LETTER

REPLY TO YOUNG AND SCOTT:
Nicotine and nicotinic acetylcholine receptor mutations in electronic-cigarette smoke lung carcinogenicity

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We recently presented results on electronic-cigarette smoke (ECS) effects in a mouse model (1, 2). These results show that in a short-term exposure, nicotine in ECS induces DNA damage in lung, heart, and bladder tissues and DNA repair inhibition in lung tissues (1); in a long-term exposure, ECS induces lung adenocarcinoma and bladder urothelial hyperplasia (2). Nicotine induces the same type of DNA damage, DNA repair inhibition, and repair protein reduction in cultured human bronchial epithelial and bladder urothelial cells. Nicotine also enhances the mutational and tumorigenic transformation susceptibility of these human cells. Based on these results we conclude that ECS, via induction of DNA damage and inhibition of DNA repair, can cause lung and bladder carcinogenesis (1, 2).

It has been recognized that nicotine can activate many tumorigenic associated activities such as enhancing cell proliferations, induction of antiapoptosis activity, angiogenesis, and lung inflammation (3–5). Very significantly, evidence from a number of long-term epidemiology studies of large human cohorts have unambiguously shown that a human population carrying a homozygote mutation (rs1051730) in nicotinic acetylcholine receptor (CHRNA) genes has a higher incidence of lung cancer and chronic obstructive pulmonary disease (COPD) (6–9). Together, these results strongly support the possibility that nicotine and nitrosamine cause lung tumorigenesis via multiple routes. We do not discuss these possibilities in our PNAS articles (1, 2). Young and Scott (10) rightly raise the possibility that nicotinic could function as a carcinogen via its interactions with the nicotine acetylcholine receptor.

Having said that, we caution that two critical factors need to be carefully addressed in relation to the proposition that nicotine functions as a direct carcinogen based on CHRNA homozygote mutant carriers having a higher lung cancer incidence than noncarriers. First and foremost, the function of mutated CHRNA compared to the wild-type gene is not known. It has been found that smokers carrying a homozygote CHRNA mutated gene smoke significantly more tobacco than noncarriers (8). These findings raise the possibility that "more smoking" induces DNA damage rather than nicotine causing a higher incidence of lung cancer on its own (11). Second, it is possible that nicotine from tobacco smoke induces a higher level of DNA damage which leads to a greater inflammation and higher incidence of COPD in homozygote CHRNA mutant carriers. To test these two possibilities, Young and Scott (10) make a very valid suggestion: to test the CHRNA allelic effect on ECS, tobacco smoke, and nicotine in DNA damage induction, DNA repair inhibition, and susceptibility to mutations and tumorigenic transformation in human lung and bladder urothelial cells and lung and bladder tumor formation in mice and humans.

Finally, we are unaware of the evidence that supports Young and Scott's statement, "Nicotine and the nAChR are not implicated in recent cases of acute lung injury and deaths, following exposure to vitamin E acetate in illicit vape fluids" (10). We believe the jury is still out on the role of nicotine and nAChR in electronic-cigarette vaping-associated lung injury.

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