Deguelin as a Chemopreventive Agent in Mouse Lung Tumorigenesis Induced by Tobacco Smoke Carcinogens

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In this issue of the Journal, Lee et al. (1) present interesting data on deguelin, a potential chemopreventive agent against lung tumorigenesis. This compound, isolated from several plant species, is already known to inhibit the PI3K–Akt pathway, to decrease expression of cyclooxygenase 2, and to induce apoptosis in premalignant and malignant human bronchial epithelial cells, with minimal effects on normal human bronchial epithelial cells. These are all potentially favorable properties with respect to chemoprevention. The study reported here demonstrates, in mouse models, that deguelin decreases expression of pAkt in lung and inhibits lung tumorigenesis induced by the tobacco smoke carcinogens benzo[a]pyrene (BaP) and 4-(methylnitrosamo)1-(3-pyridyl)-1-butanol (NNK), administered in combination. The effects were particularly striking considering the relatively low dose of deguelin, 4 mg/kg (approximately 0.2 μmol per mouse) twice a day, used in the chemoprevention study. Deguelin was effective when administered at the same time as BaP plus NNK or when given after carcinogen administration. An innovative aspect of this study was the use of microcomputed tomography image analysis to detect lung tumors in live mice.

Several chemopreventive agents have been tested in the BaP plus NNK mouse lung tumorigenesis model developed in our laboratory (2). Butylated hydroxyanisole (20 or 40 μmol per mouse) given by gavage before each dose of BaP plus NNK statistically significantly reduced lung tumor multiplicity (3). myo-Inositol, at 1% (10 000 ppm) or 0.5% in the diet, statistically significantly reduced lung tumor multiplicity when given during the carcinogen treatment period, and, at 1% in the diet, after carcinogen administration (4). Dietary 2-phenethyl isothiocyanate (PEITC) (163 or 498 ppm) or 3-phenylpropyl isothiocyanate (531 ppm) statistically significantly reduced lung tumor multiplicity when given during the carcinogen administration phase, as did a mixture of PEITC and benzyl isothiocyanate administered by gavage (12 μmol of each) 2 hours before each carcinogen treatment (5). Dietary N-acetyl-S-(N-2-phenethylthiocarbamoyl)-L-cysteine (PEITC-NAC), a major metabolite of PEITC, had similar efficacy as PEITC and was also shown to be effective when administered halfway through the carcinogen treatment phase (6). A mixture of PEITC-NAC and myo-inositol was effective when given at different times during or after carcinogen treatment (6). Moreover, dietary PEITC, PEITC-NAC, sulforaphane, and sulforaphane-NAC were recently shown to inhibit malignant progression to lung adenocarcinoma in this model (7). 1,4-Phenylenedis(methylene)selen enocyanate, given in the diet at 10 ppm selenium, statistically significantly inhibited lung tumor multiplicity when administered either during or after the carcinogen administration period (8).

Thus, deguelin joins several other agents shown to be effective at nontoxic doses in this model, but these studies were not discussed by Lee et al., nor were several other compounds that have been shown to inhibit lung tumorigenesis induced in A/J mice by BaP or NNK given individually (9–13). Some of these agents are in various stages of the pipeline toward eventual testing for chemoprevention of lung cancer in smokers and ex-smokers.

Although the lung tumor model used by Lee et al. (1) uses two important cigarette smoke carcinogens, BaP and NNK in combination, a cigarette smoke inhalation model might be more relevant for evaluation of chemopreventive agents in current and former smokers. Cigarette smoke inhalation models are plagued by various problems, but one model has been used with success in the past several years to evaluate potential chemopreventive agents. Witschi et al. (14) have shown that A/J mice treated with a mixture of 89% sidestream and 11% mainstream smoke for 5 months, followed by a 4-month recovery period, show a small but reproducible increase in lung tumor multiplicity. This model has been applied to evaluate the chemopreventive efficacy of several of the agents mentioned above, but only a combination of dexamethasone and myo-inositol has proven effective. A drawback of this model is that it is complicated by stress-induced inhibition of lung tumorigenesis (15). Furthermore, the responsible carcinogens in this model are gas-phase constituents, which contrasts with the established role of particulate-phase constituents in other smoke inhalation models and likely in humans (16–17). The first robust induction of lung cancer by cigarette smoke in a mouse model has recently been reported, and it might be of interest to test deguelin and other compounds in that system, although a relatively high cigarette smoke dose and lengthy exposure period are needed (18).

The proposed mechanism of inhibition of lung tumorigenesis by deguelin through inhibition of Akt activation is plausible because NNK has been shown to activate this pathway (19). Activation of Akt by NNK occurs rapidly through nicotinic acetylcholine receptors, leading to phosphorylation of downstream substrates such as GSK-3, p70S6K, 4EBP-1, and FKHR. Active Akt has also been detected in airway epithelial cells and lung tumors from NNK-treated mice and in human lung cancers from smokers (19). This mechanism is particularly attractive to explain the inhibition of tumorigenesis observed when deguelin was tested as a suppressor, i.e., after carcinogen administration. When given concurrently with BaP plus NNK, deguelin may have other effects, such as inhibition of the cytochrome P450s that are involved in the metabolic activation of these carcinogens, induction of the phase 2 enzymes that are involved in carcinogen detoxification, or effects on DNA repair pathways.

An important concern about deguelin is its potential toxicity, although no toxic effects were reported in this study. As the authors note, deguelin is related to rotenone, which can inhibit NADH:ubiquinone oxidoreductase and can induce cardiotoxicity, respiratory depression, and blockade of nerve conduction. Deguelin is reported to be about half as active as rotenone in...
inducing a Parkinson’s disease–like syndrome in rats (20). The Merck Index states that deguelin irritates skin and may cause fatal pulmonary damage upon inhalation (21).

There is an urgent need to develop chemopreventive agents against lung cancer. Lung cancer will kill more than 160,000 people in the United States in 2005, with cigarette smoking responsible for about 90% of this toll (22). Progress in the development of effective therapeutic agents, although promising in this age of molecular targets, is still slow. Tobacco control is making slow but steady gains in the United States, but the National Institutes of Health target of 12% smoking prevalence by 2010 will not be reached, and the number of smokers continues to increase in many parts of the world (23–24). It is currently estimated that there are more than 1.2 billion smokers worldwide (24). Smoking cessation approaches are only moderately useful, with 1-year success rates of approximately 25% (25). The addictive power of nicotine and possibly other cigarette smoke constituents is not readily overcome, even with pharmacotherapy and counseling. Although the public health community has certainly not embraced the concept of chemoprevention in current smokers (26), it is imperative that we act to help those who cannot break the tobacco habit. Many would agree that chemoprevention is needed for ex-smokers, whose risk for lung cancer remains elevated for years after smoking cessation (27). Yet, there are currently no agents that have been shown to prevent lung cancer in either smokers or ex-smokers (28). The work reported by Lee et al., as well as that being carried out in other laboratories, holds some promise for new approaches to lung cancer chemoprevention.

REFERENCES