Centennial Review

Pathogenesis of Lung Cancer
100 Year Report

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Over the past 100 years, our understanding of the pathogenesis of lung cancer has advanced impressively. Environmental carcinogens and a gene locus determining susceptibility have been identified. The pathology of lung cancer has been classified into categories with major clinical implications. The cellular and molecular genetic changes underlying lung cancer have become better understood over the past 25 years, but the stepwise progression of respiratory epithelium from normal to neoplastic is not yet well demarcated, limiting abilities to advance early detection and chemoprevention. The translation of improved understanding of dominant signal transduction pathways in lung cancer to rationally designed therapeutic strategies has had recent successes, demonstrating a proof of principle for targeted therapy in lung cancer. Improvement in overall patient outcomes has been stubbornly slow and will require concerted efforts.

In the 1912 edition of his classic textbook of medicine, William Osler stated that "primary tumors of the lung are rare." Lung cancer is now the most common cause of cancer death in both men and women in the United States and is the leading cause of cancer death overall in the world, with over 1,000,000 deaths occurring yearly (1).

Etiology

A century ago, one occupational cause of lung cancer was known. An association between lung cancer and work in the Schneeberg mines in Germany was described by Harting and Hesse in 1879 (2). Subsequently, high levels of radon gas were found in the mines and an etiologic connection between radioactive gas exposure and lung carcinogenesis was proposed early in the twentieth century.

Tobacco was used for centuries before the modern epidemic of lung cancer occurred. However, with the development of machines for the commercial production of cigarettes in the late nineteenth century, tobacco products became more widely and intensively used. Tobacco smoke was suspected as causing lung cancer as early as the late 1920s, when physicians began seeing increasing numbers of patients with this heretofore rare disease and noted that nearly all were cigarette smokers. Muller reported a case-control study implicating tobacco smoke in causing lung cancer in Germany in 1940, but the message was largely lost as the medical community was distracted by the larger disaster of World War II, as reviewed by Muller and by Witschi (3, 4). In 1950, several case-control studies were published, all showing an association between cigarette smoking and lung cancer (5, 6). A number of studies have demonstrated that risk for lung cancer decreases with smoking cessation, most recently and elegantly described in the Lung Health Study, where the efficacy of smoking cessation interventions in decreasing lung cancer deaths was demonstrated in a prospective, controlled trial (7).

In 1943, the German scientific consensus was that asbestos exposure caused lung cancer. Experiments performed by the asbestos industry showed that asbestos exposure caused lung tumors in mice, but were unpublished (8). In 1955, Doll published a landmark manuscript demonstrating a highly persuasive association between heavy asbestos exposure and lung cancer (9). Similar to tobacco, there was a long delay between the documentation of the etiologic effect of asbestos in lung carcinogenesis and implementation of policies to protect the public. Additional industrial and environmental exposures, including heavy metals and petrochemicals, causing lung cancer have been described.

Viral causation of lung cancer has been intermittently considered. Bronchioloalveolar carcinoma in sheep is transmitted by a retrovirus, but no studies in human lung cancer have supported a retroviral etiology (10). There is recent evidence supporting human papilloma viruses as possibly contributing to lung cancer, especially in never-smokers from Pacific Rim countries (11, 12).

Different carcinogens give rise to specific mutations (i.e., transitions versus transversions). Thus, sequence analysis of the mutational spectrum of target genes, such as p53, in different populations can be informative regarding the probable culprit carcinogen in that population. This approach to determining etiology has been termed molecular epidemiology or molecular archeology and has been instrumental in providing additional support for tobacco smoke as a major etiology of lung cancer (13–15).

A number of reports suggest increasing numbers of lung cancer cases in never-smokers, particularly females from Asia (16). This is particularly alarming and mandates aggressive investigation, including both standard and molecular epidemiology, to determine if new etiologies for lung cancer are emerging.

Pathologic Classification

The distinction between SCLC and NSCLC is critical, both clinically and in terms of tumor genetics and biology. Small cell lung cancer (SCLC) was first described as a tumor of the bronchus, as opposed to a round cell sarcoma, by Barnard in 1926 (17). Azzopardi further refined the pathologic description in 1959 and Watson and Berg described some of the distinctive clinical features in 1962 (18, 19). The World Health Organization (WHO) and International Association for the Study of Lung Cancer (IASLC) have sponsored workshops to develop standardized morphologic classifications of lung cancer and SCLC

(*Received in final form April 26, 2005*)

Supported by a Merit Review grant from the Department of Veterans Affairs, NCI Cancer Center Support Grant P30 CA46934 and NCI Specialized Program of Research Excellence in Lung Cancer P50 CA58187.

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Am J Respir Cell Mol Biol Vol 33. pp 216–223, 2005
DOI: 10.1165/rcmb.2005-0158OE
Internet address: www.atsjournals.org

subtypes (20, 21). Although the subtypes of SCLC are not clinically useful in determining therapy, the recognition that mixed tumors containing two or more elements of SCLC, adenocarcinoma, or squamous cell carcinoma has promoted the concept that the major forms of lung cancer are closely related, perhaps arising from a common stem cell.

Genetic Susceptibility

Mice develop pulmonary adenomas, either spontaneously or in response to carcinogens, that progress to adenocarcinomas in a strain-dependent fashion (22). This strain difference in susceptibility to lung tumors has been used to map murine pulmonary adenoma susceptibility and resistance genes. To date, murine lung tumor susceptibility genes have not lead to the identification of similar susceptibility genes in humans.

An inherited genetic susceptibility to lung cancer in humans was first suggested in the early 1960s (23). More recently, family history of lung cancer has been confirmed as a strong risk factor for the development of lung cancer (24). Segregation analysis supported the presence of a highly penetrant autosomal gene determining genetic susceptibility to lung cancer (25). In the early 1990s, discussions among the National Cancer Institute funded Specialized Programs of Excellence (SPORE) in Lung Cancer lead to a cooperative initiative (the Genetic Epidemiology of Lung Cancer Consortium) to attempt to identify lung cancer susceptibility genes by linkage. This has been a daunting task, due to the difficulties in obtaining DNA from cases, most of whom are deceased. In 2004, a locus on chromosome 6q23–25 was reported as conferring lung cancer susceptibility among families with multiple members affected by lung or head and neck cancer (26). Of great interest, in carriers even a small exposure to tobacco smoke greatly increases risk for lung cancer. The identity of this gene is currently a topic of intense research interest.

Groups used association studies to assess various candidate genes including those encoding enzymes that either activate or inactivate carcinogens found in tobacco smoke. The evidence is strongest for CYP1A1 polymorphisms and GST mu null and has been recently reviewed (27).

The inherited susceptibility for developing addiction to nicotine is potentially the most important genetic determinant of lung cancer development. This area is being actively investigated, primarily through association studies (28–31).

Chronic obstructive pulmonary disease (COPD) and lung cancer are highly associated, beyond what would be expected from smoking history alone (32, 33). Cohen and colleagues demonstrated familial aggregation of these two disorders in 1977, but common susceptibility genes remain to be identified (34).

CELLULAR AND MOLECULAR BIOLOGY

Cell Lines

Before the development of stable cell lines derived from human lung carcinomas, cellular and molecular biology of lung cancer progressed slowly. A few lung cancer cell lines were established in the 1960s. An SCLC cell line was developed and reported in 1977 to have neuroendocrine secretory granules and secrete vasopressin into the culture media (35). Investigators at the NCI-Navy Medical Oncology Branch developed serum-free media that support growth of both SCLC and NSCLC cell lines and established $\sim$ 300 such cell lines that have been invaluable tools for the analysis of lung cancer cell and molecular biology (36–38).

One early (1979) attempt at unravelling the genetic basis of lung cancer biology was a somatic cell genetic approach in which human lung cancer $\times$ mouse somatic cell hybrids were analyzed in a manner similar to the classic studies of Harris (39, 40). Specific human chromosomes associated with agarose clonability or tumorigenicity in nude mice were not identified. As molecular biology developed, however, there was more success in understanding the molecular basis of tumor characteristics. Gene amplification of dihydrofolate reductase, as denoted by the presence of double minute chromosomes, was correlated with sensitivity to methotrexate, in a study that presages the current ability to define sensitivity to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) (41).

The Chromosome 3p Deletion in Lung Cancer

Chromosomal alterations were critical in the discovery of oncogenes and tumor suppressor genes. In the early 1970s, leukemia- and lymphoma-specific translocations were identified, with subsequent identification of dominant oncogenes at the translocation breakpoints in the early 1980s (42, 43). Knudson published his seminal two-hit hypothesis regarding familial retinoblastoma in 1971. Subsequently, cytogenetic and loss of heterozygosity (LOH) analysis confirmed Knudson's hypothesis, and the Rb gene was cloned in 1986 (44, 45). Thus, when Whang-Peng reported, in 1982, that a chromosome 3p14–23 deletion was frequent in the common tumor SCLC, investigators thought that a major breakthrough was imminent (46). Initially, other groups were not able to replicate Whang-Peng's finding and the presence of the deletion remained controversial. Several groups applied the new molecular technique of LOH analysis on Southern blots to confirm the presence of the 3p deletion in SCLC (47, 48). Most surprising, however, was the report by Kok that both SCLC and NSCLC exhibit LOH, again demonstrating unexpected similarities shared by all common histologies of lung cancer (49). The identification of a lung cancer–specific deletion initially seemed to be a providential clue to the identification of a lung cancer tumor suppressor gene. The experimental approach was simple: identify genes within the deleted region, assay their expression in lung cancer cell lines, and those that were inactivated would be candidate tumor suppressors. Several such genes were identified, but lacked any likely tumor suppressor function (50–52). With time, it became apparent that the 3p deletion is quite large (likely encoding $>$ 1,000 genes), and that many of these are inactivated by gene methylation or other mechanisms. Infrequently, lung cancer cell lines exhibit homozygous deletions that are significantly smaller than the larger regions demonstrating simple LOH. These have been used to successfully restrict the numbers of candidate genes for analysis. A number of chromosome 3p genes that exhibit one or more characteristics consistent with tumor suppressor gene function have been identified and include FHIT, CACNA2D2, 101F6, NPRL2, RASSF1A, SEMA3B, SEMA3F, FUS1, DLEC1, RBSP3A, RBSP3B, and the retinoic acid receptor β (RAR-β). A thorough review of the lung cancer chromosome 3p deletion has recently been published (53). The history of investigation of the chromosome 3p deletion in lung cancer ranges from older experimental approaches such as somatic cell genetics to *in silico* gene identification made possible through the elucidation of the human genome sequence.

With the application of techniques more sensitive than traditional cytogenetics, such as comparative genomic hybridization and allelotyping, multiple additional chromosomal regions of genetic loss and amplification have been identified (54, 55).

Tumor Suppressor Genes Associated with Familial Cancer Syndromes and Lung Cancer

Known tumor suppressor genes associated with familial cancer syndromes were rapidly investigated in lung cancer. The Rb and p53 tumor suppressors were shown to be universally inactivated in SCLC and p53 is also frequently inactivated in NSCLC

(56, 57). Cyclin D1 is frequently overexpressed in NSCLC, with inactivation of the cyclin-dependent kinase inhibitor p16, providing an alternative mechanism of overriding Rb function in regulating the cell cycle (58). The von Hippel Lindau gene encoded by chromosome 3p24 frequently exhibits LOH, but second inactivating mutations are quite rare (59).

Epigenetic Gene Inactivation in Lung Cancer

Baylin and colleagues in 1986 described hypermethylation of the 5′ region of the calcitonin promoter in SCLC and lymphomas, whereas in medullary carcinoma of the thyroid, characterized by high calcitonin production, the 5′ region of the calcitonin gene is hypomethylated (60). Subsequently, the same investigators demonstrated that regions of chromosome 11p containing tumor suppressor genes are hypermethylated, suggesting that hypermethylation is one mechanism of gene inactivation in human tumors (61). Initial methylation studies were performed using Southern blotting after digestion with methylation-specific restriction enzymes. Later, DNA sequencing after bisulfite treatment was used, followed subsequently by a PCR-based test detecting sequence differences between methylated and unmethylated cytosines (62). The latter PCR test is truly a "needle in the haystack" detection method that could potentially detect early tumors in highly contaminated fluids such as sputum (63).

Application of Known Oncogenes to Lung Cancer Biology

Cooper first used the NIH 3T3 focus assay in 1982 to identify the activated K-ras oncogene in lung cancer cell lines (64). Transforming K-ras oncogene mutants have been determined to be present in a significant portion of human adenocarcinomas of the lung. Of interest, ras mutations are not found in SCLC and transfection of SCLC cell lines with activated ras results in loss of neuroendocrine characteristics (65).

The c-myc, N-myc, and L-myc oncogenes were found to be amplified in some SCLC cell lines, and myc amplification was correlated with a more aggressive variant SCLC morphology. Most myc-amplified cell lines were established from recurrences after chemotherapeutic treatment (66–69).

Autocrine Growth Factors

Expression of neuropeptides with growth factor activity was described in SCLC in the more than 25 years ago (35, 70, 71). Shortly after Sporn and Todaro's description of the autocrine growth factor concept, gastrin-releasing peptide was demonstrated to be an autocrine growth factor in SCLC xenotransplants into nude mice, providing the first validation of an autocrine growth factor in a human tumor (72, 73). The anti-bombesin/gastrin-releasing peptide monoclonal antibody used in these experiments was subsequently assessed in a clinical trial; one subject had a short-lived complete response, but the outcome was otherwise not encouraging (74). Bombesin-like peptides, likely accompanied by other bioactive peptides, are elevated in the bronchoalveolar lavage and urine of smokers and may play a role in tumor promotion (75, 76).

Neuropeptide antagonists have been developed and tested for potential therapeutic use. Those antagonists that are specific for a single neuropeptide have not been active, but certain substance P and bradykinin derivatives exhibit a broad neuropeptide antagonism and induce apoptosis of both SCLC and NSCLC cell lines by a biased agonist mechanism (77–81). These are being further evaluated for clinical use.

Multiple neuropeptides, growth factors, and chemokines are either induced by tobacco smoking or are elevated in lung tumors and cell lines. The autocrine and paracrine effects of these multiple soluble factors in processes such as angiogenesis, tissue invasion, homing of metastases, and immune modulation has been reviewed (82).

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Todaro and colleagues initially demonstrated autocrine production of transforming growth factor-α by lung cancer cell lines and its binding to the EGFR in 1980 (83). Several groups subsequently described the patterns of expression of EGFR by various histologies of lung cancer. Mendelsohn developed monoclonal antibodies to the EGFR and assessed their use in clinical trials beginning in 1988 (84). Small molecule inhibitors of the EGFR TK, gefitinib and erlotinib, have been developed and entered into clinical trials since 2000 (85). In a substantial minority of patients, these agents result in remarkable clinical responses, whereas the majority of patients do not have a significant benefit. Mutations affecting regulatory portions of the EGFR have been identified in tumors responding to EGFR TKIs (86, 87). Clinical features correlating with EGFR TKI response include never-smoker status, female sex, East Asian ethnicity, and adenocarcinoma histology (88). K-ras mutation and EGFR mutation appear mutually exclusive. However, mutation is not perfectly predictive of EGFR TKI sensitivity. Amplification of the EGFR gene, as well as increased expression by immunohistochemistry, are also predictive and provide complementary information to mutational analysis (89). Finally, the presence of phosphorylated AKT, a downstream target of the EGFR pathway, but not phosphorylated MAPK, predicts EGFR TKI sensitivity (90). Gene expression and proteomic profiles predictive of EGFR TKI sensitivity are being developed as an alternative strategy. This body of work is the first demonstration in lung cancer that rationally targeted therapy, based on signaling pathways known to be dominant in these tumors, can be successful in treating selected patients. We now have logical tests that predict treatment response. The expectation is that further understanding and exploitation of growth factor or oncogene addiction in specific tumors will take us beyond the therapeutic plateau we have now reached with cytotoxic chemotherapy.

Gene Expression Profiling

In an early use of gene expression profiling of lung tumors, Gabrielson determined that SCLC cell lines were more similar to cultured human bronchial epithelial cells than to carcinoid cell lines, whereas carcinoids were similar to brain tumors (91). This suggested that SCLC is not closely related to carcinoids or brain tumors. Additional groups have now used gene expression profiling to attempt to derive patterns classifying tumors on the basis of cell type, tissue of origin, prognosis or drug sensitivity (92, 93). Gene expression profiling has been used as a discovery tool for early detection biomarkers and for genes induced by cigarette smoking (94, 95).

Proteomic Analysis

In 1982, Baylin and colleagues used two-dimensional gels to describe cell membrane proteins that distinguish SCLC from NSCLC (96). Monoclonal antibodies have since been used for similar classification purposes, some of which are clinically useful. More recently, proteomic methodology has progressed significantly and a number of interesting applications are being assessed to classify tumors based on cell type, prognosis, and drug sensitivity, as well as to develop early detection markers in peripheral fluids, such as serum or urine (97, 98).

Animal Models

A number of animal models for lung cancer have been developed. Benfield and coworkers used radioactive or carcinogenic

tracheal implants in beagles and hamsters to induce squamous cell carcinomas (99). An early report of experimental induction of lung tumors in mice appeared in 1950; by the mid-1960s, multiple chemical- and radiation-induced murine models had been described (100). Chemically induced tumors can be produced using various carcinogens, such as urethane or ethyl carbamate, which results in oncogenic K-ras mutations (101). Initiation promotion models, such as 3-methylcholanthrene followed by butylated hydroxytoluene, appear to be dependent on the induction of pulmonary inflammation by the latter agent (102). The induction of lung tumors by tobacco smoke has been and remains difficult, but Witschi and colleagues developed a model in which the mice are removed from tobacco smoke for the last portion of the procedure, which appears to be critical for tumor development (103). Murine models have been used to assess the potential carcinogenicity of chemicals, as well as to provide preclinical evaluation of chemopreventive strategies. All of these models have resulted in pulmonary adenomas with histologic, biochemical, and gene expression similarities to human bronchioloalveolar carcinoma or adenocarcinoma.

Transgenic models resulting in adenocarcinoma in mice have been developed initially using targeted expression of portions of the SV40 genome and subsequently expressing activated K-ras (104–106). As more is understood regarding the molecular changes that lead to lung cancer, murine models are being developed to more faithfully model this process. Transgenic models have also been used to model chemopreventive therapies, avoiding problems with dosing and pharmacokinetics (107).

Although the above models have resulted in adenomas or adenocarcinomas, only recently have murine models for squamous cell lung cancer and SCLC been developed (108, 109). The SCLC model is particularly compelling, as it results from dual inactivation of Rb and p53 tumor suppressor genes, parallel to human SCLC, and exhibits early and widespread metastases.

PREMALIGNANT EVOLUTION OF LUNG CANCER

Field Cancerization

In a landmark 1953 report, Slaughter and coworkers described the field cancerization concept (110). They reviewed the pathology of 783 patients with oral cancer and found that two independent squamous cell carcinomas were present in 88 subjects (11%) within this group. In addition, in all patients, carcinomas were surrounded by abnormal, hyperplastic, and dysplastic epithelium. This lead Slaughter and colleagues to suggest "a regional carcinogenic activity of some kind, in which a preconditioned epithelium has been activated over an area in which multiple cell groups undergo a process of irreversible change toward cancer," and to postulate that this was an important factor in the persistence or recurrence of squamous cell carcinomas following therapy. The field cancerization phenomenon has been since shown to occur in lung carcinogenesis as well, with frequent occurrence of multiple primary tumors or development of second primaries after treatment. Slaughter and coworkers initially assumed that exposure to a carcinogenic agent explained field cancerization, and this is certainly true in part, as tobacco smoke is an extraordinarily potent carcinogen that is directly applied to the respiratory epithelium. However, with the advent of molecular techniques, field cancerization has become more fully understood. Initially, resected lung tumors were examined for genetic lesions, such as chromosome 3p or 17p (p53 locus) LOH (111, 112). The abnormal, non-neoplastic, epithelium at the resection margin has been reported to contain mutations, either LOH or p53 mutations, similar to those within the tumor. A statistically robust analysis has demonstrated that allele-specific LOH (termed "allele-specific mutation") is shared between resected tumors and non-neoplastic epithelium at the resection margin more frequently than would be expected by chance alone (113). Wistuba has analyzed resected adenocarcinomas for EGFR mutations and found occasional cases in which the same mutation occurs in adjacent bronchial epithelium, again supporting the concept that lung tumors arise from a larger clonal field of mutated epithelium (I. Wistuba, personal communication). Recently, gene methylation analysis has also shown epigenetic alterations shared between resected tumors and non-neoplastic epithelium at the resection margins (114). Another mechanism of field carcinogenesis is mutation affecting an epithelial stem cell that subsequently disperses throughout the airway epithelium. A case in which a dominant-negative p53 mutation found in a minority of bronchial epithelial cells dispersed throughout multiple sites in both lungs, but in no other organs, has been reported, demonstrating this to be a potential additional mechanism for multiple primary lung tumors (115). Thus, at least three plausible mechanisms for field cancerization have some support: direct exposure of the aerodigestive epithelium to high concentrations of multiple carcinogens, expansion of mutated clones of respiratory epithelium, and widespread dispersal of mutated epithelial stem cells within the respiratory epithelium.

Bronchial Epithelial Damage in Smokers

In 1956, Oscar Auerbach and colleagues published the first of a series of careful histologic investigations of the effects of tobacco smoke exposure on airway epithelium (116). The histologic grading system used was somewhat different than the current WHO/IASLC grading system, but many of these findings from rapidly processed autopsies are still highly relevant (21). Auerbach and coworkers found that the histologic changes in airway epithelium of patients with lung cancer were similar to those of smokers, supporting the etiologic effect of smoking. A dose–response relationship between smoking and histologic changes was apparent, and effects of age, sex, and urban/rural environment described (117). Auerbach and colleagues described less severe histologic changes in females, after controlling for smoking intensity, and suggested that females may be less susceptible to lung cancer (118). We now know that this is not the case; whether females are more susceptible than males is currently debated (119). Auerbach and colleagues also described progressive improvement in histologic characteristics of bronchial epithelium in ex-smokers.

Cytology was applied to bronchial secretions in the early 1950s. Saccomanno, a pathologist in private practice in Grand Junction, Colorado, observed an increased incidence of lung cancer in uranium miners and studied sequential changes leading to carcinoma in classic studies beginning in the 1960s (120, 121). Of interest, Saccomanno found that subjects exfoliated severe atypia or carcinoma *in situ* sputum for 4–10 yr before invasive lung cancer became apparent. These cytologic studies, on the background of Auerbach and coworkers' descriptions of premalignant airway epithelium, have provided the best evidence of stepwise premalignant progression of squamous cell carcinoma in humans.

With the advent of autofluorescence bronchoscopy and demonstration that this technology allows more accurate detection of premalignant lesions, studies previously limited to autopsies or resection specimens can now be extended to cohorts of patients who can be serially followed (122, 123). Several pioneering small studies of the evolution of dysplastic lesions have been published, but the data are limited and somewhat contradictory (124, 125). Although the value of various grades of sputum cytologic atypia in determining relative risk of lung cancer development has been established in prospective cohort studies, no similarly robust analyses exist for varying degrees of premalignant

endobronchial histology (126). Severe atypia sputum cytology has been reported to have a 40–50% risk of developing lung cancer within 2 yr, but the risk for severe atypia bronchial histology does not seem to be as highly elevated (personal observation).

There is much less known in regard to the precursor lesions for adenocarcinoma and SCLC. Shimosato and coworkers described atypical adenomatous hyperplasia as a precursor lesion for bronchioloalveolar carcinoma in 1990 (127). With increased discovery and resection of small peripheral nodules and ground glass opacities on CT scans, a better understanding of the natural history of peripheral adenocarcinoma and bronchioloalveolar carcinoma will likely follow. The precursor lesions for SCLC are almost completely unknown; the rare disorder diffuse idiopathic pulmonary neuroendocrine cell hyperplasia is associated with pulmonary carcinoids, not SCLC (128, 129). Molecular analysis of preneoplastic epithelium in patients with SCLC reveals more extensive DNA changes than in patients with squamous cell or adenocarcinoma, suggesting that the developmental pathways for these different cell types may differ (130).

Molecular analysis of central airway epithelium, most relevant to squamous cell carcinogenesis, began in the early 1990s (111, 131). Early reports that chromosome 3p LOH could be detected in premalignant dysplasias engendered significant excitement, as this appeared likely to be an ominous biomarker. Additional careful systematic studies demonstrated that 3p LOH occurred frequently in individuals with trivial smoking histories, making this a less robust biomarker of cancer risk (132). Extensive data regarding genetic, epigenetic, and proteomic changes in premalignant bronchial epithelium is being developed and sequential steps in the evolution of lung cancer described (133–138). It is clear that multiple clonally expanded groups of epithelial cells are present in the airway epithelium of smokers and that more advanced histologic lesions have accumulated more alterations. Lung cancer requires significantly more genetic events to develop than do childhood tumors. Unfortunately, we do not have highly predictive molecular biomarkers of lung cancer development at the present.

PREVENTION

As increasing numbers of individuals stop smoking, the burden of lung cancer shifts to ex-smokers (139). Chemoprevention of lung cancer is now assuming greater importance, as it is apparent that ex-smokers are not completely protected. Sporn and colleagues first used the term chemoprevention in 1976 and described retinoids as promising agents for several malignancies, including lung (140). Successful chemoprevention in mice has been achieved with nonspecific, but not COX-2–specific, COX inhibition, farnesyltransferase inhibition, glucocorticoids, 5-lipoxygenase inhibition, prostacyclin synthase overexpresssion, a prostacyclin analog (iloprost), and other strategies (141). Although effective in a preclinical model, inhaled budesonide was not promising in an initial intermediate endpoint biomarker trial (142). Iloprost is being evaluated in an intermediate endpoint chemoprevention trial performed by the Lung Cancer Biomarkers Chemoprevention Consortium, a group consisting of the SPOREs in Lung Cancer, and single institution trials of COX-2 inhibition are ongoing (143). Although preclinical testing of chemoprevention agents in murine models is potentially useful, we do not know if this will eventually lead to the development of effective human strategies for lung cancer chemoprevention.

In 1982, Saccomanno and coworkers published a small pioneering chemoprevention study of 13-*cis* retinoic acid, assessing sputum atypia as an intermediate endpoint, which demonstrated feasibility, but no therapeutic effect (144). McLarty and colleagues reported similar results in a larger study published in 1995 (145). Initial encouraging results of small secondary prevention chemoprevention trials using retinoids gave support to large, prospective randomized controlled trials (146). More recently, two large chemoprevention trials assessing β-carotene and retinol have demonstrated a harmful effect, with 15–35% more lung cancers in the treatment group (147, 148). Although this has been very discouraging, the development of effective lung cancer chemoprevention remains an important goal, and many different strategies appear promising.

CONCLUSION

Tremendous progress in understanding the pathogenesis of lung cancer has occurred over the past century. The lag between translation from the basic science laboratory to clinical application is decreasing. There is no better example of this than the recent ability to predict response to EGFR TKIs. However, this progress has not yet resulted in major changes in lung cancer mortality rates.

Conflict of Interest Statement: Y.A.M. was site PI for a multi-center trials sponsored by Xillix, Inc. ($39,000) in 2003, Peceptronix, Inc. ($87,000) in 2004 and a single site trial sponsored by SomaLogic ($60,000) in 2004.

Acknowledgments: Paul Bunn, Wilbur Franklin, Adi Gazdar, Fred Hirsch, Robert Keith, and John Minna provided helpful discussions of their perspectives on what have been the major advances in this area.

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