Teaching an Old Drug New Tricks: Metformin as a Targeted Therapy for Lung Cancer

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Identifying novel drugs for treatment of lung cancer remains of utmost importance, and, in recent years, targeted therapies have been acknowledged as particularly attractive. Metformin, a commonly prescribed oral hypoglycemic agent, has known effects on the mammalian target of rapamycin pathway, ultimately resulting in downstream inhibition of cellular growth and proliferation. In a recent article (Memmott RM, Mercado JR, Maier CR, et al: Metformin prevents tobacco carcinogen-induced lung tumorigenesis. Cancer Prev Res (Phila) 3:1066-1076, 2010), Memmott et al assessed the utility of metformin in an in vivo model of tobacco carcinogen-induced lung cancer. The authors show that tumor burden is decreased in animals administered metformin, suggesting that this drug may have promising potential for the treatment and chemoprevention of lung cancer.

The discovery of novel anticancer drugs remains the pinnacle achievement in cancer research. In recent years, as we have continued to seek promising new pharmacologic agents, targeted therapies have become particularly attractive, as they carry the potential to deliver highly effective, customizable treatments to cancer patients while theoretically resulting in less harm to benign, healthy cells. Such treatments can be used alone or in combination with traditional chemotherapeutic agents. By identifying specific molecular targets present in tumors, we can tailor a patient’s treatment on the basis of his or her genetic profile. The design of new targeted drugs is truly the ultimate achievement in oncology research, and lung cancer is no exception. What we may not realize, however, is that the answer may be staring us in the face. Finding new applications for existing drugs can be just as promising as developing brand-new compounds, and, further, can be particularly convenient when these drugs already have known safety profiles and pharmacokinetic properties.

Metformin is the most commonly prescribed oral hypoglycemic agent for type II diabetic patients. The use of this drug has unexpectedly been linked to lower incidences of cancer. It has been suggested that this finding may be related to metformin’s activation of the AMP-activated kinase (AMPK) pathway. This pathway is known to regulate cellular metabolism (hence the drug’s efficacy as an antidiabetic agent) and, additionally, has been hypothesized to prevent oncogenesis. AMPK inhibits the serine–threonine kinase mammalian target of rapamycin (mTOR), an important molecular target which regulates cellular growth and proliferation (Fig. 1).

In a recent Cancer Prevention Research paper titled “Metformin prevents tobacco carcinogen-induced lung tumorigenesis” Memmott et al investigate the use of metformin in inhibiting the mTOR pathway. Recognizing that aberrant activation of mTOR occurs in cases of tobacco-induced lung cancer, the authors assessed the utility of metformin in an in vivo model of lung cancer induced by the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

In the experiments described by Memmott et al, metformin was found to inhibit NNK-induced tumorigenesis in mice compared to controls in a dose-dependent fashion when administered orally, decreasing tumor burden by >50%. Importantly, the steady-state levels of metformin in the experimental animals fell within the range of achieved by standard oral dosing for diabetic patients. Although this would be particularly convenient for translation to human lung cancer patients, the authors did note an even greater efficacy when metformin was given intraperitoneally, resulting in greater peak plasma levels of the drug. As this administration decreased tumor burden by more than 70%, it will be worthwhile to explore pharmacologic techniques to deliver met-
formin or one of its analogs in a way to achieve higher peak plasma concentrations. Mechanistic investigations, such as the ones presented in this work will help focus this effort.

In this work, the authors suggest that metformin’s effect upon NNK-induced lung cancer may be a downstream effect of decreased levels of insulin and insulin-like growth factor 1 (IGF-1). Inhibition of mTOR through metformin treatment occurred in association with decreased circulating levels of these growth factors as well as impaired phosphorylation of IGF-1R, supporting this hypothesis. In accordance with this finding, other authors have found that overexpression of IGF-1 enhances NNK-induced tumorigenesis in lung tissues. While metformin’s effects on lung cancer may be the result of decreased levels of circulating growth factors, further mechanistic studies are certainly warranted.

The exact mechanism responsible for the efficacy of metformin in treating this in vivo model of lung cancer has yet to be fully elucidated. What is clear, however, is the potential feasibility of this “new” drug as an important agent in the future management of lung cancer. Further, as the authors propose, this work has important implications for chemoprevention. There is strong rationale for proceeding with a chemoprevention trial that uses metformin in heavy smokers who are at high risk for developing lung cancer.

As we continue to search for fresh answers to old problems, we must realize that the wave of targeted molecular therapy for cancer is upon us. In order to provide individualized therapeutic plans for patients, ideally delivering the greatest benefit with the least burdensome side effects, we must understand the genetics of our patients’ tumors and identify possible targets for intervention. Further, while billions of dollars and an enormous amount of effort will certainly continue to be directed toward the development and design of novel compounds, an important point has been made here: sometimes, all it takes is revisiting a “blast from the past.”