AKT and the Phosphatidylinositol 3-Kinase/AKT Pathway: Important Molecular Targets for Lung Cancer Prevention and Treatment

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The study by Chun et al. (1) in this issue of the Journal provides important evidence for both the involvement of the phosphatidylinositol 3-kinase (PI3K) signaling pathway in the early stages of lung carcinogenesis and the pharmacologic mechanism of deguelin in decreasing cancer-related increased AKT activity in the PI3K pathway. What makes these findings of great interest is the fact that there have been so few agents, natural or synthetic, tested to date that have shown potential to halt the progression of any form of lung cancer and that the authors have identified potential molecular targets for intervention in premalignant and malignant bronchial epithelial cells. As the type of cancer with the second highest incidence rate and the leading cause of cancer-related death in both men and women in the United States, lung cancer is an especially important area for prevention research. The pharmaceutical strategy described by Chun et al. (1) of molecularly targeted intervention is one approach being applied to lung cancer prevention. A related approach is improved early detection, and the National Cancer Institute recently initiated the randomized, controlled National Lung Screening Trial (NLST), an 8-year study comparing the effectiveness of low-dose spiral computerized tomography with standard x-ray in reducing lung cancer mortality among 50,000 current and former smokers. Effective early detection, intervention and, of course, decreased exposure to tobacco smoke and other toxicants are all important strategies that could potentially reduce lung cancer mortality.

The receptor tyrosine kinases were recognized as pharmaceutical targets many years ago, and inhibition of such kinases has been demonstrated to be an effective treatment strategy. Herceptin, targeting HER-2/neu, and Gleevec, targeting BCR-ABL, in breast cancer and leukemia, respectively, are drugs approved by the U.S. Food and Drug Administration. The current investigation by Chun et al. (1) characterizes the effect of deguelin on the inhibition of another kinase, AKT. What is important in the study by Chun et al. (1) is that deguelin effectively inhibits AKT in premalignant cells. According to Vivanco and Sawyers (2), cell surface activation of receptor tyrosine kinases leads to the intracellular formation of the receptor–PI3K complex and the phosphorylation of membrane phosphatidylinositol phosphates (PIP). Phosphorylation of PIP(4,5)P$_2$ at the 3-position of the inositol ring forms PIP$_3$. Dephosphorylation of PIP$_3$ is regulated by the tumor suppressor gene product PTEN. Binding of inactive AKT to PIP$_3$ leads to the phosphorylation and activation of AKT, also called protein kinase B. In turn, activated AKT can affect numerous cellular functions via intermediary molecules—including mTOR, NF-$\kappa$B (nuclear factor $\kappa$B), and p53—that control cell survival, proliferation, and growth and that are themselves molecular targets of interest for cancer prevention and treatment.

Chun et al. (1) derived several cell lines from simian virus 40-immortalized human bronchial epithelial (HBE) cells. These cell lines represented premalignant and malignant HBE cells and were evaluated along with normal HBE (NHBE) cells. Chun et al. (1) demonstrate that the level of activated phosphorylated AKT is higher in premalignant and malignant cells than in NHBE cells, that deguelin can inhibit cell proliferation by blocking cells in the G$_2$/M phase of the cell cycle, and that deguelin can increase apoptosis in premalignant and malignant cells at concentrations that are not toxic to NHBE cells. These effects could be overcome by infection with an AKT-expressing adenovirus. PI3K activity was also reduced in the premalignant cell line by deguelin, and AKT activity was still reduced 14 hours after exposure when PI3K activity was still high, suggesting that deguelin inhibits AKT possibly by both PI3K-dependent and PI3K-independent pathways. The effects of deguelin appear specific to the PI3K pathway because basal levels of unphosphory-
lated and phosphorylated P44/42 mitogen-activated protein kinase (MAPK) activity in the RAS pathway were similar among the cell lines, and deguelin did not affect insulin growth factor I-stimulated extracellular signal-related kinase 1/2 (ERK1/2) and Jun-N-terminal kinase (JNK) activity in the MAPK and stress-activated kinase pathways, respectively.

Deguelin, identified by a bioassay-guided fractionation of plant extracts (3), has cancer preventive activity, primarily attributable to antiproliferative effects from an inhibition of ornithine decarboxylase in rodent models of skin and mammary carcinogenesis (4). Deguelin is a rotenoid derived from plant roots. Rotenone and rotenoid-containing botanicals are important insecticides and fish poisons that act by inhibiting NADH:ubiquinone oxidoreductase, an enzyme complex in mitochondrial oxidative phosphorylation (5). Rotenone blocks electron transfer between NADH and coenzyme Q and is associated with cardiotoxicity, respiratory depression, and nerve conduction blockade at high doses (LD₅₀ [dose that is lethal to 50% of those exposed] = 10–100 g in humans) (6). The study by Chun et al. (1) characterizes the mechanism of action of deguelin in vitro at concentrations of 10⁻⁹ M to 10⁻⁷ M. The bioavailability, broad tissue distribution, and approximately 9-hour half-life reported in the preclinical in vivo pharmacokinetic study of deguelin suggest that the effects described in vitro by Chun et al. (1), most convincingly at concentrations of 10⁻⁷ M, may be attainable in vivo (6). Additional development will be required to evaluate any potential systemic toxicity of deguelin per se as a possible lung cancer prevention and treatment drug, and structure–activity evaluations of analogs of the rotenoid chemical class are warranted. One approach in the continued development of deguelin as a drug will be to investigate aerosolized topical delivery. The primary advantages of such an approach would be to lower the dose and to improve the margin of safety.

The study by Chun et al. (1) highlights AKT and the PI3K/AKT pathway as important targets that can be modulated for lung cancer prevention and treatment and nominates deguelin for further drug development. These exciting in vitro results should be extended by using animal models to provide in vivo evidence of efficacy, possibly to prevent early disease progression and to increase the effectiveness of chemotherapy and radiation therapy. Additionally, the observation that AKT is constitutively active in premalignant and malignant HBE cell lines, but not in the NHBE cell line, must be confirmed in clinical biopsy specimens. Interestingly, West et al. (8) have recently reported that AKT is activated in nonimmortalized human airway epithelial cells in vitro by exposure to the tobacco constituents nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Lung cancer will claim the lives of more than 150,000 men and women this year. It is urgent that promising agents acting through such molecular targets be developed rapidly and brought to clinical testing.

REFERENCES