TECHNICAL BRIEF

A Strategic Research Initiative on Chemicals of Emerging Concern and Respiratory Health Risks

Chemical Insights Research Institute (CIRI) of UL Research Institutes is investigating mechanisms of respiratory disease development in response to chemicals of emerging concern exposures.

Introduction

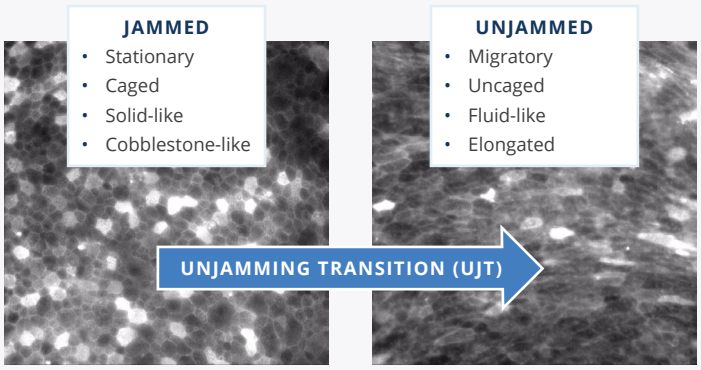
The United States Environmental Protection Agency (U.S. EPA) defines chemicals of emerging concern (CECs) as substances that pose a perceived, potential, or actual risk to human health.[1] CECs are found in pharmaceuticals and personal care products (PPCPs), and are detected in the environment where we live, eat, and breathe.[2,3] While CECs pose a risk to human health, a comprehensive understanding of their adverse effects and underlying mechanisms is lacking.

Because CECs are emergent, scientists are just beginning to understand the health consequences that result when we are exposed to them. One well-speculated adverse effect of exposure to these chemicals is a risk of developing respiratory diseases including lung cancer.[4-8] This is particularly concerning given that these chemicals are detected in humans and accumulate in lung tissue.[6,9,10] Therefore, studying the cellular events that drive lung disease development in exposed individuals is of utmost importance to public health.

One important step towards understanding how chemicals cause disease is understanding their effects on specific signaling and outcome pathways in human cells. To address this knowledge gap, CIRI's Center for Toxicology and Human Health (CTHH) will explore whether CECs activate two distinct pathways in lung cells, called epithelial-to-mesenchymal transition (EMT) and unjamming transition (UJT).[11] To achieve this, a novel

in vitro model called air-liquid interface (ALI) will be used to expose human bronchial epithelial cells to chemicals, which simulates real life exposure to CECs through the air we breathe. Importantly, EMT and UJT promote lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cancer by enabling cells to change their function and/or migrate[11,12,14] however, their roles in the disease development linked to CEC exposure are understudied.

By conducting this research, the CTHH will advance CIRI's mission of creating a healthier and more sustainable future for people who are exposed to these chemicals in their homes, schools, workplaces, and the environment. In addition to identifying whether CECs induce the EMT and UJT, this project will also identify new biomarkers of these cellular processes. These findings will enable researchers to screen potentially harmful or carcinogenic chemicals and will provide guidance to stakeholders for developing safer chemicals.



F-actin, apical focal plane

Figure 1: Unjamming transition (UJT) of human bronchial epithelial cells[13]

Study Objectives

- Establish a dose-dependent relationship between CEC exposure and cellular toxicity in primary human bronchial cells differentiated in air-liquid interface.
- Use a novel in vitro model to determine the dose-response relationship between CEC exposure and induction of EMT and UJT over various concentrations and time points.
- Identify cellular mediators of EMT and UJT, including pro-inflammatory cytokines and other factors that are released by cells undergoing these two independent pathways that could lead to disease.

Study Plan Overview

The study objectives will be achieved using the following sampling and assessment plan:

1. Airway basal stem cells and mature airway epithelial cells will be exposed to CECs. Effects on processes involved in respiratory disease development (differentiation, metabolism, and DNA damage) will be measured.
2. Markers of EMT and UJT will be measured in the mature epithelium.
3. Proteins released by the mature epithelium during EMT or UJT will be screened to identify novel biomarkers of these processes.

Scientific Outcomes

01

Establish an in vitro model of the human airway epithelium to simulate a physiologically relevant chemical exposure test for impacts on respiratory health.

02

Determine the EMT and UJT mechanism by which CEC exposures lead to disease development.

03

Establish a platform to screen/ identify potentially harmful or disease-causing chemicals and mixtures of CECs.

Research Partners

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