Electronic nicotine delivery systems (ENDS) are rapidly increasing in popularity due to the perception that they may represent a safe alternative to conventional cigarettes. However, a growing body of evidence indicates that ENDS exposure can disrupt maintenance of pulmonary immune homeostasis and antimicrobial immunity. In this issue of the JCI, Madison et al. demonstrate that in mice, chronic ENDS exposure induces profound alterations in lipid homeostasis. ENDS-exposed mice showed irregularities in the surfactant-secreting lamellar bodies within type 2 alveolar cells and increased intracellular phospholipid accumulation within alveolar macrophages. Moreover, ENDS-exposed mice displayed greater inflammation and tissue damage in response to influenza A, which may be due to downregulated expression of a viral pattern-recognition receptor in alveolar macrophages. Collectively, the results of this study identify previously unrecognized adverse effects of ENDS exposure on pulmonary lipid metabolism, although the implication of these effects on long-term respiratory health requires future exploration.

Electronic nicotine delivery systems – what’s the harm?
The adverse health consequences of long-term cigarette smoking are well established, and it remains the leading cause of preventable death worldwide (1). Although tobacco use is steadily declining, there has been a rapid increase in the popularity of electronic nicotine delivery systems (ENDS, also known as e-cigarettes), particularly among adolescents (2). This is partly due to the perception that ENDS may offer a safer alternative to conventional cigarettes and a potentially useful means to facilitate smoking cessation (3), although many of the adolescent users were previously non-smokers. ENDS deliver a liquid consisting of variable concentrations of nicotine within the solvents propylene glycol (PG) and vegetable glycerine (VG), which is then heated to produce a vapor that can be inhaled directly into the lungs. There are additionally more than 7,500 unique flavors created by the inclusion of various additives (4).

Numerous regulatory mechanisms act in concert to maintain pulmonary homeostasis, and this delicate balance can be disrupted by inhalation of toxins. Despite containing fewer potentially harmful chemicals than tobacco smoke, emerging evidence indicates that inhalation of ENDS vapor can disrupt a wide range of processes involved in maintenance of pulmonary immune homeostasis. In vitro exposure to components of ENDS liquids/vapors induces proinflammatory effects in bronchial epithelial cells (5, 6), alveolar macrophages (7), and neutrophils (8). Impaired host-defense functions including reduced macrophage phagocytosis (9, 10), accentuated bacterial adherence (11), and altered neutrophil extracellular trap (NET) formation (9) have also been reported. As it is difficult to accurately recapitulate the complexities of cellular exposure to inhaled vapor using an in vitro system, other studies have sought to use animal models to further understand the immunological effects of ENDS. These studies have reported airway inflammation (acute transient [ref. 12] or chronic [ref. 5]), reduced lung function (13), and impaired mucociliary function (5, 14), with some (5), but not all (15), studies also reporting emphysematous lung changes. Differences in exposure delivery systems and vapor used (variable addition of nicotine or flavorings) may explain the contrasting findings observed in some of these studies, although they uniformly demonstrate that ENDS exposure affects several aspects of pulmonary immune homeostasis. There are very few human in vivo studies to date, but ENDS users have been shown to have elevated airway matrix metalloproteinase 9 and NET-related proteins (16) and increased expression of the mucin glycoprotein MUC5AC (16, 17).

Dysregulated lipid metabolism and disease
Maintenance of lipid metabolism is crucial for cellular function in all tissues, and perturbations in lipid homeostasis occur in a range of human diseases. Pulmonary surfactant, which maintains alveolar surface tension, is approximately 90% lipid (18). There is a growing body of evidence indicating that pulmonary surfactant and associated lipid metabolism has broader roles in maintenance of pulmonary immune homeostasis and host defense. Thus, any exposure that interferes with these critical processes may be expected to have profound effects on the lung microenvironment.

In this issue, Madison et al. employed a mouse model of chronic inhalational exposure to study the in vivo effects of ENDS-associated vehicle solvents PG and VG in comparison to conventional tobac-
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Madison et al. also showed that ENDS exposure in mice was associated with downregulated M1-associated macrophage markers including Tlr7, a pattern-recognition receptor (PRR) that senses viral single-stranded RNA (19). This prompted further investigation into the effects of ENDS in a mouse infection model of the common respiratory virus influenza A. Compared with air-treated controls, ENDS-treated mice challenged with influenza had augmented airway inflammation, evidence of lung hemorrhage/edema, and greater weight loss, suggestive of increased virus-induced pathology. Whether these effects were driven by an impaired innate antiviral response secondary to downregulation of viral PRRs or an alternative mechanism was not explored, and represents an area of future interest. Furthermore, it is unclear as to whether the adverse response to influenza challenge observed in ENDS-treated mice is a direct consequence of the aberrant lipid homeostasis, or an independent manifestation of ENDS use. A previous study revealed that ENDS liquid impairs in vitro induction of the epithelial host-defense peptide SPLUNC1 in response to rhinovirus infection (23), and thus numerous protective antiviral responses could potentially be impaired by ENDS use. Interestingly, SP-D has previously been shown to play a role in host defense against influenza virus infection in mice (24), suggesting that reduction in this protein could be central to the deleterious effects of ENDS.

Future directions

What are the implications of these findings for the ever-growing number of ENDS users? Clearly, these potentially adverse effects on lipid homeostasis with associated impairment of innate immune function could translate to greater frequency and/or severity of respiratory tract infections in individuals who persistently use these devices. The long-term consequences of such episodes for respiratory health, particularly related to lung development in younger individuals, is unclear. Notably, a previous study reported that ENDS use is associated with increased rates of chronic bronchitic symptoms in adolescents (25). The long-term consequences of the profound changes in lipid metabolism associated with ENDS exposure are also unclear. Altered lipid homeostasis has been reported in chronic obstructive pulmonary disease (COPD), characterized by increased airway expression of sphingolipids (26), although it remains to be determined whether altered lipid homeostasis is causally related to chronic lung disease. However, use of ENDS as smoking cessation devices in COPD patients may potentially expose patients with preexisting altered lipid homeostasis to more profound perturbations. Additionally, COPD is associated with increased propensity for virus-induced exacerbations, impairment of antiviral immunity by ENDS use could further accentuate the frequency and/or severity of exacerbations in these already susceptible patients.

As it is difficult to recapitulate the complexities of vapor inhalation in a small-animal exposure system, human vapor-challenge studies will be required to confirm that the effects observed in mouse models also occur in humans. Whether alternative solvents to PG and VG that exert lesser effects on immune homeostasis could be employed requires future consideration. Furthermore, the ENDS used in the study by Madison et al. (19) are only used by less than 10% of vapers. Alternative flavorings and different delivery devices add a further layer of complexity that may affect these altered processes, warranting future investigation. These important studies add to the growing consensus that promotion of ENDS as safe alternatives to tobacco should be viewed with caution, and have important implications for the manufacturing, marketing, and consumption of ENDS.

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