FGFR3-TACC3 fusion proteins act as naturally occurring drivers of tumor resistance by functionally substituting for EGFR/ERK signaling

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The epidermal growth factor receptor (EGFR) is a clinically validated target in head and neck squamous cell carcinoma (HNSCC), where EGFR-blocking antibodies are approved for first-line treatment. However, as with other targeted therapies, intrinsic/acquired resistance mechanisms limit efficacy. In the FaDu HNSCC xenograft model, we show that combined blockade of EGFR and ERBB3 promotes rapid tumor regression, followed by the eventual outgrowth of resistant cells. RNA sequencing revealed that resistant cells express FGFR3-TACC3 fusion proteins, which were validated as drivers of the resistant phenotype by several approaches, including CRISPR-mediated inactivation of FGFR3-TACC3 fusion genes. Interestingly, analysis of signaling in resistant cell lines demonstrated that FGFR3-TACC3 fusion proteins promote resistance by preferentially substituting for EGFR/RAS/ERK signaling rather than ERBB3/PI3K/AKT signaling. Furthermore, although FGFR3-TACC3 fusion proteins promote resistance of additional EGFR-dependent HNSCC and lung cancer cell lines to EGFR blockade, they are unable to compensate for inhibition of PI3K signaling inPIK3CA-mutant HNSCC cell lines. Validation of FGFR3-TACC3 fusion proteins as endogenous drivers of resistance in our screen provides strong evidence that these fusions are capable of substituting for EGFR signaling. Thus, FGFR3-TACC3 fusion proteins may represent a novel mechanism of acquired resistance in EGFR-dependent cancers of multiple cell lineages.

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