tumor-free omentum, indicating a niche for ovarian cancer cells toward omental metastasis. 

**Conclusion** Our data demonstrate that α2,6 sialylation on integrin α2 triggers ovarian cancer cell adhesion to metastatic sites. Therefore, blocking sialylation and integrin α2 may be a therapeutic target for preventing ovarian cancer metastasis in the future.

**PO-174** EVALUATION OF IMMUNOHISTOCHEMICAL EXPRESSION OF MICROFIBRILLAR-ASSOCIATED PROTEIN 5 (MFAP5) IN INVASIVE BREAST CARCINOMA OF NO SPECIAL TYPE

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10.1136/esmoopen-2018-EACR25.213

**Introduction** Breast cancer (BC) remains the most prevalent female cancer in Egypt and worldwide. Microfibrillar-associated protein 5 (MFAP5) is a multifunctional glycoprotein. Although MFAP5 gene was among the genes that found globally expressed in human cancers, it had been only recently reported in few cancer research studies.

**Material and methods** This is a retrospective study that has been conducted on 66 Egyptian patients who had invasive carcinoma of no special type (IC-NST). Immunohistochemical staining for MFAP5 was applied on the archival formalin-fixed paraffin-embedded blocks. Staining was assessed semiquantitatively and correlated with the available clinicopathological parameters and immunohistochemical subtypes of BC.

**Results and discussions** MFAP5 epithelial cytoplasmic expression was observed in 89.4% (59/66) of cases. In contrast, nuclear expression was seen in normal breast lobules and pre-malignant lesions adjacent to tumours that also exhibited constant staining in myoepithelial layer. Statistical analysis of epithelial cytoplasmic expression revealed association of MFAP5 expression with tumour size (p=0.046), high histological grade (p=0.007), presence of lymph node (LN) metastasis (p=0.014), poor Nottingham Prognostic Index (NPI) (p=0.001), late stage (p=0.008), immunohistochemical subtypes of BC (p=0.018), and increased MVD using CD34 immunostaining (p=0.04). MFAP5 cytoplasmic expression was also observed in an adjacent DCIS component in 37/45 cases (82.2%).

**Conclusion** This study showed that MFAP5 is a novel myoepithelial cell marker that appears to be up-regulated in duct epithelium in DCIS and IC-NST during tumourogenesis and that its cytoplasmic expression in invasive tumours seems to have a poor prognostic role manifested by its association with poor prognostic parameters such as high grade, late stage, lymph node invasion and increased MVD.

**PO-175** THE SECRETARY MIR-141 FACILITATES OVARIAN CANCER METASTASIS THROUGH REPROGRAMMING STROMAL FIBROBLAST CELLS IN PRE-METASTATIC NICHE FORMATION

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10.1136/esmoopen-2018-EACR25.214

**Introduction** Regardless of the modern advances in cancer therapeutics, cancer metastasis is still a major obstacle in the clinical management of ovarian cancer. Emerging evidence discloses exosomal miRNAs act as critical roles in cancer development. One of the possibility is the secretary miRNAs mediating communications between tumour cells and their tumour microenvironment. However, the functions and mechanisms of miRNAs in regulating cancer metastasis are not fully understood. We have previously identified that Hsa-miR-141 (miR-141) is not only aberrantly expressed in aggressive ovarian cancer but also enhances anoikis resistance in metastatic progression of ovarian cancer through targeting KLF12/SP1/Survivin axis. Here, we report that miR-141 is also a tumour secretary miRNA which can remodel the stromal cells to facilitate the formation of pre-metastatic niches for ovarian cancer metastasis.

**Material and methods** QPCR analysis was used to evaluate the level of exosomal miR-141 in the conditioned medium of ovarian cancer cells. T-HESCs and WPMY-1 were used for miR-141 mediated reprogramming stromal cells. Cytokine array, ELISA, QPCR and Western blot analyses were used for measuring the levels of EMMPRIN and GRO-α. LC-MS/MS and proteome analyses to identify miR-141-mediated target, Yes Associated Protein 1(YAP1).

**Results and discussions** miR-141 was frequently overexpressed in ovarian cancer cells and also secreted to the surroundings through exosomal pathway. Functional analyses revealed miR-141 enables to reprogram the stromal cells because miR-141-expressing stromal cells showed an escalating secretion of cytokines GRO-α and EMMPRIN in cultured media. By co-culture with ovarian cancer cells with above conditioned media, or the recombinant proteins of GRO-α and EMMPRIN, ovarian cancer cells exhibited increased cell proliferation. Proteomic profiling of miR-141 reprogrammed stromal cells revealed YAP1, a key downstream effector of the Hippo pathway was suppressed. Depletion of YAP1 in stromal cells also increased the expression of GRO-α and EMMPRIN in the conditioned media. On the contrary, restoration of YAP1 attenuated the escalated secretion of GRO-α and EMMPRIN, indicating the reduction of YAP1 might be required for increased YAP/TAZ – mediated transcriptional activities of GRO-α and EMMPRIN.

**Conclusion** Our preliminary findings suggest the exosomal miR-141 could reprogram stromal cells through altering Hippo/YAP1 signalling in production of GRO-α and EMMPRIN, to facilitate metastatic colonisation of ovarian cancer.

**PO-176** HEPATOCYTE GROWTH FACTOR ACTIVATOR INHIBITOR-2 SUPPRESSES HUMAN PROSTATE AND LUNG CANCER CELL INVASION AND METASTASIS

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10.1136/esmoopen-2018-EACR25.215

**Introduction** Cancer metastasis is a main cause for mortality. Dysregulation of pericellular proteolysis usually accounts for cancer cell invasion and metastasis. In this study, we are interested in delineating the role of hepatocyte growth factor activator inhibitor-2 (HAI-2) in prostate and lung cancer cell invasion and metastasis.

**Material and methods** We used different prostate and lung cancer cells and animal models to examine the role of HAI-2 in prostate and lung cancer cell invasion and metastasis.
**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 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 VEGF-C 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 TGFβ-induced EMT.

Material and methods MCF10DCIS and MDMAB231 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. TGFβ induction was obtained by 5 ng/ml TGFβ 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 MDMAB231 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 TGFβ 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 TGFβ treatment can be abrogated in WDR5-deficient cells, suggesting that the EMT induced by TGFβ 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 TGFβ response and its inhibition may be a successful approach to prevent progression of metastatic BC.