Transformation of XPV Cells by E6 and E7 Genes of HPV Sensitizes the Cells to UVB Light: Synthetic Lethality and Perspectives to the Treatment of Cervical Cancer

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The human syndrome Xeroderma Pigmentosum (XP) is a rare genetic disease characterized by high sensitivity to sunlight, and, in some cases, early aging and neurodegeneration. Defects on eight different genes are responsible for this disease, and they encode for proteins involved in DNA damage processing, either a lack of Nucleotide Excision Repair (NER) (XP-A to XP-G genes) or a deficiency to encode a DNA polymerase known as XPV variant (XPV or Pol eta) with a normal NER. As a consequence, the cells from these patients are sensitive to UV light, culminating in genomic instability and predisposition to skin cancer. This project aims to evaluate the responses of cellular cultures of fibroblasts from XPV patients (mutated in the XPV gene) to the UVB light after the transformation by E6 and E7 genes of HPV-16 virus. These two proteins (E6 and E7) degrade p53 and pRb proteins respectively, which play essential roles in DNA damage responses and cell cycle regulation. To test cell sensitivity, I performed XTT assay (cellular viability) and flow cytometry. The results confirm that transformation highly sensitized the cells to UVB light, mostly due to increased apoptosis induction. This indicated clearly that the impairment of the two regulator proteins (P53 and pRb) and the Pol eta, simultaneously, can lead to a synthetic lethality situation, where at least two pathways are blocked, resulting in cell death in situation of DNA damage. Therefore, I propose that inhibiting or silencing the XPV gene can sensitize tumor cells from cervical cancer, caused basically due to HPV transformation to DNA damaging chemotherapeutic agents. This would offer a strong tool to battle this type of cancer.

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