00478 GNA13 Supresses YAP Expression and YAP/p73 Induced Transcriptional Activity in Head and Neck Cancers

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Aims: Gα13 (GNA13) is the α-subunit of a heterotrimeric G-protein that mediates signalling through specific G protein coupled receptors (GPCRs). GNA13 is upregulated in many solid tumors and drives drug resistance and cancer stem cell (CSC)-like phenotypes in head and neck cancers (HNSCC). However, the precise mechanisms of this GNA13-induced phenotypes are not well understood. In this project, we aim to elucidate the mechanisms of GNA13-induced suppression of YAP signalling pathway and its impact on HNSCC tumor biology.

Methodology: HNSCC cells with high GNA13 expression, NCC-HN43 and NCC-HN19, and those with low GNA13 expression, NCC-HN79, NCC-HN26 and NCC-HN49, were used as a model system. GNA13 expression was silenced using sh-RNAs in GNA13-high cells, and overexpression of GNA13 was done in GNA13-low cells respectively. Analysis of mRNA and protein expression of GNA13 and YAP1 was done using real time qPCR and immunoblotting respectively. Activity of reporters specifically driven by Hippo-YAP signalling (TEAD-Luc) and p73 (MDM2- and Collagenase-Luc) were carried out as per the luciferase assay protocol. Knockdown of YAP1 was carried out using siRNA.

Result: Blocking GNA13 expression in NCC-HN43 and NCC-HN17 cells resulted in an increase in YAP1 protein, as well as TEAD- and p73-reporter activities. Enforced expression of GNA13 in NCC-HN79, NCC-HN26, NCC-HN49 cells showed a decrease in YAP1 protein, TEAD- and p73-reporter activities. GNA13 expression had no impact on YAP1 mRNA levels. Knockdown of YAP1 showed a decrease in the TEAD- and p73- reporter activities in HNSCC cells.

Conclusion: In this study, our initial analysis shows that GNA13 suppresses YAP protein expression via post transcriptional mechanisms in HNSCC cells. Most interestingly, our data indicates that GNA13-induced suppression of YAP protein levels inhibits TEAD and p73 transcriptional activity. This GNA13-mediated regulation of YAP-p73 signalling axis could be a potential mechanism of drug resistance in HNSCCs.