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Cis-regulatory network in head and neck squamous cell carcinoma: Implications for new therapies

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Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer in the world; every year an estimated 600,000 new cases and over 300,000 deaths are reported. Most cases can be attributed to smoking and/or alcohol consumption whereas human papillomavirus (HPV) infection leads to approximately 25% of HNSCC cases. The five-year survival rate is only 40-50%, hence new therapeutic targets are needed to manage HNSCC. HPV-positivity is a favorable survival predictor although there is much debate regarding molecular differences underlying HPV-positive and HPV-negative HNSCC. Here we apply DNase I-seq and ChIP-seq methods to identify genome-wide regulatory elements relevant in HNSCC, in order to highlight the drivers of HNSCC carcinogenesis and potential therapeutic targets. DNase I hypersensitivity assay was conducted in five HPV-positive or HPV-negative HNSCC epithelial cell lines, followed by transcription factor (TF) motif and gene ontology analyses. The AP-1, TP63 and TEADs TFs were identified as forming the main regulatory network in HNSCC. This was confirmed by ChIP-seq analysis which showed a major overlap between their binding, suggesting co-regulatory mechanisms involving TGFβ, WNT/β-catenin, Notch, Hippo and EGFR pathways. Gene ontology analysis confirmed previously identified regulatory pathways of therapeutic value in HNSCC, such as EGFR and WNT, but also pointed towards the significant involvement of the Hippo pathway and its main mediating TF, TEAD in both HPV-positive and HPV-negative HNSCC cells. Indeed, the Hippo pathway inhibitor, verteporfin significantly reduces HNSCC cell viability in therapeutically relevant doses and affects the regulation of genes involved in EGFR and TGFβ and WNT regulatory pathways. In addition, RNA-seq analysis indicates verteporfin acting through altering the mevalonate pathway and affecting adrenergic receptors. Therefore, we propose the Hippo pathway as a potential therapeutic target in HNSCC irrespective of aetiology and postulate its role in affecting other HNSCC-relevant pathways.

Figure 1: The Hippo pathway has been identified as a potential therapeutic target. Schematic showing the overlap between P63, TEAD and AP-1 TF binding, suggesting co-regulation between the EGFR and Hippo pathways. Verteporfin acts downstream of the Hippo pathway to block the interaction between YAP/TEAD.

Recent Publications

1. Leemans C R, B J M Braakhuis and R H Brakenhoff (2011) The molecular biology of head and neck cancer. Nat Rev Cancer 11(1):9-22.
2. Kreimer A R, et al. (2005) Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiology Biomarkers & Prevention 14(2):467-475.
3. Hopkins J, et al. (2008) Genetic polymorphisms and head and neck cancer outcomes: a review. Cancer Epidemiology & Biomarkers Prevention 17(3):490-9.

4. Kamangar F, G M Dores and W F Anderson (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24(14):2137-50.
5. Rampias T, C Sasaki and A Psyrri (2014) Molecular mechanisms of HPV induced carcinogenesis in head and neck. Oral Oncology 50(5):356-63.

Biography

Harmeet Gill is a final year PhD student in the Wiench Group at the University of Birmingham. Her research focuses on examining the differences in the cis-regulatory network of human papillomavirus (HPV)-positive and HPV-negative head and neck squamous cell carcinoma (HNSCC) with the aim of identifying stratified therapeutic targets for HPV-positive and HPV-negative HNSCC tumors. To achieve this, she employs the DNase-I hypersensitivity assay-seq, ATAC-seq and ChIP-seq methods.

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