Medical Xpress

Defeating nicotine's double role in lung cancer

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A lung cancer treatment that inhibits nicotine receptors was shown to double survival time in mice, according to Italian researchers.

The results of the early phase animal model study were reported in the June 15 issue of the *American Journal of Respiratory and Critical Care Medicine*.

Changes in genes encoding nicotine receptors are strongly associated not only with the tendency to smoke, but with susceptibility to lung cancer. Nicotine exposure also heightens the expression of the nicotine receptors, which leads to increased cell proliferation and inhibition of apoptosis, further setting the stage for cancer.

Patrizia Russo, Ph.D. and Laura Paleari, Ph.D. of the Lung Cancer Unit of the National Cancer Research Institute in Genoa, Italy and colleagues from San Raffaele Pisana Scientific Institute for Research, Hospitalization and Health Care (IRCCS), Catholic University, Campus Biomedico University in Rome, Mario Negri Institute in Milan and CEA Gyf sur Yvette in France showed in past research that an antagonist of nicotine acetylcholine receptors (nAChRs), may serve as an anticancer agent. The antagonist, called d-tubocurarine/α-Cobratoxin (α-CbT), specifically targeted the α7 subunit of nAChRs, the area primarily associated with increased cell proliferation.

In this study, the authors took the research a step further and showed that α-CbT could inhibit non-small cell lung carcinoma (NSCLC) growth and

prolong life in non-obese/severe combined immunodeficient (NOD/SCID) mice that had human NSCLC grafted to their lungs. This study attempted to mimic human cancer conditions more closely by delaying treatment until the tumors were well-established. In addition to control mice that were untreated, the researchers randomized one third of the mice to receive standard chemotherapy.

They found that NOD/SCID mice treated with the standard chemotherapy agent, cisplatin, had a 16 percent longer median survival time than untreated mice ($p= 0.05$). Mice treated with α-CbT, however, had an increased median survival time of 1.7-fold over the cisplatin-treated mice and 2.1-fold over the no-treatment controls ($p=0.0005$).

"The results of this study show that α-CbT, a powerful, high-affinity α-7-nAChR inhibitor, induces antitumor activity against NSCLC by triggering apoptosis," wrote Dr. Russo. "The prolonged survival of α-CbT-treated animals in our mouse model of NSCLC is most likely the result of several mechanisms, including various antiproliferative and antiangiogenic effects."

The research also found that unaffected (i.e., noncancerous) cells showed no inhibition of proliferation when treated with α-CbT, suggesting that the treatment would have limited if any toxic effects. Dr. Russo and colleagues postulated that this finding may be due to the reduced number of receptor binding sites on normal cells as opposed to cancerous cells. Conversely, they reported that cancer cells with the greatest number of receptor binding sites seemed to respond with the greatest sensitivity to the treatment.

"The goal of this research line is to explore the widest range of possibilities of intervention on the α7-nAChRs. We hope to move further on towards the clinical setting experimentation phase for the assessment of potentially new treatment strategies for NSCLC," said Dr.

Russo.

An editorial in the same issue of the journal asked if nicotine may be to lung cancer what estrogen is to breast cancer. Eliot R. Spindel, M.D., Ph.D., of Oregon Health & Science University, stated that estrogen can stimulate the development of breast cancer and estrogen-receptor antagonists, such as tamoxifen, provide therapeutic benefit. In support of a carcinogenic role for estrogen, the incidence of breast cancer appears to be decreasing as estrogen hormone replacement therapy is being used less often. Likewise, nicotine may promote lung cancer yet nicotine receptor antagonists may offer treatment options for patients with lung cancer.

John Heffner, M.D., past president of the ATS stated that "this research clearly has profound clinical implications regarding the role of nicotine in stimulating lung cancer and nicotine receptor antagonists in treating the disease. The highly addictive nature of nicotine, however, complicates patients' ability to quit smoking and avoid ongoing nicotine exposure."

"This [addictive nature of nicotine] underscores the importance of potential FDA regulation of nicotine in tobacco products to limit exposure to this drug that promotes tumor growth," wrote Dr. Spindel.

Source: American Thoracic Society (news : web)

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