Poster Presentation: Cancer Cell Biology

PO-098 PEROXIREDOXIN II PROMOTES HEPATIC TUMORIGENESIS THROUGH COOPERATION WITH RAS/FORKHEAD BOX M1 SIGNALLING PATHWAY

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Introduction The current study was carried out to define the involvement of Peroxiredoxin (Prx) II in progression of hepatocellular carcinoma (HCC) and the underlying molecular mechanism(s).
Material and methods Expression and function of Prx II in HCC was determined using H-ras^{G12V}–transformed HCC cells (H-ras^{G12V}–HCC cells) and the tumour livers from H-ras^{G12V}–transgenic (Tg) mice and HCC patients.
Results and discussions Prx II was upregulated in H-ras^{G12V}–HCC cells and H-ras^{G12V}–Tg mouse tumour livers, the expression pattern of which highly similar to that of forkhead Box M1 (FoxM1). Moreover, either knockdown of FoxM1 or site-directed mutagenesis of FoxM1 binding site of Prx II promoter significantly reduced Prx II levels in H-ras^{G12V}–HCC cells, indicating FoxM1 as a direct transcription factor of Prx II in HCC. Interestingly, the null mutation of Prx II markedly decreased the number and size of tumours in H-ras^{G12V}–Tg livers. Consistent with this, knockdown of Prx II in H-ras^{G12V}–HCC cells reduced the expression of cyclin D1, cell proliferation, anchorage-independent growth, and tumour formation in athymic nude mice, whereas overexpression of Prx II increased or aggravated the tumour phenotypes. Importantly, the expression of Prx II was correlated with that of FoxM1 in HCC patients. The activation of ERK pathway and expression of FoxM1 and cyclin D1 were highly dependent on Prx II in H-ras^{G12V}–HCC cells and H-ras^{G12V}–Tg livers.
Conclusion Prx II is FoxM1-dependently-expressed antioxidant in HCC and function as an enhancer of Ras^{G12V} oncogenic potential in hepatic tumorigenesis through activation of ERK/FoxM1/cyclin D1 cascade.

PO-099 TARGETING THE MITOGEN ACTIVATED PROTEIN KINASE ERK5 IN HUMAN MELANOMA

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Introduction Melanoma is the most aggressive skin cancer with a poor prognosis in advanced stages. Available treatments for melanoma are unsatisfactory, because rapidly lead to an acquired resistance in the majority of cases. Therefore, there is urgent need to identify novel possible targets involved in melanoma growth. ERK5/BMK1 is a member of the Mitogen-Activated Protein Kinases (MAPK) family and regulates cell functions critical for tumour development. Indeed, several studies reported a direct involvement of ERK5 in several types of cancer including prostate and breast cancer and hepatocellular carcinoma. However, no data have been reported about a possible role of ERK5 in melanoma.
Material and methods Cell lines and patient-derived primary melanoma cells (wild type B-RAF: SSM2c and M26c; BRAFV600E: A375, SK-Mel-5, SK-Mel-28, 501-Mel, expressing; NRASQ61R: SK-Mel-2; MeWo) have been used for *in vitro* and *in vivo* experiments. HEK293T cells were used for protein overexpression. ERK5 inhibition was achieved using ERK5 and MEK5 inhibitors or lentiviral vectors encoding shRNA specific for ERK5. BRAF inhibition was achieved using Vemurafenib, a BRAFV600E inhibitor.
Results and discussions *In silico* data analysis indicated that components of the ERK5 pathway are upregulated in up to 47% melanoma patients. Accordingly, we found that ERK5 is consistently expressed and active in commercial and patients derived melanoma cell lines. On that basis, we investigated the role of ERK5 in melanoma cell growth. *In vitro*, pharmacological or genetic inhibition of ERK5 decreased the number of viable cells in several melanoma cell lines. Moreover, xenografts performed using LV-shERK5-transduced A375 or SSM2c cells showed a reduced tumour growth when compared to those transduced with control LV-shC. We also found that oncogenic BRAF positively regulates expression, phosphorylation and nuclear localization of exogenous and endogenous ERK5. Accordingly, combined pharmacological inhibition of BRAFV600E and MEK5 is required to decrease nuclear ERK5, that is critical for the regulation of cell proliferation. Furthermore, the combination of MEK5 or ERK5 inhibitors with vemurafenib is more effective than single treatments in reducing 2D colony formation and growth of BRAFV600E melanoma cells and xenografts.
Conclusion Our results identify ERK5 as a critical regulator of melanoma growth *in vitro* and *in vivo*, and point toward the possibility of targeting ERK5, alone or in combination with BRAF-MEK1/2 inhibitors, for the treatment of melanoma.

PO-100 TARGETING YAP AND TAZ TO TREAT HIPPO PATHWAY MUTANT MALIGNANT MESOTHELIOMAS

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Introduction Malignant mesothelioma (MM) is an aggressive cancer of the mesothelium. MM has a poor prognosis with a median post-diagnosis survival of 12 months. Currently, MM is treated with platinum-based chemotherapy, resulting in side-effects to the patient. Hence, efforts have been focused on genetically analysing MM tumours to improve treatment specificity. Genetically, MMs are characterised by the loss of key tumour suppressor genes such as *NF2*. NF2 functions as a member of the Hippo signalling pathway. The Hippo pathway consists of a tumour-suppressive kinase cascade which inactivates the proto-oncogenic transcription factors YAP and TAZ. NF2 up-regulates the Hippo pathway kinases to reduce the activity of YAP/TAZ. Hence, *NF2* mutant MMs may exhibit hyperactivity of YAP/TAZ, driving oncogenic processes. So, YAP/TAZ may be ideal therapeutic targets for treating *NF2* mutant MMs.
Material and methods A panel of 7 MM cell lines and one wildtype mesothelial cell line were used to assess the potential for selectively targeting YAP/TAZ to treat MMs with