Editorial

Aerosolized Delivery and Lung Cancer Prevention: Pre-Clinical Models Show Promise

Michael J. Spinella and Ethan Dmitrovsky

Chemoprevention is an appealing approach to treat lung cancer, a major public health problem. The chemoprevention concept was first coined by Sporn et al. (1) as a framework for therapeutic interventions at early stages of carcinogenesis. These include the initiation, promotion, and progression stages of carcinogenesis (1). If chemoprevention is effective at these early stages, clinical consequences of invasive cancers might be averted or reduced. Proof of principle for clinical cancer chemoprevention was recently established for tamoxifen in breast cancer risk reduction (2). Given the high incidence and mortality of lung cancers and the lack of curative treatments for metastatic disease, effective prevention strategies are needed. Large populations of former and current smokers remain at risk for lung cancer and are candidates for clinical chemoprevention trials.

A strong rationale exists for use of the retinoids (natural and synthetic derivatives of vitamin A) in cancer prevention based on preclinical, epidemiological, and clinical findings (reviewed in Ref. 3). Preclinical studies, first reported by Wolbach and Howe in 1925 (4), indicated that vitamin A-deficient rodents developed squamous metaplasia. These metaplastic lesions were reminiscent of those found in smokers and were reversed by vitamin A repletion. Data derived from other experimental animal models revealed retinoid chemopreventive effects on the epithelium of various tissues after exposure to chemical mutagens (5). Epidemiological evidence indicated an inverse relationship between cancer incidence at specific sites and serum vitamin A or Β-carotene levels, as reviewed in Ref. 6. In vitro evidence indicates that retinoids prevent transformation of immortalized human bronchial epithelial cells (7). Taken together, these findings provided a basis for use of retinoids in clinical cancer prevention. Early trials using isotretinoin (13-cis retinoic acid) and other retinoids found reductions in second cancers of the head and neck, lung, and liver after retinoid treatments (reviewed in Ref. 8). These treatments had considerable vitamin Α-associated toxicities. Although Β-carotene and retinol are clinically well tolerated, several large-scale prevention trials of former or current smokers failed to show a clinical benefit in lung cancer reduction, especially in active smokers (Ref. 9; reviewed in Ref. 3). These findings may relate to a procarcinogenic effect of Β-carotene when combined with carcinogens present in cigarette smoke (10).

One limitation of retinoid-based lung cancer prevention is systemic vitamin Α-associated toxicities. This has led clinically to retinoid dose reductions and difficulties in administering potent retinoids on a chronic basis in prevention trials. Approaches to overcome this problem include development of retinoid receptor-selective agonists with reduced toxicity and using retinoids in combination with other classes of preventive agents. The report by Dahl et al. (11) in this issue of Clinical Cancer Research provides preclinical evidence for an alternative strategy to overcome retinoid toxicities in lung cancer prevention. The strategy involves local delivery of retinoids directly to lung tissue through aerosolized administration. This pilot study demonstrates that aerosolized retinoids retain at least some of the antitumorigenic properties of p.o. administered retinoids in experimentally induced tumor models. This strategy may be applied to other known or putative classes of preventive agents (8). Whether this strategy increases the therapeutic window of retinoids or other agents awaits future preclinical and clinical studies.

Oral retinoid administration may limit delivery to lung tissues. Contributing factors include extensive binding of retinoids to albumin and other serum proteins and marked enterohepatic clearance of retinoids (12, 13). The advantage of aerosolized delivery is the potential for drug to be deposited more uniformly over the respiratory tract, leading to local tissue levels that may far exceed those achieved with systemic administration (14). Another potential advantage is that low retinoid levels would enter the systemic circulation with aerosolized delivery, limiting the vitamin Α-associated toxicities that restrict the clinical use of retinoids (6).

Dahl et al. (11) use isotretinoin, which was previously shown to reduce the occurrence of second aerodigestive tumors in surgically resected head and neck cancer patients (15). The animal model used is the male A/J mouse strain that is prone to chemically induced lung hyperplasia and adenomas. Mice were individually exposed to the carcinogen urethane, a common experimental lung carcinogen, or benzo(a)pyrene or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, major carcinogens in tobacco smoke. Aerosolized isotretinoin was subsequently administered for up to 16 weeks. For these carcinogenic exposures, mice exposed to the highest isotretinoin dosages showed reductions of tumor formation of 56–80% as compared with vehicle controls. Similar protective effects were seen at the intermediate isotretinoin dosage for benzo(a)pyrene- and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced tumors. Generally, the number of hyperplastic lesions increased with isotretinoin treatment, suggesting an arrest of progression. Notably, even the highest dosage of inhaled isotretinoin represented less than 1% of the prior effective oral dosage of retinoids in this model (5). Consistent with the potential benefit of targeted aerosolized delivery, these authors establish that RARs

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[2] The abbreviation used is: RAR, retinoic acid receptor.
are induced in lung tissue after retinoid inhalation, indicating successful delivery of active retinoids to this target tissue. Comparison of single-cell RAR expression will more precisely define retinoid delivery throughout the lung tissue anatomy.

Aerosolized delivery, even in experimental cancer models, is challenging. Inherent limitations of these models may make extrapolation to humans difficult. For instance, there is a need for animal models that more precisely mimic clinical lung cancer (16). Although the A/J mouse is widely used, tumors in these mice do not histopathologically reflect clinical lung cancers. Also, because rodents are obligate nose breathers, inhaled retinoids are preferentially deposited in the nasal cavity. Dahl et al. (11) suggest that this leads to local toxicity unique to rodents. This toxicity is not anticipated to impact clinical application. It is important to note that considerable weight loss was observed in the present study, and several deaths occurred. Direct comparisons are needed between oral and aerosolized administrations to assess improvements in efficacy, toxicity, and patterns of lung delivery. Detailed studies defining the pharmacokinetics of inhaled preventive agents will determine optimal dosing and scheduling regimens. Direct measurement of retinoid concentrations by high-performance liquid chromatography in lung versus other tissues would be informative. Dahl et al. (11) discuss studies submitted for publication that demonstrate differential RAR activation in the lung but not in the liver during aerosolized administration of isotretinoin. In contrast, RAR activation occurred in the liver but not in the lung after oral administrations. In light of the observed weight loss with aerosolized retinoid delivery, it is prudent to confirm in this and other models the lack of apparent aerodigestive tract and systemic toxicity by conducting histopathological studies.

Another technical consideration is to optimize the formulation of retinoid-based aerosols. Considerations like particle size and choice of vehicle may be critical for optimal delivery deep within the bronchial airways. Dahl et al. (11) observe effects on weight and tumorigenicity even with vehicle treatments. Aerosols of liposomal formulations may prove especially effective in delivering highly lipophilic retinoids, as proposed recently (17). Perhaps the best indication of the promise of aerosolized delivery of prevention agents is the clinical experience with aerosolized drug delivery for asthma. Inhaled delivery of steroids and adrenergic drugs has improved asthma therapy by reducing treatment-limiting systemic toxicities. Interestingly, aerosolized administration of the glucocorticoid budesonide was recently shown to reduce lung tumor formation in A/J mice (18).

In conclusion, the study by Dahl et al. (11) provides proof of principle that retinoids can be delivered locally at low dosage without compromising immunotumorigenic responses. Additional preclinical studies are warranted to determine the efficacy and toxicity of the aerosolized approach. However, it is clear that it may be difficult to extrapolate these findings to the clinic. With inherent limitations evident in animal models, clinical trials are eventually needed to validate this therapeutic strategy. Localized delivery of preventive agents may open an exciting new phase in treatment of aerodigestive tract malignancies. Candidate cancer-preventive agents with potent in vitro activities but limiting systemic toxicities may become available for clinical use when administered via aerosolized delivery. Future work will determine the validity of this chemopreventive strategy.

References
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