Friend or Foe? Exploring the Role of Tumor-Fibroblast Crosstalk in Head and Neck Cancer Cell Survival

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Fibroblasts are key constituents of the tumor microenvironment and critically influence tumor progression and therapeutic response. In head and neck squamous cell carcinoma (HNSCC), fibroblast infiltration correlates with clinical outcome, suggesting a functional role in disease evolution and treatment resistance.
To investigate tumor–stromal interactions, we established two-dimensional coculture models using the HNSCC cell line Detroit 562 and normal human oral fibroblasts at defined ratios. After 48 hours, tumor cells and fibroblasts were isolated by fluorescence-activated cell sorting, and cell type–specific transcriptomic changes were analyzed by RNA sequencing with a focus on apoptosis and survival pathways. In parallel, mono- and cocultures were subjected to antitumor therapeutics to assess treatment response. Survival and proliferation differences of mono- and cocultures were also analysed by live-cell imaging.
Coculturing induced extensive bidirectional transcriptional reprogramming in both tumor cells and fibroblasts. Genes involved in cell cycle progression and mitosis were consistently downregulated, whereas survival-associated pathways were upregulated in both compartments, indicating a shift from proliferation toward microenvironment-driven adaptation. Functionally, cocultures exhibited enhanced survival following therapeutic exposure compared to monocultures, as well as enhanced proliferation.
These findings demonstrate that direct tumor–fibroblast interactions rapidly remodel transcriptional programs and promote therapy-resistant phenotypes. Our model highlights stromal–tumor crosstalk as a driver of adaptive survival mechanisms and provides a controlled platform to identify microenvironment-mediated therapeutic vulnerabilities in HNSCC.