

COPD and the effect of low-dose cadmium, a highly toxic metal, on airway epithelial cells

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Cigarette smoke exposure is associated with the development and severity of chronic obstructive pulmonary disease, or COPD, which is the third leading cause of death worldwide.

Cigarette smoke contains 2–3 micrograms of [cadmium](#), a highly toxic metal and environmental pollutant, per cigarette. Burning tobacco releases cadmium oxide that can be adsorbed onto microparticles in smoke that travel deep into the lungs. Furthermore, the body is not able to remove cadmium, which accumulates in longtime smokers.

In a *Scientific Reports* [study](#), University of Alabama at Birmingham researchers show how a low dose of cadmium produces a deleterious stress in lung [epithelial cells](#), and their findings highlight [potential therapeutic targets](#) to be explored in cadmium-exposure and subsequent lung injury.

The research, led by Veena Antony, M.D., a professor in the UAB Department of Medicine, focuses on microRNA-381, and the expression of a chloride channel gene called ANO1 in lung tissue samples and [airway](#) epithelial cells. ANO1 helps produce mucus in the airway; but overproduction of mucus in [chronic lung disease](#) can lead to airway thickening and mucus blockage, adding to severity of the disease. Thus, overexpression of ANO1 can exacerbate COPD.

The UAB researchers compared lung tissue samples from nine "never" smokers, who had zero history of cigarette smoking, and lung tissue samples from 13 "ever" smokers with COPD who had a history of smoking that ranged from 15 to 25 pack years per person.

One pack year is generally defined as smoking one pack of cigarettes a day for one year. The researchers found that "ever" smokers, in contrast to "never" smokers, had upregulated ANO1 expression in airway epithelial cells.

Similarly, airway epithelial cells in a bronchoalveolar lavage fluid from one non-COPD subject and one smoker with COPD showed greater ANO1 expression in the COPD-subject cells.

The researchers next tested the direct effect of very low doses of cadmium on normal human airway epithelial cells. These cells were grown on an air-liquid interface that allows the airway cells to differentiate normally. Two weeks of exposure to 0.5 or 1.0 micromolar cadmium chloride in the liquid layer increased expression of ANO1 12 to 14 times.

MicroRNAs have the ability to downregulate expression of a gene by direct interaction with that gene's mRNA sequence. The UAB team used computer software analysis to identify microRNA-381 as the microRNA with most interaction with ANO1 mRNAs, suggesting that microRNA-381 is a negative regulator of ANO1. Some [heavy metals](#) are known to negatively regulate microRNAs.

Antony and colleagues used a synthetic inhibitor for microRNA-381 to inhibit the expression of microRNA-381 in primary human airway epithelial cells from subjects with COPD, and found that ANO1 expression was upregulated significantly.

In contrast, adding a microRNA-381-mimic—a synthetic RNA that acts like microRNA-381 to increase the amount of negative regulation—to those cells decreased ANO1 expression. These results strengthened the premise of the UAB researchers that cadmium negatively regulates microRNA-381 expression to upregulate ANO1 expression in airway epithelial cells.

Lastly, researchers found that, even when primary human airway epithelial cells from subjects with COPD were also exposed to 1 micromolar cadmium chloride, the microRNA-381 inhibitor still upregulated ANO1 and the mimic still downregulated ANO1.

"Our observations from experiments involving low-dose cadmium-exposure of epithelial cells suggest that ANO1 is a direct target for

miR-381, which is downregulated upon low-dose cadmium exposure," Antony said.

"Thus, cigarette-induced cadmium-toxicity may alter cellular homeostasis mechanisms at very low concentrations, and cadmium-exposure in a person with an existing pulmonary condition can have an additive or adverse effect with increased susceptibility toward infections and environmental allergens.

"This interaction of cadmium, microRNA-381 and ANO1 suggests that microRNAs may act as potential therapeutic targets to be explored further in cadmium-exposure and subsequent lung injury."

More information: Pooja Singh et al, Low dose cadmium exposure regulates miR-381–ANO1 interaction in airway epithelial cells, *Scientific Reports* (2024). [DOI: 10.1038/s41598-023-50471-z](https://doi.org/10.1038/s41598-023-50471-z)

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