Results and discussions In this study, we identified a membrane-anchored serine protease inhibitor, hepatocyte growth factor activator inhibitor-2 (HAI-2), was down-regulated in human prostate and lung cancer. The decreased levels of HAI-2 were related to the progression of human prostate and lung adenocarcinoma. HAI-2 overexpression can repress both cancer cell migration and invasion. Recombinant HAI-2 proteins can inhibit both cancer cell motility. In addition, HAI-2 overexpression reduced the tumour growth and metastasis of prostate cancer cells, while down-regulation of HAI-2 can increase the metastatic ability of lung adenocarcinoma cells in xenografted animal models.
Conclusion HAI-2 functions as a suppressor to inhibit the cell invasion and metastasis of human prostate and lung cancer.

PO-177 THE NOVEL FUNCTION OF DUSP2/VEGF-C AXIS IN PANCREATIC CANCER PROGRESSION

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Introduction The rising incidence and extremely poor prognosis makes pancreatic adenocarcinoma (PDAC) becoming one of the most malignant cancers. Dissemination through the lymphatic/vascular system is a critical process causing poor prognosis; however, how this process is regulated remains largely unknown. We aimed to elucidate the novel function of the tumour suppressor dual specificity phosphatase-2 (DUSP2), the master negative regulator of MAPK signalling, in PDAC progression and the mechanism by which DUSP2 mediates lymphovascular invasion (LVI).
Material and methods DUSP2 expression was examined in human pancreatic tumours. Orthotopic pancreatic tumour mouse models were used to determine the gain and loss of DUSP2 in PDAC progression. RT-qPCR and Western blotting were used to measure the expression of VEGF-C regulated by DUSP2. The autocrine and paracrine effects of DUSP2/VEGF-C axis were measured by migration/invasion assays. Proprotein convertase activity assay was performed to investigate the regulation of VEGF-C. Extracellular vesicle (EV) secretion was measured by nanoparticle tracking analysis, confocal imaging and Western blotting.
Results and discussions DUSP2 knockdown (KD) tumours developed increased lymphangiogenesis and increased LVI in mouse model of pancreatic cancer. Forced expression of DUSP2 abolished pancreatic cancer development. A significant increase in the functional form of VEGF-C of DUSP2-KD pancreatic cancer cells promoted survival and migration of lymphatic endothelial cells in a VEGFR dependent manner. In addition, VEGF-C signalling mediated migration/invasion ability of DUSP2-KD pancreatic cancer cells. Knockdown of DUSP2 not only increased *VEGFC* mRNA level but also enhanced the conversion of proform VEGF-C to become the mature form, which is associated with increased activity of proprotein convertase. Loss-of-DUSP2 enhanced EV secretion thus promoted the release of mature form VEGF-C. Novel histone deacetylase inhibitor, exerting similar effect as DUSP2 re-expression, can not only diminish VEGF-C secretion but also confer synergistic effect with routinely used chemotherapeutic drug for PDAC.
Conclusion We provide new evidence demonstrating that loss of DUSP2 in pancreatic cancer cells increases expression of VEGF-C, which exerts autocrine and paracrine functions to promote early dissemination of pancreatic cancer.

PO-178 WDR5 PROMOTES METASTASIS DISSEMINATION IN BREAST CANCER

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Introduction The core subunit of the COMPASS-like complex, WD Repeat Domain 5 (WDR5) has a prominent role in cell self-renewal, reprogramming and Epithelial-to-Mesenchymal transition (EMT) in different tumour types. We have identified WDR5 as an epigenetic target in *in vivo* and *in vitro* shRNA screenings performed in MCF10DCIS.com (from now MCF10DCIS) breast cancer (BC) cells. Here, we show that WDR5 can regulate metastasis dissemination in BC by stimulating TGFB-induced EMT.
Material and methods MCF10DCIS and MDAMB231 cells and six metastatic PDXs were used for *in vivo* and *in vitro* studies. Cells were transduced to silence WDR5 (shWDR5) or a neutral control (shLuc). Transcriptomic profiles were evaluated by RNA-seq in shLuc and shWDR5 PDXs and MCF10DCIS cells. Differentially expressed genes (DEGs) were identified using Log2FC>|0.6| and FDR<0.05. Chromatin Immunoprecipitation was performed to identify H3K4me3 binding in shLuc and shWDR5 MCF10DCIS cells. Peak calling was performed using MACS2.0 and peaks distribution was analysed within ±2.5 kbp from Transcription Start Sites (TSS) region of target genes. TGFB induction was obtained by 5 ng/ml TGFB-administration for 2 days in MCF10DCIS cells. Statistical analysis was performed by applying a Student *t* test for *in vivo* and *in vitro* experiments.
Results and discussions WDR5 interference significantly inhibited tumour growth and *in vitro* migration of PDXs and MCF10DCIS cells and reduced metastatic burden of MDAMB231 cells *in vivo*. These data suggested that WDR5 may be involved in cell motility, promoting invasiveness and metastasis. Gene Ontology performed on DEGs highlighted an enrichment of functions related to EMT and TGFB signalling. Indeed, protein and mRNA levels of a series of gene implicated in EMT (e.g. SNAI1, TWIST1, CDH2, SNAI2, ZEB1) were strongly reduced in shWDR5 PDXs and MCF10DCIS cells, thus suggesting a regulatory role of WDR5 in EMT. H3K4me3 levels were globally affected and concordantly reduced at TSS level of SNAI1 and TWIST1 genes in shWDR5 MCF10DCIS cells, confirming that WDR5 can transcriptionally regulate EMT in BC. Moreover, the induction of EMT by TGFB treatment can be abrogated in WDR5-deficient cells, suggesting that the EMT induced by TGFB is WDR5-dependent.
Conclusion Our evidences support a model in which WDR5 is responsible for mediating the epithelial-to-mesenchymal transition and metastasis dissemination in BC. WDR5 is essential for TGFB response and its inhibition may be a successful approach to prevent progression of metastatic BC.