UC San Diego
MOORES CANCER CENTER

2025 Gleiberman Head and Neck Cancer Center Pilot Grant

Determining the roles apoptotic nuclease DFFB and stress response factor ATF3 in HNSCC immunotherapy response

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Scientific Abstract:
Most head and neck squamous cell carcinoma (HNSCC) patients fail to respond to immunotherapy. Overcoming immunotherapy resistance is therefore a major unmet clinical need. Our group recently identified apoptotic nuclease DFFB as a driver of tumor cell acquired resistance during targeted therapy treatment in multiple tumor types (Williams et al., Nature Cell Biology, in press, bioRxiv PMID: 40894800). DFFB exerts its functions in part by activating stress response factor ATF3 which suppresses tumor-intrinsic AP1-mediated type I interferon (IFN) signaling, enabling tumor cell escape from IFN-driven growth arrest and potentially other effects due to IFN suppression. Whether DFFB and ATF3 affect immunotherapy response is a critical open question. In preliminary data, we found that anti-PD1-treated regressed 4MOSC1 HNSCC orthotopic tumors exhibit elevated ATF3, DFFB-deficient syngeneic YUMMER1.7 melanoma tumors form less readily, and that DFFB and ATF3 are induced in CD8 T cell-tolerant antigenic human melanoma persister cells (Wang and Mauch et al., bioRxiv PMID: 40166148). Based on these observations, we hypothesize that DFFB and ATF3 cooperate in HNSCC to drive resistance to ICB. To test this hypothesis, we will determine whether DFFB (Aim 1) and ATF3 (Aim 2) promote resistance to ICB using the 4MOSC1 model. We will also profile the immune microenvironment and tumor cell features of persister cells in which DFFB and ATF3 are active. If successful, these studies will reveal a novel tumor-intrinsic mechanism of immune resistance in HNSCC and identify the DFFB-ATF3 axis as a potential response biomarker and therapeutic target to improve patient outcomes.

Lay Abstract:
Resistance to therapy remains a major problem for patients with head and neck squamous cell carcinoma. This project seeks to understand how head and neck tumor cells survive and adapt during treatment to become resistant to therapy. We have found that a protein called DFFB which is normally involved in cell death can instead help cancer cells adapt to treatment stress. DFFB activates another protein called ATF3, which dampens inflammation that is normally used by the body to fight the tumor. Together, these two proteins may allow cancer cells to block toxic signals and resist the immune system to evade therapy. To study this pathway, we will use a mouse model of oral cancer, 4MOSC1, that mimics patient responses to ICB. We will explore the role of DFFB (Aim 1) and ATF3 (Aim 2) in driving resistance to immunotherapy treatment by comparing normal tumors to tumors that are genetically modified to lack DFFB and ATF3. We will use imaging to explore how each protein affects cell signaling and the composition of pro- and anti- tumor immune cells within the tumor. In this short term, this study will reveal how head and neck cancers become resistant to immunotherapy. In the long term, this study could identify biomarkers to help predict which tumors are most likely to relapse and guide development of new therapies that target this novel tumor resistance pathway, thereby enhancing patient responses to treatment and increasing survival.