

A Computational Investigation of Tobacco Smoke Induced DNA Phosphate Modifications

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Deoxyribonucleic acid (DNA) contains the genetic information within a cell. DNA is organized into two complementary strands, each strand consisting of nucleobases, deoxyribose sugars and phosphate groups. Unfortunately, modifications to DNA can occur at either the nucleobase, sugar or phosphate moiety upon exposure to harmful agents in our environment. These modifications include alkylation, deamination and oxidation, as well as the formation of bulky DNA addition products (adducts). Although the structure and functional impact of nucleobase and sugar modifications have been well studied in the literature, there is limited information about how modifications to the phosphate backbone affect DNA structure and cellular function. A common DNA damaging agent is tobacco, with tobacco products being smoked by over one billion people worldwide. There are more than 5000 chemicals in tobacco products, including 70 known carcinogens. The most potent carcinogen is 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [1], which has been found to cause lung cancer in all species tested, regardless of the administration method [2]. In cells, it results in alkyl groups being covalently bonded to DNA phosphate oxygen atoms, yielding phosphotriester lesions. My research outlines a computational study of the alkylation of the DNA phosphate group caused by the tobacco-specific lung carcinogen NNK. Specifically, molecular dynamics (MD) simulations were performed to understand the structural impact of a modification to the DNA backbone that differ in sequence. The structural insights gained from this work provide the first glimpse of the biological impact of such modifications to the DNA backbone, which will inspire future studies to further understand their mutagenic consequences and connections with diseases such as cancer.

[1] Ma, B.; Zarth, A. T.; Carlson, E. S.; Villalta, P. W.; Upadhyaya, P.; Stepanov, I.; Hecht, S. S., Methyl DNA Phosphate Adduct Formation in Rats Treated Chronically with 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone and Enantiomers of Its Metabolite 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol. *Chemical research in toxicology*. 2018, **31** (1), 48-57.

[2] Peterson, L. A.; Context Matters: Contribution of Specific DNA Adducts to the Genotoxic Properties of the Tobacco-Specific Nitrosamine NNK. *Chemical Research in Toxicology*. 2017. **30**, 420-433.