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ROLE OF GAIN OF FUNCTION P53 MUTATIONS IN MACROPHAGE POLARIZATION AND MYELOID-DERIVED SUPPRESSOR CELLS IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Background Head and neck squamous cell carcinoma (HNSCC) is the sixth most prevalent cancer worldwide, causing over 350,000 deaths annually out of 600,000 cases. *TP53* is a frequently mutated gene in HNSCC, with gain-of-function (GOF) mutations playing a role in tumorigenesis and predicting a poor prognosis. The mutant p53 protein can impact the tumor immune microenvironment (TIME) by regulating various inflammatory pathways. Specifically, M2-like macrophages and myeloid-derived suppressor cells (MDSC) have been implicated in promoting tumor growth and immunosuppression within TIME. Our hypothesis is that distinct mutant p53 expressions in tumor cells contribute to macrophage polarization and the generation of MDSC. Here, we employed a p53-null murine oral cancer cell line (ROC2) and conditionally expressed different p53 GOF mutations.

Methods We used a doxycycline-inducible Tet-On system to reintroduce different p53 GOF mutations, specifically, p53R270H and p53R279W. We validated the induction of the p53 mutants by western blot. Conditioned media derived from the p53 mutant cell lines both with and without doxycycline induction. The collected conditioned media were then utilized to culture bone marrow progenitor cells, and the resulting cell populations were subsequently analyzed using flow cytometry.

Results Western blot analysis confirmed the protein expression levels of the p53 mutants after induction with doxycycline. Flow cytometry studies revealed that the p53R270H mutant did not significantly affect the MDSC and macrophage populations. Conversely, the p53R279W mutant led to a significant increase in M2 macrophages but a decrease in gMDSC and mMDSC populations. Furthermore, this shift towards M2-like macrophages in the presence of p53R279W was accompanied by an upregulation of M2 macrophage markers, such as IDO.

Conclusions These results suggest that the mutant p53R279W promotes the polarization of macrophages towards an M2-like phenotype and influences the differentiation of MDSC. Future experiments aim to further understand and elucidate the role of p53R279W mutation in the TIME using syngeneic in vivo models.

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Ethics Approval All animal experiments were approved by the Institutional Animal Care and Use Committee of the University of Texas MD Anderson Cancer Center (00000950-RN03)

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