SKIN CANCER (OTHER THAN MELANOMA)

DNA-PKCS MEDIATES EPITHELIAL-MESENCHYMAL TRANSITION OF CUTANEOUS SQUAMOUS CELL CARCINOMA VIA TARGETING TGF-β1/SMAD SIGNALING PATHWAY

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Introduction: Ultraviolet (UV) radiation is the most important environmental factor involved in the development of cutaneous squamous cell carcinoma (cSCC), because it can cause DNA double-strand breaks (DSBs) in epidermal keratinocytes. Studies have indicated that DNA dependent protein kinase catalytic subunit (DNA-PKcs) participates in the repair process of DNA-DSBs. Recently, DNA-PKcs has attracted extensive attention in various types of malignant tumors. However, the role of DNA-PKcs in cSCC development has not been elucidated.

Objective: In this study, we investigated the role of DNA-PKcs in cSCC and its molecular mechanisms of TGF-β1 induced cSCC progression.

Materials and Methods: We performed bioinformatics analysis and RT-PCR to examine DNA-PKcs expression level in cSCC of human skin tissues. Then, we downregulated DNA-PKcs expressopm using DNA-PK inhibitor and small interfering RNA (siRNA) to explore its effects on cell migration and invasion in SCL-1 cells. To further investigate the mechanism of DNA-PKcs in promoting cSCC progession, TGF-β1 and TGF-β receptor I/II (TGF-βR I/II) dual inhibitor LY2109761 were used to examine whether DNA-PKcs participates in TGF-β1/Smad signalling.

Results: We found that DNA-PKcs was upregulated in cSCC. DNA-PK inhibitor or knockdown of DNA-PKcs resulted in inhibiting cells migration and invasion and altering the expression patterns of epithelial-mesenchymal transition (EMT) markers in SCL-1 cells. Importantly, TGF-β1 mediated induction of EMT in cSCC cells and DNA-PKcs was identified as a TGF-β1-responsive gene. We further revealed that TGF-β1 promotes DNA-PKcs transcription and DNA-PKcs enhances TGF-β1-induced EMT program in cSCC invasion and metastasis by phosphorylating Smad2/3.

Conclusions: This study for the first time shows that DNA-PKcs mediates EMT in promoting

cSCC aggressiveness via targeting TGF-β1/Smad signaling pathway, which provide insight into how DNA-PKcs impacts cSCC progression and identify new therapeutic target.