PIF1 Gene Integration: A Novel Chemosensitizing Approach in Cancer

Zhang, Maximilian (School: Bergen County Academies)

Non-small cell lung cancer (NSCLC) remains one of the most prominent causes of cancer-related deaths across populations despite advancing treatment options. NSCLC is typically treated with a drug regimen including the chemotherapeutic, cisplatin, which induces DNA damage and cellular apoptosis through the DNA damage response (DDR). However, high-dosage chemotherapeutics have been demonstrated to induce cytotoxicity in normal cells, reduce quality of life, and promote secondary cancer lineages to form. This study analyzes PIF1, a 5'-to-3' DNA helicase as a potential target to reduce the chemotherapeutic dosage needed for an effective treatment. PIF1 is suggested to be involved in several functions including telomere maintenance and the initiation of the DDR. However, current research under oncogenic conditions is inconsistent, and primarily focused in Saccharomyces cerevisiae models. In this study, PIF1 upregulation through a stable transfection into NSCLC cell line A549, demonstrated increased phosphorylated H2AX expression and preferentially inactivated telomerase at elongated telomeres. Furthermore, results suggest that PIF1-cisplatin combination therapy caused a significantly higher rate of apoptosis than cisplatin alone through the wild-type p53 apoptotic pathway. Thus, this study advocates PIF1's potential to enhance low-dosage chemotherapeutics as PIF1 1) elongates and stabilizes telomeres, consequently reducing mutations and 2) initiates the DDR, inducing apoptosis. This study also works to develop a novel transportation plasmid to target cancer in a microfluidic lung environment. Focusing on cancer-expressed calpain cleavage sites and D-box motifs, and entering the cell through exosomal delivery, this protein may have the potential to target NSCLC in vivo.