Study reveals mechanism of lung-cancer drug resistance

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New research published in *Nature Medicine* indicates that targeted drugs such as gefitinib might more effectively treat non-small cell lung cancer if they could be combined with agents that block certain microRNAs.

The study was led by investigators with the Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James). It shows that overexpression of two genes, called MET and EGFR, causes the deregulation of six microRNAs, and that this deregulation leads to gefitinib resistance.

The findings support the development of agents that restore the levels of these microRNAs. It also offers a new strategy for treating non-small cell lung cancer (NSCLC), which is responsible for about 85 percent of the 221,000 lung-cancer cases and 157,000 deaths that occur annually in the United States.

Finally, it suggests that measuring the expression levels of certain microRNAs - those controlled by the MET gene - might predict which lung-cancer cases are likely to be resistant to gefitinib.

EGFR (which stands for "epidermal growth factor receptor") is frequently overexpressed in non-small cell lung cancer (NSCLC), and this leads to uncontrolled cell proliferation. Gefitinib selectively inhibits EGFR activation and triggers cancer cells to self-destruct by apoptosis. NSCLC cells inevitably develop resistance to the drug, however. This

study reveals how this resistance occurs.

"Our findings suggest that gefitinib resistance that is caused by MET overexpression is at least partly due to miRNA deregulation," says principal investigator Dr. Carlo M. Croce, director of Ohio State's Human Cancer Genetics program and a member of the OSUCCC - James Molecular Biology and Cancer Genetics program.

First author Michela Garofalo notes that stratifying NSCLC patients based on MET expression or the expression of miRNAs regulated by MET might allow for individualization of treatment.

"Such a strategy could improve treatment efficacy and patient quality of life by sparing patients from the side effects of treatments that are likely to fail," says Garofalo, who is a research scientist in Croce's laboratory at the OSUCCC - James.

For this study, Croce, Garofalo and their colleagues used lung cancer cell lines, animal models and analysis of human NSCLC tissue. Key technical findings include the following:

-- Both EGFR and MET control miR-30b, miR30c, miR-221, and miR-222. These miRNAs are oncogenic; they inhibit pro-apoptotic genes.
-- Overexpression of the four oncogenic miRNAs rendered gefitinib-sensitive cells resistant to treatment; inhibiting the four enhanced gefitinib sensitivity and blocked NSCLC tumor growth in an animal model.
-- MET alone controls levels of miR-103 and miR-203, which have a tumor-suppressor function. Forcing their expression enhanced gefitinib sensitivity and blocked NSCLC tumor growth in an animal model.

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