**ABSTRACT**

Ground-level ozone ($O_3$) is a ubiquitous environmental air pollutant that is a potent inducer of airway inflammation and has been linked with both respiratory and cardiovascular morbidity and mortality. Some studies using transformed or immortalized cells have attributed $O_3$-mediated expression of inflammatory cytokines with activation of the canonical NF-κB pathway. In this study, we sought to characterize the $O_3$-mediated activation of cellular signaling pathways using primary human bronchial epithelial cells obtained from a panel of donors. We demonstrate that the $O_3$-induced expression of pro-inflammatory cytokines requires the activation of the EGFR/MEK/ERK and MKK4/p38 mitogen activated signaling pathways but does not appear to involve activation of canonical NF-κB signaling. In addition to providing a novel mechanistic model for the $O_3$-mediated induction of pro-inflammatory cytokines, these findings highlight the importance of using primary cells over cell lines in mechanistic studies.