Mechanisms of Cigarette Smoke-Induced Lung Cellular Senescence
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Abstract:

Emission aerosol constituents and comparative toxicology of electronic cigarettes with flavorings in our original parent Study (NIH 2R01 HL085613: Mechanisms of Cigarette Smoke-Induced Lung Cellular Senescence), we aimed to investigate the cellular and molecular mechanisms of lung DNA damage and cellular senescence in response to tobacco smoke. In this supplemental period, we expand the scope of the original work on other tobacco products with additives, particularly electronic cigarettes (E-cigs) with nicotine and flavorings, and propose to determine aerosol constituents and cellular toxicity of E-cigs with flavorings. E-cigs with different flavors represent a significant and increasing proportion of tobacco consumption in the United States and globally. The identification of established and potential harmful chemicals/constituents, and development of measurable comparative toxicity data based on oxidative stress, DNA damage and inflammation that result from exposure to E-cigs vapor with different flavorings are urgently needed. Our preliminary data indicate that E-cigs with different flavorings cause varying levels of oxidative stress and inflammatory cytokine release in human lung epithelial cells and fibroblasts. We hypothesize that E-cigs with different flavorings have differing chemical constituents that influence cellular toxicity in terms of oxidative, DNA damage and inflammatory responses with varying intensity. We propose to directly determine chemicals formed in vapors from E-cigs with different flavors based on realistic conditions, and compare their effects on oxidative stress, DNA damage and inflammation using gas chromatography-mass spectrometry (GCMS) and *in vitro* cell-based assays upon realistic exposure systems. Specific Aims: 1) determine comparative chemical constituents present in selected E-cigs with flavorings by GCMS based on realistic exposure using our newly generated topography instrument based data, and 2) determine comparative oxidative, DNA damage and inflammatory responses to E-cigs with flavorings in human lung epithelial cells and mouse lung epithelial cells from the state-of-the-art reporter models (existing NF- B luciferase and DNA repair/NHEJ reporter cells) as well as 3D cell culture based on realistic exposures to demonstrate the predictive nature of toxicity for adverse health outcomes. Our goal is to determine comparative emitted aerosol chemical constituents (including some on FDA's top 20 Harmful and Potentially Harmful Constituents (HPHCs), 93 HPHCs and other newer based on flavorings) and toxicological effects of E-cigs with different flavorings in response to this administrative supplement to directly support the FDA's regulatory efforts. Assessment of comparative chemical constituents and toxicity will provide crucial information related to hazard ranking and adverse health outcomes associated with E-cigs with specific flavorings as well as relevant to FDA regulation of tobacco products.