Transcriptome-Guided Framework for Overcoming Radioresistance in HNSCC: THBS1-Centered Targeting to Repurposing

Radiation therapy is central to the management of head and neck squamous cell carcinoma (HNSCC), yet radioresistance remains a major barrier. We assembled a transcriptome-guided framework to prioritize targets and radiosensitizing drugs and then cross-checked clinical relevance. Across eight HNSCC cell lines stratified by SF2, analysis of baseline CCLE RNA-seq with t-test/DESeq2/edgeR identified 17 shared DEGs; network mapping highlighted matrisome/Complex I modules with **THBS1** as a hub. THBS1 expression correlated with proton resistance and, in functional follow-up, siRNA knockdown in radioresistant Cal27 and Detroit562 increased proton sensitivity and suppressed tumor growth, supporting its relevance while not claiming causality. Transcriptomic profiling linked the THBS1-high state to blunted ER-stress apoptosis (PERK–eIF2α–ATF4), whereas low-THBS1 long-survivors in TCGA-HNSC showed enrichment of ER-stress programs; high THBS1 associated with poorer overall survival, especially in radiotherapy-treated and HPV-negative subsets. To derive actionability, we compared siTHBS1 down-signatures with drug-induced signatures from Connectivity Map (CMap) and public GEO perturbations, nominating repurposable candidates—**dasatinib** among the top—predicted to invert the THBS1-linked program. Collectively, our compact pipeline—baseline transcriptomics → THBS1 nomination → pathway context → drug prediction → survival evidence—offers a data-driven basis for THBS1-oriented radiosensitization hypotheses in HNSCC and a pragmatic shortlist for prospective testing in proton-treated cohorts.