# Research identifies the beginnings of chronic obstructive pulmonary disease

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The third most deadly disease in the U.S., chronic obstructive pulmonary disease (COPD), appears to be partly driven by the action of immune cells circulating in the blood entering into the tissues of the lungs. UC Davis scientists have discovered that this key process begins in the blood vessels around the large airways in the center of the lung. The discovery helps clarify how smoking can bring about this severe respiratory condition.

The research also identifies a potential new target for directed drug therapy to counter the disease, which kills about three million people a year in the U.S. The study is published online today in PLoS ONE, an open-access science journal.

"Understanding how a disease begins an important step to develop new therapies, and knowing the mechanism and location of white blood cell recruitment to the lung early on in the development of COPD in this model will allow us to more rapidly screen drugs and determine how they work," said Benjamin Davis, a researcher with the Center for Health and the Environment and the lead study author.

"We are currently testing whether statin drugs that may prevent the development of COPD in this model. The model appears to be ideal for screening drugs to treat early COPD, but the ultimate test comes when a treatment is transitioned from the lab to COPD patients," Davis said. "Our primary goal is to save lives."

Davis and his colleagues used a highly reproducible animal model of COPD to show, in effect, that the equivalent of approximately 10 years of one-pack-a-day cigarette smoking leads to a striking immune response in the lungs: bronchial airways -- the air passages to the lungs -- are completely physically damaged and scarred accelerating inflammation and cellular changes that in turn can obstruct airflow and reduce normal lung function.

In people who smoke for 30 to 40 years, inflammation destroys the delicate balance of cells lining the airways, increasing the respiratory system's vulnerability to infection and the ability to clear inhaled particles. This is full-blown COPD.

Researchers had not known if the immune cell-triggered inflammation started in the blood that feeds bronchial airways or if instead, it started in alveoli deep in the lungs where oxygen is transferred to blood vessels. The new finding resolves the question.

The research demonstrates tobacco smoke exposure stimulates a specific type of white blood cell called a neutrophil to migrate out of bronchial blood vessels and accumulate in the lung tissues.

Davis and colleagues found that these cells leave the circulation due to the production of "adhesion molecules" and immune proteins call chemokines in bronchial blood vessel cells. Although neutrophils aid in tissue repair, when present in excess numbers and activated, these white blood cells can release enzymes that kill cells and accelerate inflammation.

"Now that we have determined where the process starts, we hope that therapeutic drugs can be developed to target this inflammatory process in the bronchial airways to reduce severe lung damage," said Kent Pinkerton, a coauthor of the study, professor of pediatrics and director

of the Center for Health and the Environment at UC Davis.

More than 80 percent of COPD is caused by smoking. Inhaling on a lit cigarette exposes smokers to some 4,000 different compounds present in vapors, particles and smoke. All of this material comes in contact with, and eventually kills, fragile airway epithelial cells that are lined with cilia and films of mucus to facilitate passage of air into the lungs.

The researchers studied rats that appear to have a genetic defect making them react to smoke exposure much like people who develop smoking-related diseases. The scientists showed that the animals develop all of the physiological and anatomical traits of COPD found in humans, making them ideal models to study the disease. The rats experience these symptoms and conditions much faster than other laboratory animals that have been studied, and the development of the rat model is expected to be useful in future studies on COPD and ways to treat it.

In the research, a "smoking machine" automatically loads, lights and puffs on cigarettes. Rats are exposed to smoke proportional to a two-pack-a-day smoker. However, due to the sensitivity of these rats to tobacco smoke, exposures are only for six hours a day, three days per week.

The researchers found that 12 days of exposure over a period of 4 weeks led to physiological changes reflective a 10- to 20-year smoker who develops respiratory complications of wheeze, cough and reduced respiratory function. With 12 weeks of smoke exposure, the conditions in these rats approximate those found in a 30- to 40-year smoker who has developed severe limitations in breathing and COPD.

The scientists now plan to test a variety of potential drugs with the long-term aim of finding new ways to treat people with the disease.