Molecule plays early role in nonsmoking lung cancer

July 27 2009

The cause of lung cancer in never-smokers is poorly understood, but a study led by investigators at the Ohio State University Comprehensive Cancer Center and at the National Cancer Institute has identified a molecule believed to play an early and important role in its development.

The findings, published online recently in the Proceedings of the National Academy of Sciences, may lead to improved therapy for lung cancer in both never-smokers and smokers, including those with tumors resistant to targeted drugs such as gefitinib.

The study examined lung tumors from people who had never smoked and found high levels of a molecule called miR-21. The levels were even higher in tumors that had mutations in a gene called EGFR, a common feature of lung cancer in never-smokers.

"Several important lung cancer drugs target EGFR mutations, but these agents are ineffective in about 30 percent of cases in which the mutation is present," says co-principal investigator Dr. Carlo M. Croce, professor of molecular virology, immunology and medical genetics at the Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute. "Our study suggests that developing agents to inhibit miR-21 might improve these anti-EGFR therapies."

About 15 percent of the 219,000 lung cancer cases expected this year in the United States - 32,850 people - will occur in individuals who have

never smoked.

Croce and his colleagues began their study by comparing 28 cases of lung tumor tissue and nearby healthy lung tissue from never-smokers for changes in microRNA, molecules that help cells regulate the kind and amount of proteins they make.

The cancer cells showed abnormally elevated levels of five microRNAs, with miR-21 increased two and a third times, the highest of all. An earlier study of smoking-related lung cancer by the same investigators also showed elevated levels of that molecule.

Furthermore, the molecule was equally high in early stage tumors and late stage tumors, suggesting that this change happens early in lung cancer development, says Croce, who also directs Ohio State's Human Cancer Genetics program.

Using lung cancer cell lines, the investigators learned that EGFR regulates miR-21. For example, altering EGFR levels caused corresponding changes in miR-21.

Last, the investigators took cells that had a mutated EGFR gene and treated them with an anti-EGFR agent (the agent was related to gefitinib and erlotinib, targeted drugs used to treat lung cancers with EGFR mutations). As expected, many of the cells died. But when they blocked both EGFR and miR-21, the proportion of cells killed rose still more.

Overall, Croce says, "Our study suggests that the combined use of an EGFR inhibitor and a miR-21 inhibitor might improve therapy for many cases of lung cancer, and rescue lung cancer cases that have acquired resistance to several targeted drugs."

Source: Ohio State University Medical Center

Citation: Molecule plays early role in nonsmoking lung cancer (2009, July 27) retrieved 4 July 2023 from https://medicalxpress.com/news/2009-07-molecule-early-role-nonsmoking-lung.html

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