Conclusion Our model showed significant up-regulation of the functional HH activity in HGSC and FTSC compared to normal oviduct epithelium, suggesting the HH STP has a tumour-promoting role in most HGSC. This subset of HH-active HGSC might be of interest for HH targeted therapies.

**Gene Expression, Transcriptional Regulation**

**PO-140** MAPKAPK2 REGULATES THE TRANSCRIPT STABILITY OF TNF-$\alpha$, VEGF, P27 AND MKP-1 IN THE PROGRESSION OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Introduction Globally, head and neck squamous cell carcinoma (HNSCC) having an estimated annual burden of 6 33 000 new cases with 3 55 000 deaths is the sixth most common cancer. 90% of head and neck cancers are HNSCCs with environmental and lifestyle risk factors including sustained tobacco exposure and alcohol consumption as the primary causes. The p38 mitogen-activated protein kinase (MAPK) pathway has been implicated in a variety of pathological conditions including inflammation and metastasis. Post-transcriptional regulation of genes harbouring adenine/uridine-rich elements (AREs) in their 3′-untranslated region (3′-UTR) is controlled by MAPK-activated protein kinase 2 (MAPKAPK2 or MK2), a downstream substrate of the p38 MAPK. In response to diverse extracellular stimuli, MK2 influences crucial signalling events, regulates inflammatory cytokine release, mRNA stability and cellular processes including cell cycle regulation, angiogenesis, proliferation, metastasis and cell death. Till date, the biological significance of MK2 pathway in cancer progression is not well elucidated.

Material and methods Human clinical samples were processed for histopathological, immunohistochemical, western blotting and quantitative real-time polymerase chain reaction analysis. The findings were validated in vitro in HNSCC cell lines. Transcript levels of susceptible genes harbouring RNA-binding sites in their 3′-UTRs were evaluated along with their post-transcriptional stability in MK2-knockdown (MK2KD) cells in both normoxic and hypoxic conditions.

Results and discussions In the present study, we have reported that MK2 is reproducibly overexpressed in HNSCC and plays a crucial role in its pathogenesis by altering the translational landscape. The increased stability of cyclin-dependent kinase inhibitor 1B (p27) and mitogen-activated protein kinase phosphatase-1 (MKP-1) transcripts and the decreased half-life of tumour necrosis factor-alpha (TNF-$\alpha$) and vascular endothelial growth factor (VEGF) transcripts in MK2KD cells suggested that MK2 regulates their mRNA turnover.

Conclusion Taken together, our results portray a critical role of MK2 in modulating HNSCC pathogenesis and implicate MK2 as a prominent tumour marker. Majority of p38 inhibitors have already failed in the clinical trials, hence, we have tried to unveil MK2 as a potential novel anticancer therapeutic target in the management of HNSCC.
oncogene or tumour suppressor depending on tissue types in human cancers. Our lab has identified that FAT1 has oncogenic role in glioblastoma (GBM). miRNAs are noncoding RNAs which bind to the 3’UTR of target mRNA and repress their expression. miR-221–3p has been reported to have oncogenic role and targets tumour suppressors (e.g. CDKN1B, PTEN, PUMA etc.) in many cancers including GBM. Here, we have analysed the role of FAT1 gene in the regulation of miRNAs in glioblastoma.

**Material and methods** In-silico analysis of miR targets was done by target prediction software mirDB, TargetScan, miR-TarBase. FAT1 knockdown was done using specific siRNA and mRNA expression analysis was done for FAT1 and miR targets by using gene specific primers and miR-221/222–3p using LNA-primers (locked nucleic acid) in GBM cell lines (U87MG, U373MG, A172 and LN229). Expression and correlation analysis of FAT1 and miR-221–3p was done in GBM tumour samples (n=30).

**Results and discussions** We have observed increased expression of FAT1 and miRNAs (miR221-3p/miR222-3p) in different GBM cell lines (U87MG, U373MG, A172 and LN229). On FAT1 knockdown, using FAT1 specific siRNA we observed significantly decreased expression of miR-221/222–3p. In-silico analysis identified CDKN1B, CREBZF, TIMP3, PDCD10, PUMA and PTEN as potential targets of miR-221/222–3p. Furthermore, FAT1 knockdown-down cells showed significantly augmented expression of PDCD10, PUMA and PTEN in all studied glioma cell lines. In order to confirm our in-vitro observation and its clinical relevance, we have done expression and correlation study in GBM tumour samples. We observed significant positive spearman correlation between FAT1 and miR-221–3p (r=0.5669, p≤0.0011) and negative correlation of FAT1 with PTEN (r=−0.5007, p≤0.0048) PUMA (r=−0.5378, p≤0.0022 and PDCD10 (r=−0.3492, p≤0.0585)). These results suggest that FAT1 expression positively regulates the expression of miR-221–3p leading to downregulation of miR targets in GBM cell lines as well as in GBM tumours.

**Conclusion** Taken together our in-vitro and GBM tumour data, for the first time, suggest FAT1 to positively regulate the expression of miR-221/222–3p in GBM and reflecting the oncogenic role of FAT1 gene in GBM. We are analysing the effect of miR-mimic and anti-miRs to further validate its effect and as a possible target in therapeutic intervention.

**PO-143 RECURRENT TRANSCRIPTIONAL REMODELLING EVENTS REPRESENT CLINICALLY ACTIONABLE TARGETS IN BREAST CANCERS BRAIN METASTASIS**

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Introduction Breast cancer brain metastases are defined by complex adaptation to both adjuvant treatment regimens and the brain microenvironment. Consequences of these alterations remain poorly understood, as does their potential for clinical targeting. We aimed to comprehensively elucidate the transcriptome evolution in breast to brain metastases and to define key regulators of metastatic spread, thus, aiding in the identification of novel therapeutic strategies.

**Material and methods** 21 patient-matched primary breast tumours and their associated brain metastases from two academic institutions were RNA-sequenced. A comprehensive computational pipeline was used to investigate transcriptome evolution in breast to brain metastases. Gene expression changes were determined and prioritised based on clinical utility. To determine if these longitudinal alterations can be targeted in *in vitro*, *ex vivo* and *in vivo* experiments were performed.

**Results and discussions** Our studies revealed a comprehensive list of genes enriched in brain metastases compared to patient-matched primary breast tumours, including genes previously implicated in experimental models in the early events of vascular co-option, and those found to be essential for early survival and brain metastatic outgrowth. Our work also points to many novel candidate breast to brain metastasis genes. We observe that breast cancer-specific genes shift their expression profile upon brain metastasis, and demonstrate recurrent enrichment in druggable kinase-driven signalling (RET, ERBB2) and conclusive activation of the HER2 pathway in brain metastasis. In line with these observations, inhibition of aberrant RET and HER2 results in significant anti-tumour activity in breast cancer brain metastasis patient-derived xenograft models and patient resected brain metastasis cultured ex-vivo. We report on clinically and biologically relevant gene expression alterations occurring as breast cancer cells metastasize to the brain. Altogether, this study establishes recurrent, acquired vulnerabilities in brain metastasis that warrant immediate clinical investigation and suggests paired specimen expression profiling as a compelling and underutilised strategy to identify targetable dependencies in advanced cancers.

**Conclusion** Our findings deliver compelling proof-of-principle for exploiting longitudinal transcriptional changes in advanced cancer, which is especially important given the field’s current focus on DNA-level changes in tumour profiling.