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Cigarette smoke may alter immune response in COPD exacerbations

Smoking cigarettes is not only the principle cause of chronic obstructive pulmonary disease (COPD), but it may change the body's immune responses to bacteria that commonly cause exacerbations of the disease, according to new research in a mouse model.

"It is well established that smoking is the main risk factor for COPD. But our research also suggests that cigarette smoke substantially changes the immune response to bacteria, which means that patients with COPD who smoke are weakening their body's ability to deal effectively with bacterial invaders. This may cause even further progression of the disease," said Martin Stämpfli, Ph.D., an associate professor at McMaster University, the principle investigator of the study.

"We wanted to see whether and how cigarette smoke would change the inflammatory response to the bacteria that is the culprit behind many COPD exacerbations, nontypeable *Haemophilus influenzae* or NTHI."

Their results were published in the second issue of April of the *American Journal of Respiratory and Critical Care Medicine*.

Dr. Stämpfli and colleagues tested the effects of cigarette smoke exposure on inflammation and immune response in mice that were exposed to cigarette smoke twice daily five days a week for either eight weeks or four days then challenged with an intranasal inoculation of NTHI. The cigarette smoke exposure roughly approximated that of an "average" human smoker (within the limitations of a model with differing metabolic processes.) Control mice were not exposed to cigarette smoke, but were inoculated with NTHI as were the cigarette smoke-exposed mice.

The researchers found that mice that were exposed to cigarette smoke, whether for four days or for eight weeks, showed distinct shifts in their immune-response profile, namely an increase

in inflammation of the lungs after the NTHI challenge, increased weight-loss in response to the bacterial infection and, notably, a shift in the expression of inflammatory markers.

"Many interventions are developed with a homeostatic model in mind," said Dr. Stämpfli.

"However, if our findings are borne out in clinical research, they would indicate that treatment targets for smokers with COPD may be markedly different than in non-smokers. Smoking may change the underlying inflammatory pathways elicited after bacterial infection."

Because of the shift in the inflammatory profile, the researchers wondered if it would have an effect on the efficacy of treatment with the usual corticosteroids.

Interestingly, they found that while the corticosteroid dexamethasone was effective in controlling the inflammation following bacterial challenge in both control and cigarette smoke-exposed mice, but it appeared to compromise the body's ability to clear the bacteria from the lungs.

"This was true for both control- and cigarette smoke-exposed mice and raises questions about the long-term use of corticosteroids in COPD. Certainly, there is evidence that corticosteroid treatment reduces the number of exacerbations in patients with COPD. This, however, is associated with occurrence of pneumonia, which is mirrored by our results. Therefore, inflammation is not altogether bad in the context of a bacterial infection, as it is required to clear the bacteria. It is the excessive inflammation observed in smokers that is of concern, as it may lead to lung damage."

The researchers note that the NTHI bacterium is an obligate human pathogen, and therefore an imperfect fit for a mouse model of COPD. "In the context of this present study, NTHI challenge was used as a tool to address the hypothesis of cigarette smoke exposure on the ensuing inflammatory response, and may not be perfectly suited to address pulmonary clearance, as a mouse-adapted pathogen may demonstrate different kinetics of clearance," Dr. Stämpfli noted.

Dr. Stämpfli intends to focus future research on detailing the precise immunological changes elicited by cigarette smoke exposure. "We must have a better understanding of which inflammatory markers are changing and how in order to develop a better understanding of potential targets for interventions," he said.

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