The pluripotency transcription factor Oct4 contributes to head and neck squamous cell carcinoma radiosensitivity via regulation of DNA repair and the stem cell phenotype

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Summary:

- Oct4 contributes to the CSC phenotype and radiosensitivity.
- Oct4 regulates DNA repair and cell cycle progression.
- Oct4-mediated knockdown decreases clonogenic survival of HNSCC cells after irradiation.

Background:

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.1,2 In contrast to HNSCC caused by human papillomavirus (HPV) infections, HPV-negative HNSCC cases often exhibit considerable resistance to radiotherapy.1,3 Yet knowledge about radioreistance factors and potential therapeutic targets in HPV-negative HNSCC is limited. The local control probability after radiotherapy crucially depends on the eradication of cancer stem cells (CSCs), a sub-population of tumour cells characterized by pluripotency and an active DNA repair.3,4 This study provides evidence that the cancer stem cell (CSC)-related transcription factor Oct4 contributes to HNSCC radiosensitivity by regulating the DNA damage response and stem cell phenotype.

Understanding the role of Oct4 in HPV-negative HNSCC radiosensitivity is challenged by the existence of different Oct4 transcript variants and protein isoforms with presumably different functions.5,6

Cell models:

- siRNA-mediated knockdown of all Oct4 isoforms (total Oct4 knockdown) in Cal33 and UTSCC5 (HPV-negative HNSCC cell lines)
- CRISPR/Cas9-mediated Oct4 isoform A knockdown in UTSCC5 cells

Results:

- Oct4 contributes to HNSCC radiosensitivity and self-renewal. (A) siRNA-mediated Oct4 knockdown decreased the clonogenic survival of HNSCC cells after irradiation in a 2D colony formation assay. scrambled (scr) siRNA was used as control. (B) Self-renewal capability, as assessed by the ability to grow as tumour spheres, was also reduced. Scale bar: 50 μm. ***p < 0.001; error bars indicate SD.

Conclusion:

Our results in HPV-negative HNSCC cell models emphasize the interplay between DNA repair factors and the HNSCC CSC phenotype. The involvement of Oct4 in the regulation of DNA repair and cell cycle progression provides new insights into HNSCC radiosensitivity and opens possibilities for combination therapy with PARP inhibitors.

References