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Smoke exposure alters gene expression and estrogen metabolism in the lungs of mice

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Lung cancer rates are increasing substantially in women, particularly in non-smoking women, with no known reason for the increase. Now researchers at Fox Chase Cancer Center may have uncovered a critical piece in the puzzle.

Working in a mouse model of smoking-induced lung cancer, Margie Clapper, Ph.D., Co-leader of the Cancer Prevention and Control Program at Fox Chase Cancer Center, and colleagues found that smoke triggers rapid changes in gene expression in the lungs of female mice, including increasing expression of a network of genes involved in estrogen metabolism. Based on these data, to be presented at the 2010 annual meeting of the American Association for Cancer Research, the team hypothesizes that estrogen metabolism may contribute to lung cancer in non-smoking women as well.

Following smoke exposure for 3, 8, or 20 weeks, Sibele Meireles, Ph.D., an assistant member in the Clapper Lab, found that 10 genes were differentially expressed in the lungs of smoke-exposed female mice as compared with control animals. The gene most affected by smoke was cytochrome P450 1b1 (Cyp1b1), which is responsible for breaking down toxins and is a key enzyme for estrogen metabolism. Additionally, when the team looked at networks of genes, they saw that genes involved in estrogen metabolism were altered within the lungs of animals exposed to smoke as compared to controls.

"We found a link between hormones and lung cancer through Cyp1b1

when we weren't looking for it -very exciting," says Clapper. "Previous work has suggested that estrogen may play a role in lung cancer, but no one has shown that smoke can actually accelerate the metabolism of estrogen within the lungs; the suggestion from our data."

The investigators hypothesize that estrogen plays a role in the formation and progression of lung cancers, similar to the role it plays in some breast cancers. The idea is consistent with previous studies indicating that women with lung cancer who take hormone replacement therapy have a poorer prognosis than women who do not, regardless of their smoking history. Additionally the observation that estrogen can be detected within the lungs and that its metabolism is upregulated in the lungs of smoke-exposed female mice may provide new insight into why lung cancer is rising so quickly in women, including non-smoking women world wide, according to Clapper.

The investigators decided to look at gene expression changes after short-term smoke exposure in hopes of finding ways to intervene in or reverse the process. "If we can identify the earliest events that happen within the lungs when you begin to smoke, we might be able to use therapeutics to block them as well as lung cancer," says Clapper, who runs a chemoprevention laboratory at Fox Chase.

Provided by Fox Chase Cancer Center

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