Editorial

Lung Cancer Prevention: Retinoids and the Epidermal Growth Factor Receptor—A Phoenix Rising?

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The widespread use of tobacco in the 20th century has resulted in a lung cancer epidemic extending into the 21st century. Worldwide, >1.3 million lung cancer-related deaths are expected in 2001. In the United States, there will be an estimated 157,400 lung cancer-related deaths in the year 2001, accounting for 28% of all cancer deaths (American Cancer Society statistics). Despite improved methods of lung cancer detection and technical advances in local and systemic treatment modalities, modest progress has been made in the outcome for patients diagnosed with lung cancer. The 5-year survival rate for all stages of lung cancer combined was 5% in the 1950s compared with 14.5% for 1992–1997 (1, 2).

These sobering data have led to a greater emphasis on public health and research strategies to prevent lung cancer, either by removing tobacco carcinogens through smoking cessation or by a pharmacological attack aimed at the multistep tumorigenic process caused by tobacco carcinogens. This latter approach, better known as chemoprevention, has been characterized by a mixture of successes and failures in regard to tobacco-related epithelial cancers. Specifically, the use of the selective retinoid 13 cis-retinoic acid is effective in the treatment of oral premalignant lesions and the prevention of second primary head and neck cancers (3). However, this treatment has been associated with considerable toxicity precluding chronic administration, and efficacy is not sustained on discontinuation. Furthermore, in several clinical trials, retinoids, α-tocopherol, and β-carotene have either not been shown to be effective or have shown possible harmful effects in the chemoprevention of NSCLC (4, 5).

Lonardo et al. (6) use RA as a tool to demonstrate the potential importance of the EGFR as a chemoprevention target in lung cancer. Using an in vitro model of human bronchial carcinogenesis, RA blocked the cellular phenotypic change of increased EGFR expression and signal activation resulting from transformation with the carcinogen N-nitrosamine-4-(methylamino)-1-(3 pyridyl)-1-butanone. This decrease in EGFR expression was attributable to the transcriptional down-regulation of EGFR expression by RA (Fig. 1). These results agree with other studies that have described the effects of retinoids on the transcriptional regulation of the EGFR promoter leading to suppression of the growth of tumor cells (7–10). The current study additionally suggests that RA-inhibited cyclin D1 regulation of mitogenesis occurs through two independent mechanisms: (a) post-transcriptional proteasome-dependent proteolysis (11, 12); and (b) decreased EGFR transcription leading to reduced cyclin D1 expression (Fig. 1).

The results of the present study build on earlier work pointing to the importance of the EGFR in the pathogenesis of NSCLC and the potential for this transmembrane receptor tyrosine kinase as a target for chemoprevention of this disease. Rusch et al. (13) first demonstrated that the EGFR was overexpressed in NSCLC tissue compared with adjacent normal lung, with overexpression in 45% of tumors. Subsequent studies implicated the EGFR in bronchial metaplasia (14) and in the development of lung cancer rather than in tumor progression (15, 16). EGFR expression has been shown to correlate with poor prognosis in patients with p53 overexpression (17) or high coexpression of HER-2/neu (18).

Activation of the EGFR pathway may be involved in several aspects of cellular carcinogenesis and growth. Binding of a ligand (such as epidermal growth factor or transforming growth factor-α) to the extracellular domain causes receptor dimerization and subsequent autophosphorylation of the intracellular tyrosine kinase domain, initiating a cascade of events (Fig. 1). The RAS/mitogen-activated protein kinase cascade is important in carcinogenesis, leading to increased mitogenesis via induction of cyclin D1. Additionally, EGFR is implicated in the control of tumor cell apoptosis, angiogenesis, and metastasis (19). Additional studies show that the EGFR activation can promote the release of vascular endothelial growth factor (20, 21), a key promoter of angiogenesis, and the ability of cancer cells to metastasize (22).

The importance of EGFR biology to the cancer process has been realized by the availability of targeted EGFR therapies that inhibit activation of the signal transduction pathway and thereby inhibit mitogenesis and other cancer-promoting processes (23). Monoclonal antibodies, such as C225 (24), that prevent ligand-dependent activation and small molecules such as ZD1839 (“Iressa”; Ref. 25) and OSI-774 (26), that selectively inhibit the intracellular tyrosine kinase domain of EGFR, are well tolerated after chronic administration and have shown regression of tumors in patients with tobacco-related head and neck cancer and NSCLC, respectively. Multicenter Phase III trials of ZD1839 in combination with standard chemotherapy and Phase II trials of ZD1839 monotherapy in patients with advanced NSCLC are nearing completion.

In the present report, Lonardo et al. (6) used a retinoid to demonstrate the importance of EGFR expression and signal activation in bronchial carcinogenesis. The data might have
been even more compelling if additional experiments with a small molecule EGFR inhibitor such as ZD1839, alone and in combination with RA, showed significant inhibition of the activated pathways associated with the transformed cell phenotype and its proliferation. Nonetheless, their findings have exciting implications for clinical lung cancer prevention given the availability of these promising EGFR tyrosine kinase inhibitors. In contrast with retinoids that have relatively narrow therapeutic margins, EGFR tyrosine kinase inhibitors have been well tolerated for long durations in early clinical trials (25, 26). These findings have provided the rationale for a multi-institutional Specialized Programs of Research Excellence Phase III trial of ZD1839 versus placebo in former/current smokers with a previous history of cancer as a pilot trial of lung cancer prevention (Fig. 2). Additionally, as suggested by Lonardo et al. (6), combining an EGFR tyrosine kinase inhibitor with a selective retinoid may result in additive therapeutic effects because of the distinct ways in which these treatments regulate cyclin D1. This additive effect may allow for lower, nontoxic doses of both agents to be administered when given together in contrast with doses required as single agents.

Thus, from the ashes of the failure of retinoid chemoprevention of clinical lung cancer may rise the phoenix of EGFR tyrosine kinase inhibition to realize meaningful chemoprevention of this devastating disease. The results of future basic and clinical studies to test this hypothesis will be awaited with keen anticipation.

Fig. 1 Effects of RA on EGFR expression and EGFR-associated transcriptional and post-transcriptional events.

Fig. 2 Proposed schema for Specialized Programs of Research Excellence Phase IIB/III trial of ZD1839 versus placebo in former/current smokers.

References

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