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Abstract

The Pluripotency Transcription Factor Oct4 Contributes to Head and Neck Squamous Cell Carcinoma Radioresistance via Regulation of DNA Repair and the Stem Cell Phenotype †

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Abstract: Despite being the sixth most common cancer type worldwide, head and neck squamous cell carcinoma (HNSCC) exhibits low five-year survival rates for advanced-stage patients. The local control probability after radiotherapy crucially depends on efficient depletion of the pluripotent subpopulation of tumor cells. These cancer stem cells (CSCs) are characterized by an active DNA repair and, consequently, an enhanced radio(chemo)therapy resistance. This study provides evidence that due to its involvement in the regulation of the DNA damage response and stem cell phenotype, the CSC-related transcription factor Oct4 contributes to HNSCC radioresistance. In a siRNA-mediated Oct4 knockdown model, we observed reduced self-renewal capacity and partial radiosensitization of HNSCC cell lines accompanied by decreased expression of the cell cycle checkpoint kinases Chk-1 and WEE1. Consequently, Oct4 knockdown impaired the G2 checkpoint induction after irradiation, linking Oct4 to the HNSCC DNA damage response. Upon CRISPR/Cas9-mediated knockout of the pluripotency-related isoform Oct4 A, radiosensitization of HNSCC cells could only be achieved in combination treatment with the PARP inhibitor Olaparib. In addition, irradiation-induced upregulation of DNA repair genes, such as the homologous recombination repair (HRR) gene *BRCA1*, was abolished in Oct4 A knockout cells, indicating that Oct4 A depletion leads to HRR deficiency in HNSCC cells. Further analysis of the Oct4-correlating gene signature in the HNSCC TCGA patient dataset identified the HRR genes *PSMC3IP* and *RAD54L* showing a significant correlation with the overall survival of radiotherapy-treated HNSCC patients. The HNSCC self-renewal capacity and clonogenic cell survival after irradiation was reduced upon siRNA-mediated *PSMC3IP* and *RAD54L* knockdown, emphasizing the interplay between DNA repair and the CSC phenotype in HNSCC radioresistance mechanisms. All in all, the involvement of Oct4 in the regulation of DNA repair and cell cycle progression provides new insights into HNSCC radioresistance and opens possibilities for combination therapy with PARP inhibitors.

Keywords: head and neck squamous cell carcinoma (HNSCC); cancer stem cell (CSC); radiotherapy

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