1. **No.**

   FP01902045

2. **Title**

   Pharmacological Analysis of Novel Action Via EGF Receptors Induced by Metabolites of Ingredients/Smoke in Cigarette

3. **Period**

   2018-2020

4. **Summary**

   The purpose of this study is to investigate the effect of 1,2-NQ, an electrophile in cigarette ingredients/smoke or metabolite of naphthalene, on cell survival signaling in human lung adenocarcinoma A549 cells. We found that 1,2-NQ is a novel chemical activator of EGFR. 1,2-NQ formed a covalent bond, a reaction referred to as N-arylation, with EGFR at a ligand-binding domain, Lys80. After this modification, 1,2-NQ resulted in the formation of EGFR puncta, similar to EGF treatment and internalization in a cetuximab-sensitive manner. Also, 1,2-NQ activated the PI 3-kinase–Akt signaling pathway and induced the significant phosphorylation of mTOR, TSC2, and BAD. To assess the ability of 1,2-NQ on apoptotic stimuli, we incubated A549 cells with 1,2-NQ and induced apoptosis by treatment with serum-free medium, which deprives cells of growth factors, in order to suppress EGFR-dependent antiapoptotic effects. As a result, 1,2-NQ exerted a cytoprotective effect against serum deprivation-induced apoptotic cell death. These data emphasize that N-arylation by 1,2-NQ is a novel aberrant chemical modification of EGFR and may contribute to carcinogenesis by inducing aberrant activation of EGFR-Akt signaling. To our knowledge, this evidence is the first to indicate that extracellular posttranslational modifications regulate EGFR activity.