Molecular Targeting: the New Challenge in Lung Cancer Prevention

Ugo Pastorino

Negative results from large-scale clinical trials (1–3) have resulted in a general skepticism toward lung cancer chemoprevention in humans. One has to consider, however, the enormous difficulties that clinicians encountered in their early attempts to counteract lung carcinogenesis, including attempts at intervention in individuals with decades of intense smoking exposure, or even during active smoking, using single chemopreventive agents that had limited proven efficacy and substantial side effects.

From this first generation of clinical trials, we have learned that retinoids may be active only at relatively high doses, where toxicity becomes a limiting factor, and their biologic effect, when clinically detectable, is not permanent (4). For example, neither the reversal of oral premalignancy nor the reduction in the incidence second primary cancers was sustained after retinoid treatment was discontinued (5,6). This phenomenon is indicative of phenotypic growth suppression without the concomitant eradication of neoplastic clones. Moreover, the number of individuals who had to be treated and tested for a long period of time was large given the relatively low underlying cancer incidence, which was only 0.5% per year in heavy smokers (1,2) and up to 2% per year in prior lung cancer patients (7). Nonetheless, the fundamental achievements of such chemoprevention trials were their contributions to our understanding of the preclinical phases of lung cancer and the identification of biomarkers relevant to field carcinogenesis (8). Knowledge of the molecular targets of chemopreventive agents represents the most valuable byproduct of otherwise “negative” studies and provides a basis for future research extending from early detection to pharmacologic intervention and gene therapy.

In this issue of the Journal, Soria et al. (9) report on the ability of N-(4-hydroxyphenyl)retinamide (4-HPR) to reduce the expression of human telomerase reverse transcriptase catalytic subunit (hTERT) in bronchial biopsy specimens obtained from heavy smokers enrolled in a double-blind chemoprevention trial (10). The authors reported that the reduction in hTERT messenger RNA (mRNA) expression after 6 months of 4-HPR treatment compared with baseline values in the 4-HPR arm or post-treatment values in the placebo arm was statistically significant when the analysis was based on biopsy sites (P = .01) but not when the analysis was based on individual participants (P = .37). Of interest, there was no relationship between the modulation of hTERT expression and other histopathologic features, such as the presence of squamous metaplasia or Ki-67 expression. Moreover, it appears from the first report of the same chemoprevention trial (10) that 4-HPR did not alter the levels of retinoic acid receptor (RAR)-β mRNA in the bronchial epithelium as was observed after 13-cis-retinoic acid administration with a similar trial design (11). These results highlight a new and possibly RAR-independent molecular mechanism of action of 4-HPR against telomerase. In the chemoprevention trial (10), 4-HPR was unable to reverse metaplasia or dysplasia. However, it is possible that the significant reduction of serum retinol levels may have altered the overall effect of 4-HPR treatment.

Although several studies (12–14) have explored the role of telomerase activation in lung cancer, the report by Soria et al. demonstrates that telomerase activation is a frequent event in the bronchial epithelium of chronic smokers, regardless of its histopathologic appearance. Their results also suggest that hTERT may represent a specific molecular marker for the detection of preinvasive disease in early lung carcinogenesis and a potential intermediate biomarker to evaluate the efficacy of chemopreventive agents. It has long been clear that a single biomarker could not play the leading role in a process that was as heterogeneous as lung carcinogenesis. Rather, it appears more likely that a panel of molecular markers will be required to meet the goals of preclinical detection, to select high-risk individuals for chemoprevention, and to monitor intermediate time points for treatment effect.

In addition to hTERT expression, the expression of other promising biomarkers, such as p53 (15,16), p16 (17), Fhit (18), EGFR (19), and RAR-β (20), needs to be concurrently validated in future intervention trials. Specifically, the triad of suppressor genes (i.e., p53, p16, and FHit) offers the opportunity to explore new targeted intervention schemes by use of a gene therapy approach. A pilot study using adenovirus-mediated p53 gene transfer in advanced lung cancer has proven that such an approach is feasible and has limited toxicity (21). Preclinical studies (22) have shown that adenovirus-mediated p16 gene transfer may be effective for treating ovarian cancer and, perhaps, even more effective than adenovirus-mediated p53 gene transfer in inhibiting the growth of tumor cell lines in vitro and xenografts in vivo. Ji et al. (23) observed that adenovirus-mediated FHit gene transfer into human lung cancer cell lines that have lost Fhit expression induced apoptosis and inhibited tumorigenicity and tumor growth in nude mice (23). More recently, gene therapy with adenoviral and adeno-associated viral vectors expressing Fhit has been applied to heterozygous Fhit(+-) knockout mice treated with chemical carcinogens. Mice exposed to carcinogen while receiving viral vectors expressing the human Fhit gene were protected from tumor development (24). These studies suggest that gene transfer could be a novel clinical approach not only in the management of invasive disease but also in lung cancer prevention. Pulmonary delivery of gene therapy, alone or in combination with other agents, represents another challenge in lung cancer research.

In conclusion, the study by Soria et al. (9) represents an outstanding contribution to translational research in the field of chemoprevention. The value of hTERT expression and modula-
tion should be further explored in future chemoprevention trials, possibly in combination with other molecular markers, such as those encoded by tumor suppressor genes.

REFERENCES