**PO-092** INHIBITION OF THE MTORC1-PATHWAY CAN FEEDBACK-ACTIVATE H-RAS OR K-RAS

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Introduction PJ3K/mTORC1- and Ras/MAPK-signalling pathways are aberrantly regulated in most cancers. Specific resistance to drugs targeting these pathways can emerge during tumour evolution. Preexisting, innate resistance mechanisms, such as stemming from feedback-loops, should ideally be known already during drug-target nomination. However, as the example of B-Raf-inhibitors that paradoxically activate MAPK-signalling has shown, feedback mechanisms may only become apparent at very late drug development stages.

Material and methods HEK cells expressing FRET-pairs of Ras proteins were used to study specific effects on Ras isoforms (nanoclustering). Breast cancer cells were grown in 2D for Western blotting of Ras and mTORC1-pathway proteins, or as spheroids to analyse stemness traits.

Results and discussions Here, we describe two broad feedback loops from the mTor-pathway back to the nanoscopic membrane signalling complexes (nanocluster) of H-ras and K-ras4B (hereafter K-ras). Increased nanoclustering typically correlates with increased Ras output. The first, upstream loop leads to an inadvertent rapalog induced promotion of stemness traits and tumorigenicity in Ras transformed cells. This is due to an induction of the H-ras nanocluster scaffold galecin-1, when FKBP12 levels are low. Surprisingly we find that rapalogs do not only bind to but induce a loss of FKBP12 protein. Thus, rapalog treatment induces galecin-1, which stimulates H-ras signal output and stemness traits.

Secondly, modulation of the activity in the mTORC1 pathway downstream of the major lipidode regulator SREBP1, oppositely regulates H-ras and K-ras nanoclustering. Thus, ablation of SREBP1 increases K-ras, but decreases H-ras nanoclustering and signal output. We show that altered levels of phosphatidic acid downstream of SREBP1 are sufficient for the opposite regulation of the two Ras isoforms.

Conclusion The described feedback loops may only become apparent in certain tumour settings. For example, tumour promotion during rapalog-treatment may only be relevant in H-ras mutant cancers, which make up a small portion of human cancers. In those cases, rapalog efficacy may be improved in combination with novel anti-galecin-1 drugs. Targeting the mTORC1 pathway downstream of SREBP1, may have opposite effects in H-ras and K-ras mutant cancers. Thus, care may have to be taken when targeting the mTORC1-pathway in a mutant Ras setting.

**PO-093** LIPOCALIN 2 SUPPRESS METASTASES OF ORAL CANCER THROUGH MRNA-29A-REGULATED DIPETIDYL PEPTIDASE-4

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Introduction Lipocalin 2 (LCN2), a secreted glycoprotein, is up- or downregulated in different human cancers and it has been found to play a different role in tumorigenicity. Dipeptidyl peptidase IV (DPP4), a membrane-bound peptidase on the cell surface of a wide variety of cell types and plays an important role through enzyme activity. Several recent studies have shown that DPP4 affects tumour progression and invasion in several human malignancies. However, how LCN2 and DPP4 involved in tumour progression and metastasis in oral cancer have not been studies yet.

Material and methods DPP4 expressed in LCN2 overexpression OSCC cells by protease array assay. MicroRNA array analysis and microRNA target prediction (TargetScan and PitaR) reveal that DPP4 is one of the target gene of miR-29 family.

Results and discussions Overexpression of LCN2 in oral cancer cells lines reduced in vitro migration/invasion. Mechanistically, LCN2 inhibited the cell motility of oral cancer cells through transcriptional expression of the DPP4. Knockdown DPP4 in LCN2 overexpressed cell line significantly increased cell invasion and migration. Moreover, in oral cancer cells, LCN2 significantly decreased the levels of miRNA-29a, which increased the DPP4 expression. Overexpression of miRNA-29a significantly suppressed DPP4 expression and increased OSCC cell migration and invasion (p<0.05).

Conclusion We concluded that LCN2 suppresses oral cancer cell invasion and migration through miRNA-29a-regulated DPP4.