**Nrf2 Induction of Antioxidant Response Increases Bioactivation of the Mutagenic Air Pollutant 3-Nitrobenzanthrone**

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3-Nitrobenzanthrone (3-NBA) is a potent mutagen and suspected human carcinogen detected in diesel exhaust particulate and ambient air pollution. It requires metabolic activation via nitroreduction to promote DNA adduct formation and tumorigenesis. NAD(P)H:quinone oxidoreductase 1 (NQO1) has been implicated as the major nitroreductase responsible for 3-NBA activation. We investigate the roles of human aldo-keto reductases (AKR1C1-1C3) in 3-NBA reduction and found that catalytic ef- ficiencies (*k*cat/*K*M) values for AKR1C1, AKR1C3, and NQO1 were equivalent. We also determined that AKR1C1-1C3 and NQO1 contribute equally to the nitroreduction of 3-NBA in lung epithelial cell lines (A549 and HBEC3-KT) and combined they represent approximately 50% of the intracellular nitroreductase activity towards 3-NBA. These enzymes are induced by Nrf2 signaling which raises the question whether Nrf2 activation as a chemopreventive strategy may exacerbate 3-NBA toxification. To evaluate the role of Nrf2 signaling on nitroarene activation, we tested the effects of Nrf2 inducers (e.g. sulforaphane, synthetic triterpenoids) in human bronchial epithelial cells (HBEC3-KT). Since A549 cells have constitutively active Nrf2 signaling due to a KEAP1 mutation, we examined the effect of heterozygous (Nrf2-Het) and homozygous (Nrf2-KO) Nrf2 knockout by CRISPR-Cas9 gene editing. Upregulation of AKR1C1-3 and NQO1 by Nrf2 inducers and downregulation by CRISPR-Cas9 KO was confirmed and quantified by qPCR, immunoblots, and enzyme activity assays. We observed 40% increases in 3-NBA bioactivation due to Nrf2 inducers in HBEC3-KT cells and a reduction of 3-NBA activation in the A549 Nrf2 KO cell lines (53% reduction in Nrf2-Het A549 cells and 82% reduction in Nrf2-KO A549 cells). Enhanced 3-NBA metabolic activation due to Nrf2 activity may lead to an increase in DNA adduct burden which would promote mutagenesis. Nrf2 signaling is considered protective against cancer initiation despite the well-recognized dark side of Nrf2 in cancer promotion and progression. Given these data, it may be appropriate to explore whether Nrf2 activation plays a role in cancer initiation in certain exposure contexts (i.e. diesel exhaust).

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