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Tobacco smoking-induced toxicity in cardiomyocytes derived from human pluripotent stem cells

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Cigarette smoking is an important risk factor for heart disease. Mechanistically-relevant biomarkers could provide timely assessment of the toxicity of tobacco products, including new products that wish to make claims with reduced health risks. The goal of this study is to investigate toxic effects and identify biomarkers of harm in induced pluripotent stem cell (iPSC)-derived human cardiomyocytes. Two cigarette smoke condensate (CSC) concentrations were tested: Low (10 μg/ml) and high (30 μg/ml) following 1-30 day exposures. RNA was isolated at defined time points (1, 7, 14, 30 days) and global gene expression was analyzed using next-generation sequencing. Exposure of cardiomyocytes to CSCs resulted in significant changes to multiple transcripts. The Nrf2-mediated oxidative stress pathway was consistently up-regulated across all time points. Moreover, microRNA-34a, which is involved in the regulation of Nrf2, was down-regulated (two-fold) in CSC-treated cardiomyocytes as early as 24 hours. The high concentration caused the largest reduction in cell viability at the longest exposure time (30 days). Interestingly, induction of the DNA damage and repair pathways occurred only after 30-day exposure .Transcriptional regulation of the Nrf2 pathway may be involved in the underlying mechanism associated with smoking-induced cardio-toxicity. Significantly dysregulated transcripts, such as heme oxygenase 1, glutathione S-reductase and microRNA-34a, in this pathway are potential biomarkers of harm that may be useful as surrogate markers in epidemiological studies and clinical trials to evaluate new tobacco products.

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