Decoding the Link Between XPC and Lung Cancer Susceptibility: A Study of Cigarette Smoke-Induced DNA Damage in the Setting of XPC Deficiency

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Background/Objective:

Despite the known mutagenicity of cigarette smoke, only 10-15% of smokers will develop lung cancer in their lifetimes. What determines a smoker’s susceptibility to lung cancer is poorly understood. We identify the nucleotide excision repair (NER) protein Xeroderma pigmentosum Complementation Group C (XPC) as a tumor suppressor that may contribute to lung tumorigenesis when mutated and combined with cigarette smoke. Micronuclei, which are chromosome fragments and/or lagging chromosomes separated from the main nucleus, occur in many cancers, and indicate genomic instability. We hypothesize that cigarette smoke and XPC knockdown will cause genomic instability that will activate the DNA Damage Response (DDR) and increase the frequency of micronuclei and nuclear aberrancies.

Methods:

A human bronchial epithelial cell line (Beas-2B), and two lung adenocarcinoma cell lines (H1299 and A549) with stable XPC lentiviral knock-down (shXPC) or control shRNA (shCtrl) were treated with cigarette smoke extract (CSE) or air control (AC). DNA Damage Response (DDR) proteins were analyzed via immunoblot (Western). Micronuclei and nuclear aberrancies were quantified through cytokinesis-block micronucleus assay (CBMT) using immunofluorescence microscopy (DAPI).

Results:

Both CSE and XPC knockdown independently amplify expression of phospho-ATM (pATM), a DDR protein, in H1299 cells. Nuclear aberrancies increased significantly (p<0.05) with CSE in all three cell lines. Micronucleus frequency increased significantly with CSE in H1299 and Beas-2B cells (p<0.05) and with XPC knockdown in Beas-2B cells compared to shCtrl (p<0.001).

Scientific Impact and Implications:

We identified a previously uncharacterized role of XPC deficiency in augmenting cigarette-smoke induced chromosomal breaks manifesting as micronuclei, particularly in non-cancerous Beas-2B cells. These findings offer insight into tumorigenesis in cigarette smoking and shed light on mechanisms of continued DNA damage in cancer cells. Future research should clarify the mechanisms of micronucleus formation in human translational specimens and pinpoint additional functions of XPC beyond NER, including in replication repair.