Poster Presentation: Tumour Biology

Animal Models of Cancer

PO-195 INTEGRATIVEANALYSIS OF *IN VIVO* MODELS OF PANCREATIC CANCER REVEALS COMPLEX MECHANISMS BEHIND TREATMENT FAILURE AND PROVIDES NEW TOOLS FOR EFFECTIVE TARGETING

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Introduction Pancreatic cancer remains a highly lethal cancer where response is limited by both intrinsic and acquired chemoresistance. Understanding resistance mechanisms may therefore lead to improved therapeutic strategies. We have recently defined specific molecular subgroups of pancreatic cancer associated with pre-clinical and clinical response to select tailored treatment strategies.[1–3]

Material and methods Using robust patient-derived xenografts (PDXs) of pancreatic cancer, here we generated novel *in vivo* models for the study of intrinsic and acquired chemoresistance mechanisms to clinically-used agents, gemcitabine, mitomycin C, and cisplatin. Here, we used whole genome sequencing (WGS) and microarray analysis to compare gemcitabine-resistant and gemcitabine-sensitive pancreatic tumours to identify relevant resistance mechanisms.

Results and discussions Integrative analysis of WGS and microarray profiling of gemcitabine-resistant tumours revealed complex but potentially targetable resistance mechanisms, including increased DNA repair through activation of PARP1, MCM genes and RRM1, and changes within the tumour microenvironment. Importantly, acquired resistance to gemcitabine was effectively reversed by a novel PARP inhibitor, rucaparib, indicating that combination therapy involving this low toxicity agent may be useful in treating gemcitabine-resistant tumours defined by high genomic instability. Similarly, modulation of key components of the tumour microenvironment with fasudil, as recently achieved,[2] provided another effective way of reversing gemcitabine resistance.

Conclusion Significance our findings demonstrate the promise of patient-derived xenograft models for the study of *in vivo* mechanisms of chemotherapy resistance and efficacy testing of novel agents for the treatment of human pancreatic cancer.

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PO-196 VAV1 AND MUTANT K-RAS SYNERGIZE IN PANCREATIC DUCTAL ADENOCARCINOMA DEVELOPMENT: LESSONS FROM MOUSE MODELS

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Introduction The overall 5 year survival rate of Pancreatic Ductal Adenocarcinoma (PDAC) is less than 5% and has remained stubbornly unchanged long time ago, despite the efforts in preclinical and clinical science. PDAC, the main form of pancreatic cancer, develops via acinar-ductal metaplasia (ADM) and neoplastic precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN). Mutant K-Ras is present in >90% of PDAC and is the most frequent and the earliest genetic alteration, being found in low-grade lesions. Identification of other molecular lesions that affect PDAC is of cardinal importance. One such potential protein is Vav1, a hematopietic specific signal transducer. Overexpression of wild-type Vav1 is implicated in human cancers, such as neuroblastoma, lung and PDAC. The expression of Vav1 in PDAC is indicative of a worse survival rate. Our goal was to determine whether Vav1 plays a causative or facilitatory role *in-vivo* in PDAC development.

Material and methods We generated several transgenic mouse models that express Vav1, K-Ras^{G12D}, or Vav1 and K-Ras^{G12D} in the pancreas. K-Ras was induced by tamoxifen and Vav1 by Dox. Pancreata were analysed at different times post transgenes induction.

Results and discussions Vav1 Expression together with K-Ras^{G12D} in the pancreas has a dramatic synergistic effect enhancing ADM formation already at 3 months post transgene induction, resulting in at least 3 times the number of lesions in the pancreata of Vav1;K-Ras^{G12D} mice compared to K-Ras^{G12} mice. No lesions were observed in the pancreas of Vav1 mice. The number of Ki-67 positive cells in Vav1;K-Ras^{G12D} mice was significantly higher than in Vav1 or K-Ras^{G12D} transgenic mice. The increase of pancreatic lesions was also accompanied with an increase in staining of Sox9 and Keratin and various pathways such as pERK, pEGFR and Rac1-GTP., highlighting the synergistic effect of Vav1 and K-Ras^{G12D} in the development of PDAC. Notably, removal of Dox, thus ablating the expression of Vav1 in the pancreas of Vav1;K-Ras^{G12D} led to a significant reduction in malignant lesions, thus further highlighting the necessity of expression of both oncogenes to cancer development in the pancreas.

Conclusion Vav1 contributes to the development of malignant lesions in the pancreas when expressed with mutant K-Ras. Identification of Vav1 as a protein that synergizes with mutant K-Ras in PDAC development might pave the way to choosing good candidates for therapeutic drug design.

PO-197 PATIENT-DERIVED XENOGRAFT (PDX) MODELS OF GLIOBLASTOMA: FROM BASIC RESEARCH TO PRECLINICAL STUDIES

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Introduction Animal models are essential tools for basic research and preclinical therapeutic interventions. Although numerous clinical cancer trials are being conducted, many fail due to inappropriate selection of compounds at the preclinical stage. Therefore better preclinical models are crucial for predicting successful clinical impact. Orthotropic PDX models are