subtypes of CSCs: primary tumour cancer stem cells (pCSCs) and metastatic cancer stem cells (mCSCs). The first, pCSCs, constitute the original population of tumorigenic cells that initiate the formation of haematopoietic and solid tumours and are the centre of most CSC. The second group, mCSCs, represent a distinct population of cells with the intrinsic properties to disseminate from the primary site and generate the distant metastases. Although other cell subpopulations may break free of the primary tumour and invade the blood stream, mCSCs, like their pCSCs counterparts, are solely responsible for the initiation of tumours. mCSCs are related to pCSCs in the essential properties of self-renewal and differentiation that are needed for the propagation of the bulk of the tumour, but the two cell types differ in key ways. Unlike pCSCs, mCSCs disseminate from the tumour, colonise foreign tissue, and likely have additional alterations (whether mutational, epigenetic, or adaptive) that allow survival and propagation in secondary sites. The key to developing effective future therapies thus seems to be the identification and characterisation of these cancer stem cells and the development of drugs that specifically target these cells. Classically, the stem/progenitor cells of the pulmonary epithelium have been considered the basal cells in the proximal airways, Clara cells in the bronchioles and type II pneumocytes in the alveoli. There is evidence that the basal and parabasal cells are stem cells in the human lung. Clara cells have been shown to be the progenitors of themselves and of ciliated cells in the bronchioles. Recent research has established that a subset of Clara cells fulfils the criteria of adult, niche-specific stem cells. Pools of stem cells have been discovered that express Clara cell secretory protein (CCSP) but are not typical Clara cells. These variant CCSP-expressing (or vCE) cells show multipotent differentiation. The vCE cells are located in discrete pools in neuroepithelial bodies and at the broncho-alveolar duct junction. In the trachea and bronchi, the basal cells are widely believed to be stem cells. The basal cells and the parabasal cells that lie just above them certainly form a pluripotential reserve cell that, unlike the surrounding epithelium, usually survives injury. Procedures that involve denuding the trachea have demonstrated the capacity of basal cells to produce all of the major cell phenotypes found in the trachea, including basal, ciliated, goblet and granular secretory

cells. Controversially, pulmonary neuroendocrine cell (PNEC) populations have been suggested to be able to proliferate and serve as a reservoir of progenitor/stem cells that are capable of epithelial regeneration.

Stem/progenitor	Daughter	Lineage progression
Basal	Basal	
	Mucous	Ciliated
	Secretory	Ciliated
	PNEC	
Tracheal	Basal	
Gland duct	Mucous	
	Ciliated	
Clara	Clara	
	Ciliated	
	PNEC	
	Type II?	
Type II	Type II	
	Type I	
	PNEC	
	Clara	
PNEC	Clara	

Table 2. Possible lung cell lineages. Adapted from Otto WRJ. Pathol. 2002.

5. Small cell lung cancer

SCLC is the most common lung tumour in the spectrum of pulmonary neuroendocrine malignancies, which include typical carcinoid (TC), atypical carcinoid (AC), large-cell neuroendocrine carcinoma (LCNEC), and small-cell lung carcinoma (SCLC). The histological classification of SCLC has evolved substantially over the past several decades

	WHO (1967)	WHO (1981)	IASLC (1988)
Oat cell	Lymphocyte-like	Oat cell	Small-cell carcinoma
Polygonal	Polygonal	Intermediate	Small-cell carcinoma
	Fusiform		Mixed small-cell/large-cell carcinoma
	Other	Combined oat cell carcinoma	Combine small-cell carcinoma

WHO: World Health Organization
IALSC: International Association for the Study of Lung Cancer

Table 3. Classification of small-cell lung carcinoma

Interestingly, a large proportion of SCLC contains a component of NSCLC. Approximately 5% to 10% of patients diagnosed with SCLL will have mixed tumours, meaning that other pathologies, such as adenocarcinoma or squamous cell carcinoma, can be found within the pathologic specimen. The WHO classification of SCLC includes only one variant, combined small cell carcinoma, an SCLC with a mixed non-small-cell component (adenocarcinoma,

squamous cell carcinoma, large cell carcinoma, or spindle cell or giant cell carcinoma). Although various synonyms are in the current clinical terminology (anaplastic small-cell carcinoma, small-cell undifferentiated carcinoma, small-cell neuroendocrine carcinoma, oat cell carcinoma, and mixed small-cell/large-cell carcinoma), the use of these terms is discouraged to avoid confusion. Although the precise cell of origin is not known for SCLC, there is probably a pluripotent bronchial precursor cell that can differentiate into each of the major histologic types of lung cancer. However, within the spectrum of neuroendocrine tumours, a closer morphologic and genetic similarity exists between large cell neuroendocrine carcinoma and small cell carcinoma than either typical or atypical carcinoid. Although classified as a neuroendocrine (NE) tumour, the biological origins of this cancer have remained a matter of conjecture. Recently, SCLC has been shown to be dependent on the activation of Hedgehog signalling, an embryonic pathway implicated in the regulation of stem cell fates. This finding sheds new light on the potential histogenesis of SCLC. SCLC and carcinoid tumours both show high-level expression of neuroendocrine genes. Only a few markers are shared between SCLC and carcinoids, whereas a distinct group of genes defines carcinoid tumours, suggesting that carcinoids are highly divergent from malignant lung tumours, as has been reported. Recent studies have shown that the most useful neuroendocrine markers for SCLC in formalin-fixed, paraffin-embedded tissue sections are chromogramin A, synaptophysin, Leu-7, and certain neural cell adhesion molecules (NCAMs). Bombesin or gastrin-related peptide (GRP), keratin (AE1/AE3) and membrane antigen (EMA). DNA analysis of SCLC reveals a high percentage of aneuploidy in up to 85% of cases. Finally, the expression of proliferative markers, such as PCNA, thymidylate synthase, MCM2 and MCM6, is highest in SCLC, which is known to be the most rapidly dividing lung tumour.

6. Targeted agents that have been evaluated in SCLC

Various chemotherapy schemes have been evaluated for SCLC, but the combination of cisplatin and etoposide is widely considered the standard, with observed response rates of 80-85% and approximately 25% of patients obtaining a complete response. However, most patients experience disease relapse, and neither maintenance chemotherapy nor dose-intensive chemotherapy regimens have led to improved outcomes.

6.1 Topoisomerase I and II inhibitors

A topoisomerase I inhibitor, Topotecan, has shown response rates of 14% to 38% in chemosensitive patients, but the response rates in patients with chemorefractory disease are lower. Irinotecan, another topoisomerase I inhibitor, has demonstrated 10% partial response and 22% stable disease in refractory or relapsed SCLC. Etoposide-containing regimens currently remain the standard first line therapy in North America, while irinotecan-containing regimens are used in Japan. Thus, the combination of carboplatin and irinotecan may be a viable alternative to etoposide-containing regimens. Novel topoisomerase I and II inhibitors appear to continue to exhibit activity in patients with SCLC and warrant further investigation in this disease (particularly in non-Asian populations). However, whether these agents will be more active than etoposide remains to be determined.

6.2 Alkylating agents

The results are similar to those seen with other regimens.

6.3 Picoplatin

The role of picoplatin in SCLC is still not well defined and should be further explored in the future.

6.4 Antimetabolites

Pemetrexed has been shown to have minimal activity as a second-line agent in the treatment of patients with SCLC. Elevated thymidylate synthase expression in SCLC tumours has been proposed as one of the reasons for the observed lack of efficacy.

6.5 Antiangiogenic agents

Bevacizumab combined with standard first line therapy of cisplatin plus etoposide has shown a 64% response rate (RR), 4.7 months of progression-free survival (PFS), 30% of PFS at 6 months and 10.9 months of overall survival (OS). Upon employing bevacizumab to cisplatin plus irinotecan, the RR, PFS and OS were similar to those in the study conducted by ECOG. Another trial has reported an 84% overall RR, with PFS of 9.1 months and OS of 12.1 months. The importance of maintenance bevacizumab following combined modality treatment in patients with LD-SCLC is questionable; the response rate and OS are similar to what is seen with traditional chemotherapy with cisplatin, etoposide and radiation alone. Cediranib, a potent inhibitor of both VEGFR-1 and VEGFR-2, also has activity against c-kit, platelet derived growth factor beta (PDGFR-β), and FMS-like tyrosine kinase 4 (Flt-4). The response rate for Cediranib in recurrent SCLC that had progressed following platinum-based chemotherapy did not meet the predefined target. Vandetanib is an oral inhibitor of angiogenesis that targets VEGFR-2 and VEGFR-3 and inhibits tumour growth through activity against RET and EGFR/HER1. No difference in PFS or OS exists in vadetanib-treated patients compared with placebo-treated patients. Sorafenib, an oral multi-kinase inhibitor that targets both tumour proliferation via inhibition of Raf, stem cell factor receptor (KIT), and Flt-3 and angiogenesis by targeting VEGFR-2, VEGFR-3, and PDGFR-β, has been recommended for further evaluation in SCLC. Sunitinib is a novel, multi-targeted, small-molecule inhibitor of VEGFR-1, -2, and -3, PDGFR-α and –β, Flt-3, c-kit, the receptor encoded by the rearranged during transfection (*ret*) proto-oncogene, and Flt3. Thalidomide initially appeared to be a promising drug, but inclusion of this drug has ultimately failed to show any benefit in OS. Thalidomide in combination with chemotherapy in patients with SCLC shows, contrary to the results of the prior study, no significant difference between the thalidomide-treated patients and placebo-treated patients in OS. Based on the results of these trails, the role of anti-angiogenic therapy in the treatment of patients with SCLC remains to be determined. All agents studied to date appear to produce similar response rates and OS that are similar to the results achieved with chemotherapy alone (in most cases). Maintenance therapy with these agents does not appear to be beneficial in patients with SCLC.

6.6 MMP inhibitors

Many trials with MMPIs in SCLC have been equally disappointing. Of the multiple MMPs elevated in SCLC, marimistat targets MMP-1, MMP-2, MMP-9 and MMP-12 at low concentrations, while BAY 12-9566 targets MMP-2 at low concentrations.

6.6.1 mTOR inhibitors

At this time, mTOR inhibitors do not appear to be beneficial in the treatment of patients with SCLC.

6.7 Kit inhibition

Imatinib appears not to be beneficial in SCLC, even in patients with known c-kit mutations.

6.8 B cell leukaemia/lymphoma-associated gene 2 (Bcl-2)

Despite these discouraging results, a new class of oral BCL-2 antagonists is currently being developed and evaluated in patients with SCLC.

7. Signalling pathways that drive cancer stem cells

In cancer tissues, homeostasis is tightly regulated to ensure the generation of mature cancer cells throughout life without a depletion of the cancer stem cell pools. Each tissue is composed of a cellular hierarchy including stem cells able to generate all progeny, committed progenitors, and terminally differentiated cells. The stem cells in each tissue are believed to communicate with their microenvironment or surrounding stroma to maintain their homeostasis. Thus, the pathways that control stem cell self-renewal and the microenvironment in which the cancer stem cells (CSCs) reside may both play roles in targeted therapies

7.1 Hedgehog (Hh)

The Hh gene family encodes several secreted glycoproteins, including Indian Hedgehog (Ihh), Desert Hedgehog (Dhh), and Sonic Hedgehog (Shh). These proteins mediate signalling in embryogenesis and development through activation of the Gli family transcription factors. The Hh pathway is somewhat unique in that the signals serve to relieve a series of repressive interactions. The receptor for Hh, the transmembrane protein Patched 1 (Ptch), normally binds and inhibits smoothened (Smoh), a G-protein-coupled receptor that is related to Frizzled (Frz). When secreted Hh binds both Ptch and Hedgehog-interacting protein (Hip), Smoh initiates a transcriptional response. Specifically, Smoh activates the serine/threonine kinase Fused (Fu) to release Gli from sequestration by Suppressor of Fused (SuFu). Subsequently Gli proteins are able to translocate to the nucleus and regulate transcription of cyclin D and E, c-myc, and other genes involved in cell proliferation and differentiation. Shh is one among several important factors derived from the lung endoderm and is required for proliferation, differentiation, and patterning of the mesenchyme. Shh regulates pattern formation of a variety of developing structures, including the formation of the primary lung bunds. However, Shh is expressed in the ventral foregut endoderm. Shh is subsequently expressed in a gradient fashion (in the developing lung epithelium) with the highest levels in cells at the tips. In turn, most components of the Shh pathway, including Shh target genes and its receptor Ptch1, are found in the mesenchyme. Shh signalling is initiated upon binding to Ptch1 and results in activation of Shh target genes by Gli transcription factors. Ptch expression in the lung follows the proximal-distal gradient of Shh. Gli1, 2, and 3 are expressed in overlapping but

distinct domains in the lung mesenchyme. The proximal-distal gradient is evident in Gli1, which together with Ptch, is transcriptionally upregulated by Shh and is expressed in the subepithelial mesenchyme. All three Gli genes are expressed in the lung mesenchyme during the pseudoglandular stage of development, and mutations in the Gli genes give rise to various lung and foregut defects. Shh signalling has been implicated in the regulation of Gli genes, notably in Gli1 and Gli3 transcription in the lung. Gli2 has also been implicated in the regulation of Ptch1 and Gli1 components of the Shh signalling cascade in the lung. Thus, Shh is part of an epithelial network of regulators that restricts fibroblast growth factor 10 (FGF-10) expression. Shh-FGF-10 interaction supports a model in which the growing epithelial bud, which expresses high levels of Shh, interacts with a chemotactic source (FGF-10) in the distal mesenchyme for its elimination. This model supports the idea that not only the presence of FGF-10, but also its correct spatial distribution, is necessary for patterning. If FGF-10 signals are diffuse rather than localised, direct clues are lost and branching is disrupted. Importantly, the data suggest that under normal conditions, Shh plays a role in controlling FGF-10 expression in the distal lung. Expression of Shh and Ptch does not seem to be influenced by FGF-10; however, both genes are down-regulated by FGF-7 in lung explant cultures.

7.2 Gli genes

The vertebrate Gli gene family currently consists of three members, Gli1, 2 and 3, which are orthologous to Drosophila cubitus interruptus and encode DNA-binding proteins with five zinc fingers.

7.3 BMP-4

Bone Morphogenetic Protein (BMP) belongs to the TGFβ superfamily of growth factors, and at least three members (BMP-4, -5 and -7) are present in the developing lung. BMP-4 is an important regulator of epithelial proliferation and proximal-distal cell fate during lung morphogenesis. During branching morphogenesis, BMP-4 is dynamically expressed in the distal epithelium of branching airways. BMP-4 stimulates distal lung formation but might preferentially induce alveolar type I cell fate.

7.4 TGFβ-1

TGFβ-1 is a member of a sub-family of peptides having at least two other members, all expressed in the developing lung. TGFβ signalling is mediated by serine-threonine kinase receptors (type I and II) and Smad transcription factors. TGFβ-1 transcripts are uniformly expressed in the sub-epithelial mesenchyme. TGFβ-1 protein accumulates later at sites of cleft formation and along proximal airways. TGFβ-1 promotes the synthesis of the extra-cellular matrix, which, when deposited in the epithelial-mesenchymal interface, is thought to prevent local branching.

8. Perspectives and future directions in therapy for SCLC

The recurrence of tumours after initial tumour regression by conventional therapies is also frequent. One potential reason for this recurrence is the failure of current therapies to target CSCs. The design and development of new cancer treatments is therefore necessary to target

stem cell properties, i.e., self-renewal and differentiation. If the malignancy results from a blocked ontogeny, the treatment of cancer by inducing differentiation should be possible. These strategies have had variable success. In addition to inducing differentiation, a number of stem cell self-renewal pathways have been targeted for the treatment of various human tumours. If most solid tumours are composed of a minor population of self-renewing (stem) cells and a large fraction of non-renewing cells, cancer therapy failure following radiation and chemotherapy treatment is not the result of a rare cell evolving from within the tumour but the result of regrowth of the cancer stem cells. Of course, tumour stem cells could accumulate genetic changes that render them even more drug resistant, radiation resistant, or aneuploid. Because cures are achieved for many types of cancer, the cancer stem cells must be eliminated by a given therapeutic strategy. Regardless of which therapeutic paradigm turns out to be most effective, SCLC will clearly have to be treated with a "targeted medicine" approach if chemotherapy is to be widely successful in the clinic. This approach requires that each patient be segregated into a specific treatment group according to the constellation of molecular alterations that define his or her disease. The remarkable variation in genetic profiles across patients suggests that each tumour represents a distinct disease state that can only be effectively treated with precision therapy that targets the specific signalling pathway that is unique to each tumour. An important molecular mechanism that promotes cell differentiation is signal transduction. Signal transduction pathways ensure the reception of the concentration gradients of morphogens and their transformation into the differentiation of cells within tissues and organs. Hence, the key molecular rearrangements at the molecular level may be assumed to be related to changes in genes that participate in signal transduction pathways. In some contexts, these signals may be independently responsible for distinct aspects of tissue self-renewal, such as survival, proliferation and inhibition of differentiation. In other cases, the various signalling cascades may act in a hierarchy and regulate each other. Studies in which pathways are antagonised by treatment with pharmacological agent antagonists and/or agonists of Hh pathway signalling further demonstrate an ongoing requirement for pathway activity in the growth of additional cancer types. As a specific Smo antagonist, cyclopamine may be generally useful in the treatment of such cancers and represents a therapeutic strategy that may be further supported by the absence of observable toxicity in cyclopamine-treated animals. Cyclopamine inhibits Hh pathway activation by binding directly to Smo. This binding interaction is localised in the heptahelical bundle. Moreover, the binding influences the Smo protein conformation. Cyclopamine binding is also sensitive to Ptch function and provides biochemical evidence for an effect of Ptch on the structure of Smo. Cyclopamine appears to interfere with these signalling events by influencing Smo function; cyclopamine antagonises Hh pathway activity in a Ptch-independent manner and exhibits attenuated potency toward an oncogenic, constitutively active form of Smo. Pharmacologic inhibition of the Hh pathway has been necessary as a research tool to understand Hh pathway biology and is an attractive mechanism to evaluate antitumour activity. The first evidence that Smo could be antagonised came with the isolation of compounds called cyclopamine and jervine from corn lilies, which caused teratogenic effects (including cyclopia) in lambs. Significant new therapeutic strategies in SCLC will result from a deep understanding of the biology of response and resistance to targeted therapy. These approaches are in development to block embryonic pathways that play a role in cancer stem cells, including the Notch, Hh, and Wnt pathways.

9. Conclusions

The introduction of effective targeted agents for SCLC has lagged behind that for non-small-cell lung cancer. However, the number of agents now being tested has increased and includes agents that have shown some anti-tumour activity against other types of cancer, such as inhibitors of the Hh signalling pathway. This activity has prompted the development of agents that can inhibit Hh signalling. If the cancer stem cells that are responsible for driving the growth of cancer types associated with Hh pathway activation indeed come from stem cells trapped in a state of active renewal by pathway activities, then a logical therapeutic approach for these cancers would be to impose a state of pathway blockade. As we look towards the future, an important area of investigation will clearly involve analysing how the Hh pathway exerts its effect and whether shared molecular targets are involved in influencing self-renewal in the context of stem cells and cancer. Additionally, Hh probably integrates with other niche-derived signals, such as BMP (Bone Morphogenic Protein), Wnt and Notch. By understanding the molecular events governing CSCs, the development of therapeutics aimed at targeting these cells will become possible. The development of such therapeutics is of paramount importance because CSCs may mediate the resistance to current treatment and the relapse of the most aggressive tumours. This resistance may in part result in the reactivation of several signalling cascades, such Hh, Wnt, Notch, and EGF, in the CSCs combined with an increase in DNA repair mechanisms and ABC transporter-mediated multi-drug resistance.

10. References

10.1 Introduction

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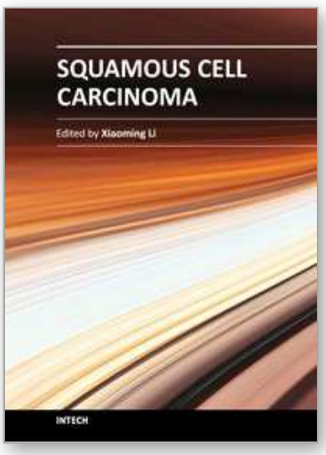

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This book points to some new areas for investigation on squamous cell carcinoma (SCC). Firstly, the features and management of some specific SCC is discussed to give the readers the general principles in dealing with these uncommon and sophisticated conditions. Some new concepts in adjuvant therapy including neoadjuvant therapy and gold nanoparticle-based photo dynamic therapy are introduced. Secondly, a detailed discussion of molecular aspects of tumor invasion and progression in SCC is provided with the emphasis on the roles of some important factors. The role of tumor microenvironment in head and neck SCC is specifically discussed. Thirdly, the roles of cancer stem cells (CSC) in cancer therapy of SCC are described. Molecular mechanisms involving therapeutic resistance and new therapeutic strategies targeting CSC are discussed in detail. Finally, other aspects concerning SCC are included, which involve the assessment, genetic manipulation and its possible clinical implications for the treatment of SCC.

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