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Mechanistic insights into diesel exhaust-induced lung cancer cell survival through AhR signaling

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Diesel exhaust (DE), a Group I human carcinogen, is a major environmental pollutant that significantly contributes to global lung cancer burden. Nitro-polycyclic aromatic hydrocarbons (PAHs), particularly 1-nitropyrene (1NP) and its metabolite 1-aminopyrene (1AP), are key markers of DE exposure. Although DE has been strongly linked to genomic instability, the molecular mechanism underlying this process remains poorly understood, especially the role of aryl hydrocarbon receptor (AhR) in promoting lung cancer cell survival and carcinogenesis. To address this gap, we examined the effect of 1NP/1AP in A549 cells. Exposure to 1NP/1AP significantly induced reactive oxygen species (ROS, $P<0.01$) and DNA damage ($P<0.0001$, as evaluated using Dichloro-dihydro-fluorescein diacetate and the comet assay, respectively. AhR activation was confirmed by AhR nuclear translocation (immunofluorescence, $P<0.0001$) and *CYP*-gene expression by qRT-PCR analysis ($P<0.0001$). Despite such genomic instability, A549 cells continued to exhibit colony formation, migration, and spheroid growth, which were not significantly altered. Conversely, inhibition of AhR activity enhanced apoptosis ($P<0.0001$), and markedly reduced cell migration, colony formation, and spheroid growth ($P<0.001$). Furthermore, an increased γ-H2AX expression was positively correlated with DNA damage ($P<0.001$), suggesting that AhR activation may regulate DNA damage repair and facilitate the survival of A549 cells under 1NP/1AP insult. Our findings highlight the previously unexplored role of AhR in promoting DNA repair and lung cancer cell survival and suggest that AhR inhibition may serve as a promising therapeutic strategy for preventing DE-induced lung carcinogenesis.

Keywords: Lung cancer, AhR, 1-nitropyrene, 1-aminopyrene, Genomic instability, DNA damage