Review Article

Histopathological transformation to small-cell lung carcinoma in non-small cell lung carcinoma tumors

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Abstract: Lung cancer is the principal cause of cancer-related death worldwide. The use of targeted therapies, especially tyrosine kinase inhibitors (TKIs), in specific groups of patients has dramatically improved the prognosis of this disease, although inevitably some patients will develop resistance to these drugs during active treatment. The most common cancer-associated acquired mutation is the epidermal growth factor receptor (EGFR) Thr790Met (T790M) mutation. During active treatment with targeted therapies, histopathological transformation to small-cell lung carcinoma (SCLC) can occur in 3–15% of patients with non-small-cell lung carcinoma (NSCLC) tumors. By definition, SCLC is a high-grade tumor with specific histological and genetic characteristics. In the majority of cases, a good-quality hematoxylin and eosin (H&E) stain is enough to establish a diagnosis. Immunohistochemistry (IHC) is used to confirm the diagnosis and exclude other neoplasia such as sarcomatoid carcinomas, large-cell carcinoma, basaloid squamous-cell carcinoma, chronic inflammation, malignant melanoma, metastatic carcinoma, sarcoma, and lymphoma. A loss of the tumor-suppressor protein retinoblastoma 1 (RB1) is found in 100% of human SCLC tumors; therefore, it has an essential role in tumorigenesis and tumor development. Other genetic pathways probably involved in the histopathological transformation include neurogenic locus notch homolog (NOTCH) and achaete-scute homolog 1 (ASCL1). Histological transformation to SCLC can be suspected in NSCLC patients who clinically deteriorate during active treatment. Biopsy of any new lesion in this clinical setting is highly recommended to rule out a SCLC transformation. New studies are trying to assess this histological transformation by noninvasive measures such as measuring the concentration of serum neuron-specific enolase.

Keywords: Anaplastic lymphoma kinase (ALK); epidermal growth factor receptor (EGFR); neuroendocrine cells; drug resistance

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Introduction

Lung cancer represents the primary cause of cancer mortality worldwide (1). The World Health Organization (WHO) classifies lung cancer into two subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (2). NSCLC represents 85% of cases of lung cancer, and is divided into adenocarcinoma, squamous-cell, and large-cell carcinoma (3). SCLC represents 14–15% of all lung cancers, and more than 30,000 new cases are diagnosed each year in the United States (4).The oncogenes involved in lung cancer development have been studied extensively and a great variety of tumor promoter and suppressor genes play important roles in the development of lung cancer (5).

Promoter gene alterations: in NSCLC it is common to observe mutations in *KRAS* (6), *HRAS* (7), and *NRAS* (11p15.5; 1p13) (8). Specifically, lung adenocarcinoma can harbor overexpression of the epidermal growth factor receptor (*EGFR*) (9), *ROS* proto-oncogene 1 (10), and rearrangements of the anaplastic lymphoma kinase (*ALK*) (11). All of these alter autocrine and paracrine cell growth (12). Adenocarcinoma and neuroendocrine large-cell carcinoma, can have amplification and overexpression of *c-myc* (13), *l-myc* (14), and *n-myc* (1p32; 2p2.41) (15). These augment proliferation and inhibit cell differentiation (16). Suppressor gene alterations: neuroendocrine carcinoma and NSCLC can have missense mutation in *p53* (17p12-13), which inactivates tumor suppression (17). In SCLC, mutation and deletion in retinoblastoma 1 (*RB1*) (13q14) can be observed, which produces loss of control of the G1 phase of the cell cycle and the arrest of the cell cycle (18).

Alterations in the methylation pattern of DNA have been recognized in many human cancers, and lung cancer is no exception. Aberrant promoter methylation has been shown in various genes, including the retinoid acid receptor β-2, tissue inhibitor of metalloproteinase-3, p16, O6-methylguanine-DNA-methyltransferase, death-associated protein kinase, E-cadherin, p14, glutathione S-transferase P1, the ras effector homologue *RASSF1A*, and the protein tyrosine phosphatase receptor type O. The presence of aberrant methylation in precursor lesions of lung carcinomas identifies it as a reasonable candidate biomarker for early lung cancer diagnosis (5).

Advanced clinical stages of NSCLC that harbor mutations in *EGFR*, *ROS-1*, or *ALK* rearrangements have a distinct clinical course compared with conventional NSCLC. The use of modern therapies for lung cancer such as tyrosine kinase inhibitors (TKIs), some of which inhibit *EGFR* and others *ALK*, has improved survival in patients with specific genetic anomalies of their tumors (19-21). These treatments are preferred over standard intravenous chemotherapy, not only because of their advantages in terms of outcomes, but also because of the better quality of life that patients report. Other advantages include fewer visits to chemotherapy infusion centers and the convenience of administration (22). However, most patients develop resistance to the treatment after 12–15 months of continuous therapy (23-26). This review is focused on standards not only for analysis of the histopathological structure, but also in the molecular mechanisms that drive the histopathological transformation to SCLC in NSCLC tumors.

Histological and genetic characteristics of lung adenocarcinoma and SCLC

Lung adenocarcinoma is the most prevalent subtype of lung cancer among women, nonsmokers, and young men. It commonly presents with *EGFR* mutations or *ALK* translocations, which represent the main objective of current targeted therapies. It is defined as a malignant epithelial neoplasia with glandular differentiation, pneumocyte phenotype, or mucus production. The WHO recognizes many histological subtypes: lepidic, acinar, papillary, micropapillary, and solid (2). In general, the same tumor can have many subtypes and the pathology report must state which one is the most prevalent: this is very important because it can impact the prognosis (27). Immunohistochemistry (IHC) is only recommended in cases in which diagnosis is not made with conventional hematoxylin and eosin (H&E) stain. Typically, the IHC markers used are cytokeratin 7 (CK7) and thyroid transcription factor 1 (TTF-1) (27).

With the development of targeted therapies, molecular testing must be included in the work-up of these tumors. The most common genes targeted by mutations in adenocarcinoma include *EGFR*, *KRAS* and *BRAF*, *ALK*, *ROS1* and *RET* translocations, *MET* and *FGFR1* amplification. *EGFR* mutations are observed in 10–15% of European patients, most commonly in nonsmokers and women, but in up to 40% of Asian patients (3,28,29). Commonly, patients with these mutations respond to targeted treatment and these therapies are approved as first-line treatment in these patients (30,31). *EGFR* activation promotes tumor proliferation and arrests cell apoptosis through stimulation of oncogenic pathways such as *MAPK* and *PIK3/Akt/PTEN/mTOR*. Activating mutations of *EGFR* are localized in exons 18–21, which is the coding region of the intracytoplasmic tyrosine kinase receptor. Ninety percent of these activating mutations are small deletions in exon 19 (deletions of codons 747–750) or point mutations in exon 21 (L858R). Between 5% and 8% are insertions in exon 20 and 2–5% are point mutations of exons 18 and 20. *KRAS* mutations and *MET* amplification are associated with a worse prognosis and *EGFR* mutations with acquired resistance (32,33).

A fusion between echinoderm microtubule-associated protein-like 4 (*EML4*) and *ALK* is present in 2–7% of adenocarcinomas and is more commonly observed in nonsmokers. This group of patients benefits from *ALK* inhibitors (34). The physiological function of *ALK* is not

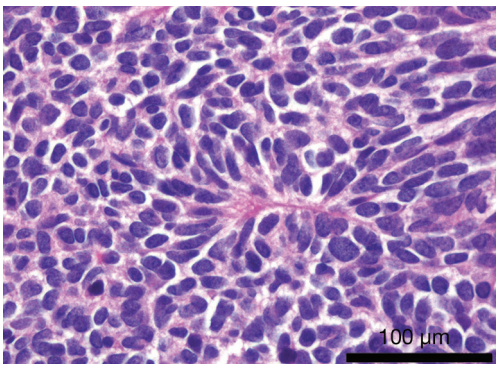

Figure 1 Small cell lung carcinoma. Hematoxylin and eosin (H&E) stain. Tumor composed of nests of small cells with fine granular chromatin nuclei, inconspicuous nucleoli, and scarce cytoplasm.

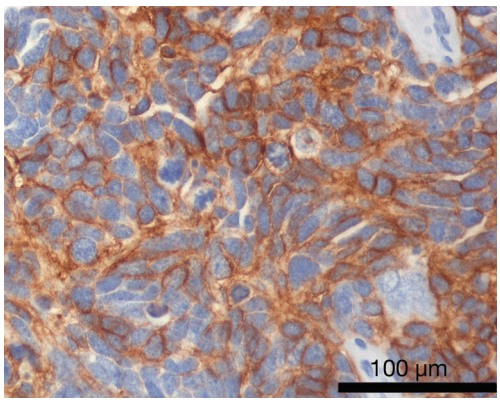

Figure 2 Small cell lung carcinoma. Positive immunohistochemistry (IHC) for CD56, with membranous pattern. This supports the neuroendocrine lineage of the neoplastic cells.

clearly defined; in adult human tissues it is found in low levels in the small intestine, testicles, and nervous system. Histological subtypes of adenocarcinoma that more commonly harbor *ALK* rearrangements include the solid—cribriform, papillary, and micropapillary, and the presence of signet cells with abundant intracellular mucin (34-36).

On the other hand, SCLC usually affects men with a mean age of 60 years and 99% of the patients are smokers (37). By definition, it is a high-grade tumor, so it is very aggressive and very common that patients already have mediastinal lymph node metastases at the time of diagnosis. Histologically, it is a malignant epithelial neoplasia composed of small, oval, rounded, and fusiform cells with scarce cytoplasm, irregular borders, fine granular chromatin, and inconspicuous nucleoli. The cells generally have nuclear molding. Necrosis is extensive and the mitosis count is high (19). It was previously known as oat-cell carcinoma, small-cell anaplastic carcinoma, undifferentiated small-cell carcinoma (SCC), intermediate cell type, and mixed small-cell/large-cell carcinoma; however, these terms are no longer recognized (2). By light microscopy, mitotic rates are high, with an average of 80 mitoses per 2-mm^2 area (2,38-40). The tumor can show different growth patterns, including nests, rosettes, organoid pattern, tubules, ductules with glandular differentiation, and/or peripheral palisading (2). DNA encrustation on vessel walls, which can be observed as basophilic material (also known as the Azzopardi effect), can also be observed in some necrotic zones (19).

The most recent consensus statement of the WHO in 2015 recognizes only two types of SCLC: pure SCLC and combined SCLC (2). When the tumor is composed exclusively of small cells, it is classified as pure SCLC. However, if in addition to the small cells observed in the tumor, it contains at least 10% of large cells, it is classified as a combined SCLC. In surgical samples, neoplastic cells have better formalin fixation and under the microscope the cells can appear larger (19,38). In addition to combined carcinoma composed of small and large cells, one can have combined SCLC with squamous-cell, spindle-cell, or giant-cell carcinoma or adenocarcinoma. Diagnosis of adenocarcinoma or squamous-cell carcinoma can be made if there is any level of frank disease; unlike combined SCLC, no minimum percentage is required. The frequency of diagnosis of mixed carcinoma depends specifically on the size of the biopsy, the type of specimen, and the pathologist's experience (1). In a surgically resected case series, Nicholson *et al*. (38) found combined SCLC in 28% of cases, with 16% combining SCLC with large-cell carcinoma, 9% with adenocarcinoma, and 3% with squamous-cell carcinoma.

Pure SCLC is easily diagnosed in small biopsies (obtained through bronchoscopy) and cytology specimens. The most important technical aspect for accurate diagnosis is a good histological slide and a high-quality H&E stain (*Figure 1*). In most cases, an H&E stain is enough to establish the diagnosis. IHC is used to confirm the diagnosis and in difficult cases. Staining with pancytokeratins such as AE1/AE3 helps to demonstrate that the tumor is a carcinoma rather than a lymphoid lesion (2,19). The most useful neuroendocrine markers include CD56, chromogranin, and synaptophysin, which are best used as a panel (19,38,41). Up to two-thirds of SCLC will be negative for chromogranin and synaptophysin (19). CD56 will stain 90–100% of cases (*Figure 2*) (42-44). Nonetheless, neuroendocrine marker

staining may be focal or weak and only one or two markers may be positive. In <10% of cases, all neuroendocrine markers may be negative and the diagnosis can still be established by morphology (19).

Although a high percentage of SCLC and large-cell neuroendocrine carcinoma (LCNEC) show genetic changes, with some aberrations also seen in carcinoids, some genetic differences between LCNEC and SCLC have been demonstrated (44,45). Therapeutic strategies for SCLC and LCNEC differ substantially. Therefore, because they are two different pathological entities (46), identification of a noninvasive way to detect potential disease transformation before repeated biopsy is crucial.

In addition, an augmented expression of insulin-like growth factor type 1 receptor (IGFR-1) protein and gene copy number has been observed in SCLC, with a significant correlation between protein expression and gene copy number. IGFR-1 inhibitors are beginning to be tested for SCLC in research trials (19,47).

SCLC and LCNEC show a high frequency of loss of heterozygosity (LOH) for 3p, *RB*, 5q21, 9p, and p53 compared with typical carcinoid and atypical carcinoid (19). LOH of 5q21 was found significantly more frequently in SCLC than in LCNEC, and in high-grade carcinoma than in carcinoid (48). The *P16^{INK4}/cyclin D1/RB* pathway that is involved in the regulation of G1 arrest in the cell cycle is frequently affected in neuroendocrine tumors (49,50). *RB* loss is frequent in SCLC and LCNEC, but not in typical carcinoid, although it can be found in 60% of atypical carcinoid. Igarashi *et al*. demonstrated overexpression of cyclin B1 in a high percentage of LCNEC and SCLC (50).

Positive membranous-cytoplasmic expression of the c-kit protein (also known as CD117) is frequently observed in high-grade pulmonary neuroendocrine tumors. Pelosi *et al*. reported expression in 44–77% of LCNEC and 67–80% of SCLC (51), but in only 7% of carcinoid tumors. Araki *et al*. (52) and Casali *et al*. (53) found c-kit staining in 55% and 61% of SCLC and LCNEC, respectively. Casali *et al*. reported a significantly worse prognosis and a higher rate of recurrence for patients with c-kit-positive LCNEC (53). In contrast, neither Pelosi *et al*. (51) nor Araki *et al*. (52) found any prognostic significance of c-kit expression within LCNEC or SCLC tumors.

Mechanisms of acquired resistance to targeted cancer therapies

This section reviews the molecular characteristics that are secondarily acquired during histopathological transformation. Oral TKI-targeted therapies approved for locally advanced or metastatic *EGFR*-mutated NSCLC adenocarcinoma have changed substantially the way this aggressive tumor is treated. They are approved as first-line therapies, based on the observation that 90% of active mutations arise from exon 19 deletion and exon 21 L858R point mutation (54,55). Currently, three drugs are available in most countries as first-line therapies: afatinib, gefitinib, and erlotinib (23,24,56). Unfortunately, some patients develop resistance to the therapy after 1 year or less of response to active treatment (57).

Repeated biopsies in this group of patients have been the vehicle to understand the underlying molecular mechanisms of acquired resistance to *EGFR* TKIs. These include mechanisms that are related to the reactivation of intracellular signal pathways: secondary mutations of *EGFR* Thr790Met (T790M), *MET* receptor tyrosine kinase amplification, and *PIK3CA* mutations (1,58).

These biopsies have also been very useful to observe the phenotypic and histological changes of the so-called histological transformation from NSCLC to SCLC (1,3,59) and epithelial-to-mesenchymal transition (EMT) (60). EMT consists of the loss of the epithelial morphology of the neoplastic cells that develop into a form that resembles that of mesenchymal neoplasms. These phenotypic changes include changes in the IHC-detected expression of vimentin and E-cadherin and also the preservation of the *EGFR* mutations (1).

The most common acquired resistance mechanism is the T790M mutation of *EGFR* (1,61), which is reported in 50–60% of biopsies of patients who develop resistance to current targeted therapies. This acquired mutation augments the ATP receptor and allows signaling from the *EGFR* in the presence of the inhibitor drug (59). Published data from clinical trials focused on this subgroup of patients showed that treatment with a new generation of TKIs resulted in excellent outcomes and drug tolerability (62,63). Other mechanisms that do not involve signaling through the *EGFR*, such as *MET* and *HER2* amplification, make up 15–20% of acquired resistance to *EGFR*-targeted therapies (64-66).

Histopathological transformation to SCLC from NSCLC has been reported as a mechanism of acquired resistance to *EGFR* TKIs in 3–15% of patients (1,3,67). This phenomenon of transformation has been previously reported in case reports and has been confirmed with repeated biopsies in patient cohorts (59,60,68,69). Clinicians

must be aware of this possibility in patients receiving targeted therapies who clinically deteriorate. Little is known about the exact mechanisms that lead to this transformation, but two hypotheses have been proposed to explain it. One states that NSCLC and SCLC have a common cell of origin and that the morphological-phenotypic transformation occurs after treatment with TKIs. The other hypothesis proposes that at the time of the original tissue diagnosis, both types of carcinoma were present, but because of the sampling only the adenocarcinoma was diagnosed (54). The scientific evidence suggests that this latter hypothesis is probably wrong and in many cases it is discredited because some patients originally respond to targeted therapies for months or even years (3).

Synchronous development of adenocarcinoma and SCLC has been observed in *EGFR*-mutated tumors before active targeted therapy (67). This observation suggests that the presence of SCLC in *EGFR*-mutated carcinomas is not exclusively the result of *EGFR* inhibition. In addition, in a series of cases of combined carcinoma, the original biopsy of two adenocarcinomas that transformed to SCLC did not show an *EGFR* mutation. It is improbable that the original *EGFR* report of the tumors was a false-negative result, because both cases were whole resections and one had a *KRAS* mutation (67). This suggests that the transformation can occur independently of the *EGFR* mutational status.

In a 1986 case series, before the discovery of the *EGFR*-activating mutations, when some patients developed conventional chemotherapy or radiotherapy resistance, around 5% of patients with an original diagnosis of NSCLC presented with recurrences in the form of SCLC (70). It is unknown whether the tumors of these patients had any *EGFR*-activating mutations, but they showed SCLC transformation independent of *EGFR* inhibition. Sequist *et al*. (1) did not find any SCLC transformations among 79 patients with stage III NSCLC using surgical samples of tumors with nonmutated *EGFR* that were treated with chemotherapy and radiotherapy (1). This suggests that NSCLC with nonmutated *EGFR* has less tendency to SCLC transformation compared with *EGFR*-mutated tumors. There is a need for studies of larger cohorts of patients to understand better the histological transformation to SCLC from NSCLC with mutated and nonmutated *EGFR*.

In addition, the common clinical presentation differs between these two clinical entities. *EGFR*-mutated adenocarcinomas are more common among nonsmokers and have a more indolent clinical course compared with classical SCLC, which is exclusively a disease of smokers with a rapid growth and early metastases. Clinically, patients with histological transformation to SCLC have an accelerated decline after an initial response to therapy (60).

In many cases that have been studied with repeated biopsies, all the SCLC-transformed tumors retained the initial *EGFR* mutations of the adenocarcinoma (68,69). An autopsy of a patient with histological transformation of NSCLC into extensive metastatic SCLC disease in the lungs, mediastinal and subdiaphragmatic lymph nodes, and liver demonstrated conservation of the *EGFR* L858R mutation of the original lung adenocarcinoma without any additional mutation. However, there are reports of rare cases where tumors not only maintain the original mutations, but also acquire additional changes such as mutations in *PIK3CA* (3,70). These findings suggest that resistance mechanisms involve the phenotypic transformation of the tumor.

Zhang *et al*. (71) reported the case of an 80-year-old man with lung adenocarcinoma (stage IB) who had an *EGFR* mutation (deletion of exon 19). Second-line treatment with *EGFR*-TKI after progression failed, and the progression was accompanied by increased concentrations of the serum tumor marker neuron-specific enolase. The patient's disease progressed during one month of active TKI therapy. Later, repeated biopsies of the metastatic and primary surgical lesions identified a pathological transformation from adenocarcinoma to SCLC, which retained the same *EGFR* mutation. Chen *et al*. (46) suggest that, in the case reported by Zhang *et al*. (71), the transformation occurred before the initial period of TKI treatment. By contrast, in most cases, patients have a long progression-free survival under TKI treatment, which supports the possibility that the transformation might occur during TKI treatment. These conflicting findings suggest the possible existence of factors other than *EGFR* inhibition that might promote the transformation from *EGFR*-mutant adenocarcinoma to SCLC (46). In this case, in addition to the poor response to TKIs, the increased concentration of serum neuron-specific enolase, which rose from 17.9 ng/mL at the early stage of the disease to 211.10 ng/mL at the stage when progression was detected (reference range <15 ng/mL), could be a way to predict potential disease transformation (71).

Genetic analyses of *EGFR*-mutated adenocarcinomas with acquired resistance to TKIs secondary to histological SCLC transformation showed that these tumors can lose *EGFR* expression and have low levels of *EGFR* amplification (60). It is known that SCLC has lower expression of *EGFR*

Table 1 Demonstrated mechanisms of acquired resistance to EGFR TKIs. The most common is the acquired mutation of EGFR Thr790Met, which has been reported in 50–60% of studied biopsies

Secondary mutation of EGFR (T790M)
MET receptor tyrosine kinase amplification
HER2 amplification
PIK3CA mutations
Histopathological transformation from NSCLC to SCLC
Epithelial to mesenchymal transition

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; T790M, Thr790Met; NSCLC, non-small cell lung carcinoma; SCLC, small-cell lung carcinoma.

compared with NSCLC, but the underlying mechanism of this is unknown (68). SCLC with *EGFR* mutations responds less strongly to TKIs compared with *EGFR*-mutated NSCLC, probably secondary to mechanisms that suppress *EGFR* expression in these tumors (3). However, Araki *et al*. (52) reported the case of a patient with SCLC with mutated *EGFR* that responded to conventional TKI treatment. This must be confirmed with studies that include more patients. A summary of mechanisms of acquired resistance to *EGFR* TKIs is listed on *Table 1*.

EGFR-mutated carcinomas that transform to SCLC also have epigenetic changes; miRNA analyses have demonstrated that SCLC-transformed cells express miRNAs that are commonly upregulated in classical SCLC. However, SCLC-transformed cells also express miRNA subtypes that are typically expressed in adenocarcinomas, but not in SCLC. This suggests that transformed SCLCs have some characteristics of the original adenocarcinoma, but that the mRNA expression profile and the clinical course indicate that this neoplasia behaves similarly to classical SCLC (60,62,63,72).

In laboratory studies, the *BCL-2*, *BCL-XL* inhibitor *ABT-263* is one of the few therapies to date to exhibit marked efficacy against SCLC, although recent results from single-agent clinical trials with *ABT-263* demonstrated responses in only a minority of SCLC patients. Transformed SCLC *EGFR*-mutant cells were highly sensitive to single-agent *ABT-263*, and markedly more sensitive than *EGFR*-TKI-resistant NSCLC cell lines harboring the T790M resistance mutation. *ABT-263* treatment induced a robust apoptotic response in *EGFR*-mutant SCLC compared with the resistant *EGFR*-mutant NSCLC. The gene expression and drug sensitivity of the SCLC-transformed cells more closely resemble classical SCLC than *EGFR*-mutant NSCLC (73).

ALK inhibitors provide a better response than cytotoxic chemotherapy in patients with *ALK*-positive NSCLC (34,36). Despite these favorable results, a group of patients will have progression of the disease after 1 or 2 years of active treatment. The resistance mechanisms to TKIs for *ALK*-positive patients include *ALK* domain modification and upregulation of parallel signaling pathways such as those involving *EGFR* and *cKIT* (36,74). To our knowledge, there are only three case reports in the literature describing SCLC transformation in *ALK*-positive patients. The first detected an *EML4-ALK* fusion gene through *ALK* IHC analysis and direct sequencing of cDNA in a surgically resected specimen (75). The second confirmed *ALK* rearrangement by multiplex reverse transcription-polymerase chain reaction (PCR) in a biopsy before treatment (76). The third case described a 67-year-old nonsmoking woman with a diagnosis of *ALK*-positive adenocarcinoma that underwent SCLC transformation during active treatment with the *ALK* inhibitor alectinib (36).

Molecular mechanisms involved in the transformation from NSCLC to SCLC

Two SCLC genome-sequencing projects have been completed, which included analysis of the genome, transcriptome, and the copy number. Both identified a high prevalence of *TP53* and *RB1* mutations (77,78). *MYC* amplification was observed in 16% of the studied cases (77). *MYCL1* knockdown produces diminished proliferation in cells of SCLC (78), which suggests that *MYC* can function as an oncogenic controller in a subgroup of SCLC tumors. Signal activators including *ERK*, *EGFR*, and *KRAS* are more common in adenocarcinomas. By contrast, the loss of *RB1* is more common in SCLC (79).

Because the loss of *RB1* was found in 100% of sequences of SCLC tumors in humans, it was concluded that it plays an important role in tumorigenesis and is essential for its development (3,77,79). Analyses of repeated biopsies of patients with *EGFR*-mutated adenocarcinomas that underwent SCLC transformation have shown that all the tumors had lost *RB1* (60). Evaluation of *RB1* status in 11 samples of *EGFR*-mutated tumors by analysis with IHC, quantitative PCR, next-generation sequencing (NGS), and array comparative genomic hybridization showed that classical SCLC had alterations in *RB1* and did not express *EGFR* (60,77,79-81). However, it is of interest that in *RB1* knockdown experiments in *EGFR*-mutant cell lines, the

loss of *RB1* was insufficient to cause resistance or induce neuroendocrine differentiation. These cell lines do not possess the pluripotent cells that are present in a tumor *in vivo* and that have the capacity to differentiate into many cell types including SCLC. It is suggested that pluripotent cells differentiate to NSCLC when *EGFR* is active, in the same way as *EGFR* activity is associated with alveolar differentiation (60,82). The SCLC transformation could suggest that adenocarcinoma and SCLC originate from a common cell, probably a multipotent stem cell (3). If this could be confirmed, the genetic heterogeneity of neoplasia would again be demonstrated.

Western blotting revealed loss of *RB* expression specifically in resistant *EGFR*-mutant cell lines with SCLC histology also lacking *RB* expression. The universal nature of *RB* loss suggests that this may be a necessary event for the resistant SCLC tumors to emerge. *RB*-deficient adenocarcinomas serve as further evidence that loss of *RB* alone is insufficient to promote transformation to SCLC (83).

Achaete-scute homolog 1 (*ASCL1*) is a basic helix-loop-helix transcription factor pivotal for neuroendocrine differentiation that is expressed in pulmonary neuroendocrine cells and in SCLC. *ASCL1* promotes more aggressive adenocarcinoma growth *in vivo* and may interact with the central retinoblastoma protein-tumor protein 53 (*RB-p53*) axis in the carcinogenesis of neuroendocrine lung cancers. *ASCL1* contributes to enhanced proliferation and migration in lung cancer cells *in vitro* by targeting cyclin-dependent kinase 5 (CDK5). *ASCL1* expression is regulated downstream of neurogenic locus notch homolog (*NOTCH*) signaling, mediated through four different receptors, which causes polyubiquitination-mediated *ASCL1* degradation. Alteration in *NOTCH* receptor signaling is frequently found in malignant neoplasms. The mutated domain determines the functionality, because activating mutations are located in the proline-glutamic acid-serine-threonine-rich (*PEST*) domain and inactivating mutations in the *EGF*-like and ankyrin (*ANK*) repeats. Meder *et al*. investigated signaling via the *NOTCH*- and *ASCL1*-dependent pathway *in vitro* (83). They used amplicon-based NGS to identify mutations on *RB1* and *TP53*. Mutual RB1 and *TP53* mutations were identified only in SCLC cell lines. Thus, *RB1* mutations correlated with the lack of *RB* protein expression. Using different amplicon-based panels, they identified other oncogenic mutations, including *EGFR* mutations in *PC9* and H1975, while *RB* can be inactivated by phosphorylation. They also performed Western blot analysis to determine the total *RB* protein and phosphorylation status. *ASCL1* clones showed higher expression of serine-phosphorylated *RB*. Therefore, *ASCL1* overexpression caused inactivation of *RB* by phosphorylation. Phosphorylation of *RB* is triggered by CDKs. CDK5 was upregulated in *ASCL1* clones compared with the EV control. Because *ASCL1* is targeted by *NOTCH* signaling, Meder *et al*. also performed siRNA-mediated knockdown of *NOTCH1* and *NOTCH2* in PC9 cells, and observed increased *ASCL1* and CD56 expression. Flow cytometry revealed stable *RB* protein expression and significantly increased phosphorylation of *RB* at Ser780, but this was not as strong as in *ASCL1* clones. Meder *et al*. proposed that *ASCL1* overexpression induced CDK5 upregulation and thereby *RB* inactivation by phosphorylation, and that *p53*-mutated cells had a selective advantage when *RB* was inactivated. *ASCL1* assists the central *RB-p53* signaling axis in the establishment of a SCC phenotype. Meder's group examined four mutations in *NOTCH* genes (*NOTCH1-4*), *RB1*, and *p53* by NGS and also assessed representative cases of neuroendocrine pulmonary carcinomas. They suggested that mutual biallelic alterations of both genes were a prerequisite for SCC formation. For secondary SCC, biallelic *TP53* mutations in the non-small-cell precursor, which are more frequent in squamous cell carcinoma than in adenocarcinoma, may be a prerequisite. *ASCL1* expression alone was not sufficient to induce a full SCC phenotype but it was reported that *ASCL1* may cooperate with *RB* and *p53* loss when forming SCC. However, clinical observations also suggest that SCCs may arise as secondary neoplasms from a non-small cell cancer background in the form of relapses after genotoxic chemotherapies or targeted therapies (1,84,85). The complex patterns of inactivating *NOTCH* mutations in the context of mutual *RB1* and *TP53* alteration in tumors with neuroendocrine differentiation indeed suggest that some neuroendocrine neoplasms may represent a NSCLC-dependent secondary tumor overgrowing its non-small cell origin. The results suggested that one inactivating *NOTCH* mutation was sufficient to induce neuroendocrine differentiation from nonneuroendocrine tumor cells or tumor precursors (*Figure 3*). Reactivating *NOTCH* signaling may represent an important therapy option for SCLC patients (86,87).

We lack clinical trials that address the best way to treat SCLC transformed from NSCLC tumors. Case-reports and series of cases in the literature, used standard chemotherapy (platinum-based and etoposide) and reported a response in 75% of the patients. The benefit of radiotherapy to the chest is unknown in this group of patients (1,69,88).

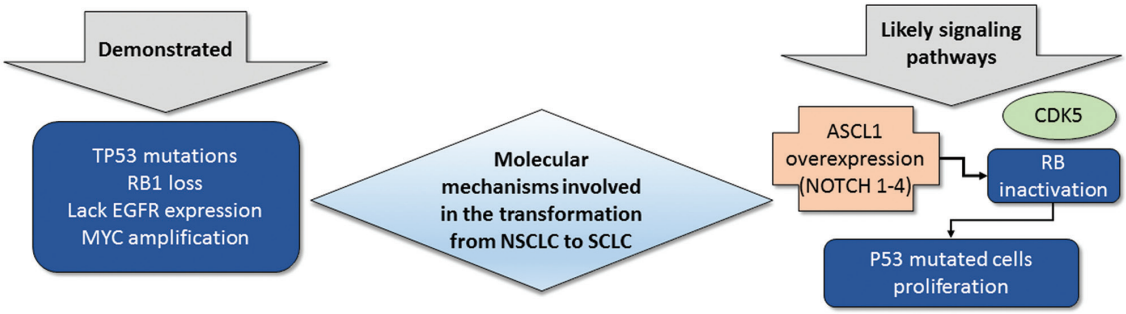

Figure 3 Molecular mechanisms involved in the transformation from NSCLC to SCLC. They include *TP53* mutations, *RB1* loss, lack of *EGFR* expression and *MYC* amplification. The most studied signaling pathway is the *ASCL1* which is regulated by four different *NOTCH* receptors. NOTCH alterations promote *ASCL1* and CD56 overexpression. These changes induce CDK5 activity and inactivation of *RB* by phosphorylation. With inactivated *RB*, *p53* mutated cells have a selective advantage. NSCLC, non-small cell lung carcinoma; SCLC, small cell lung carcinoma; *RB1*, retinoblastoma 1; *EGFR*, epidermal growth factor receptor; *NOTCH*, neurogenic locus notch homolog; *ASCL1*, achaete-scute homolog 1; CDK5, cyclin-dependent kinase 5.

Conclusions

Clinicians must be aware that transformation to SCLC from NSCLC can occur at any time during active treatment. The specific moment when the transformation occurs has not been elucidated. After *EGFR*-specific TKI treatment, resistant pluripotent cells can accumulate genetic alterations (such as the loss of *RB1* and *TP53*), which give them a distinct epigenetic state and capability of differentiation in a lineage that does not require *EGFR* signaling, such as SCLC. The *EGFR*-specific TKIs silence that signaling pathway, facilitating differentiation to other lineages. This same mechanism could also explain SCLC transformation in patients with *ALK*-positive NSCLC receiving targeted therapy. Other genetic pathways that are probably involved in the histopathological transformation are *NOTCH* and *ASCL1*. A biopsy is recommended for patients with NSCLC and rapid clinical decline to rule out SCLC transformation.

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Footnote

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