CDK5 AS A PROGNOSTIC AND PREDICTIVE FACTOR IN COLORECTAL CANCER PATIENTS

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CDK5 has been related to cancer progression and metastasis and to response to DNA damage in cancer. In colorectal cancer (CRC), our previous results showed that CDK5 was overexpressed in CRC tumours as compared to normal tissues. CDK5 gene knockdown was associated with decreased migration and invasion of colon cancer cells but has no effect on cell proliferation; this effect was not observed in cell lines with decreased cell migration only in SW48 G12V cells, while there was no difference in the MDA-MB-433. IHC staining for CDK5 for the 3 TMAs is currently being performed.

Conclusion Our preliminary data suggest that CDK5 inhibition is effective in reducing cell viability and migration in BC cell lines. Due to SRF cross-talk with AR, its inhibition in combination with current anti-androgens represents a promising therapeutic approach not only for CRPC but also for TNBC.

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THE AP-1 TRANSCRIPTIONAL COMPLEX REGULATES AXL-INDUCED RESISTANCE TO PI3K PATHWAY INHIBITION IN HEAD AND NECK AND ESOPHAGEAL CANCER

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Introduction Phosphoinositide-3-kinase (PI3K) pathway is often hyper activated in Head and Neck and Esophageal squamous cell carcinoma leading to tumour cell proliferation and survival. Inhibition of the PI3K pathway using the isomor specific inhibitor BYL719, has shown clinical activity in patients bearing mutations or amplification of PIK3CA gene which encodes the a-subunit of PI3K. Unfortunately, the efficacy of the drug was limited by the emergence of resistance, that was driven by overexpression of the receptor tyrosine kinase AXL. The molecular mechanisms underlying AXL overexpression in resistance to PI3K inhibitors in HNSCC and ESCC remained elusive.

Material and methods RNA-seq was performed to identify transcription factors linked with resistance. Immunohistochemistry (IHC), western blotting and quantitative-PCR(qPCR) were applied demonstrating the expression levels of AXL, c-JUN, c-FOS Biomedical studies illustrated the effect of drug combination in-vitro and in vivo.

Results and discussions Q-PCR analysis of AXL mRNA level indicated a 25-fold increase in BYL719 resistant compared to sensitive cells, indicating the upregulation of AXL on the transcriptional level. By performing an RNA-seq analysis we screened for transcription factor signatures linked with resistance and correlated them with the potential binding sites for the AXL promoter. We found that the AP-1 transcription complex may play a role in AXL overexpression in resistance to BYL719. In agreement, silencing of c-JUN and c-FOS downregulated AXL mRNA and protein levels and sensitised the cells to BYL719. A positive correlation between AXL and c-JUN expression levels was demonstrated across a panel of HNSCC and ESCC cell lines, and patient tumour samples. More over, resistance to BYL719 was associated with upregulation of the transcription factor c-JUN concomitantly with an increase of AXL on the transcriptional level. The molecular mechanisms underlying AXL overexpression in resistance to PI3K inhibitors in HNSCC and ESCC remained elusive.
a superior anti-tumour activity in vivo, in both cell line derived and patient-derived xenograft models.

**Conclusion** The AP-1 transcriptional complex plays an important role in the resistance mechanism of HNSCC and ESCC cancer to inhibition of the PI3k pathway. These results support the rational for combined inhibition of JNK/c-JUN/AXL and PI3K in HNSCC and ESCC patients.

**References**

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