as in the in-situ serous carcinoma of the FT. The down regulation results from hemizygous loss in many of the tumours and from activation of the PI3K/AKT and the Ras/MEK/ERK pathway, which targets FOXO3a for degradation, and in some cases due to up-regulation of miR-182. We managed to restore partial activity of FOXO3a using inhibitors of these pathways.
Conclusions: The immortalized benign FTSEC lines are an important asset for the identification of early-detection biomarkers and 'drugable' pathways in serous carcinoma. FOXO3a loss may be a key event in the progression into an invasive disease. It is possible to rescue FOXO3a activity with currently available experimental drugs.

1062 POSTER

Blood and Lymphatic Vessels: Early Crucial Players of Malignancy and Metastasis in Cervical Cancer

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Background: Cervical neoplasia remains one of the most controversial issues for clinicians, pathologists and researchers. Screening programs reduced the incidence of invasive neoplastic lesions but did not change the rate of precursor lesions. Usually, malignant lesions of the uterine cervix are considered more important than precursor lesions.
Angiogenesis and lymphangiogenesis are accepted as important factors favouring tumour growth and metastases. But, questions about (i) startpoint of angiogenesis and lymphangiogenesis in cervical lesions, (ii) proliferative and/or activated status of cervical neovessels or (iii) the origin of lymph vessels and prognostic impact of lymphangiogenesis in precursor lesions of the uterine cervix still remain without a precise response.
Material and Methods: One hundred and twenty eight specimens of benign, premalignant and malignant cervical lesions were included in the present study. Co-localisation of Ki67 proliferation marker with CD105 in blood vessels endothelium and D2−40 in lymphatic endothelium was obtained by applying doublestain method followed by use of two different chromogens (3.3′diaminobenzidine for nuclear brown staining of Ki67 and aetil amino charbazole for cytoplasmic red staining of CD105 and D2−40).
Results: Specimens evaluation of normal, premalignant and malignant lesions of the uterine cervix revealed that activation and proliferation of blood vessels in cervical lesions are distinct processes. Activation of endothelial cells is an early event which predominate in benign and premalignant conditions of the uterine cervix while endothelial cell proliferation is observed in tumour vessels endothelial cell from cervical invasive carcinoma. Lymphangiogenesis is an early event in the pathogenesis of cervical lesions. The highest number of proliferative lymphatic vessels (D2/40+/Ki67+) was significant correlated with low grade intraepithelial lesions (LSIL, $p = 0.009$), high grade intraepithelial lesions (HSIL, $p = 0.044$), and microinvasive carcinoma ($p = 0.002$). The last correlation also persist in invasive carcinoma.
Conclusions: Our data showed that early lymphatic endothelial proliferation in preneoplastic stages of cervical lesions preceed the development of the angiogenic switch. Angiogenic process also begin in preinvasive lesions stages of cervical lesions and had different and distinct mechanisms.

1063 POSTER

Vasohibin-1 and Vasohibin-2 Are Expressed in Both Gastric Cancer Cells and Tumour-associated Macrophages and Play Roles in Anti-Angiogenesis Not Only as Intrinsic Inhibitors

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Background: Recently, Vasohibin-1 and vasohibin-2 are found in endothelial cells and considered as two intrinsic anti-angiogenesis factors. However, So far, we don't know whether they are expressed in cancer cells themselves and tumour-associated macrophages (TAMs) which have been confirmed to contribute to tumour progression.
Materials and Methods: Realtime RT-PCR were used to quantitatively investigate the vasohibin-1 and vasohibin-2 expression in four gastric cancer cell lines including non-metastatic cell line AGS and metatatic cell lines HGC-27, Hs-746T and NCI-N87 with or without co-cultured with TAMs, as well as their expressions in TAMs under normal or hypoxia condition. Furthermore, the correlation between vasohibin-1, vasohibin-2 and VEGF-A expressions were analyzed under different culture condition.
Results: Both vasohibin-1 and vasohibin-2 were expressed in four gastric cancer cell lines and TAMs. Under normal condition, vasohibin-1 and vasohibin-2 expression were up regulated significantly by macrophages in four gastric cancer cell lines. Under hypoxia condition, both vasohibin-1 and vaosohibin-2 expression were decreased significantly in distant metastasis cancer cell line Hs-746T ($P < 0.001$), moreover, the increase induced by macrophages was also down regulated significantly in Hs-746T cell line($P < 0.001$). The regulations for vasohibin-1 and vasohibin-2 expression by macrophages and hypoxia had correlation with VEGF-A expression. In addition, hypoxia induced vasohibin-1 and vasohibin-2 significant up-regulations in TAMs co-cultured with metastatic cancer cell lines ($P < 0.05$).
Conclusions: Both vasohibin-1 and vasohibin-2 was expressed in gastric cancer cells and TAMs, and their expression were regulated by TAMs and hypoxia. Vasohibin-1 and vasohibin-2 might not only be an intrinsic angiogenesis inhibitors in endothelial cells, but also play important roles in anti-angiogenesis as an extrinsic inhibitors mediated by TAMs. Vasohibin-1 and vasohibin-2 might be as a novel anti-angiogenesis target in the treatment of gastric cancer.

1064 POSTER

Adaptive Exploitation of Stromal Cell Metabolism by Tumour Cells

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Background: Tumour cells secrete factors to recruit and activate stromal cells in the tumour microenvironment (TME) leading to reciprocal paracrine support of tumour growth by stroma-derived growth factors. This is an important means by which tumours adapt their microenvironment to facilitate their growth. Indeed, breast cancer development and metastatic progression is highly dependent on stromal support, particularly from carcinoma associated fibroblasts (CAFs). As a result of aerobic glycolysis, tumour cells produce and secrete high levels of lactate, thought to be a toxic byproduct that needs to be extruded into the tumour milieu.
Using *in vitro*-generated CAFs, we investigated the role of lactate in CAF-mediated support of tumour growth. In addition to extruding lactate as a byproduct of glycolysis, we suggest that tumour cells secrete it to recruit and subsequently exploit stromal cells to recycle lactate into utilizable metabolites, such as pyruvate, to fulfill metabolic demands of tumour cells.
Materials and Methods: We used a lactate analyzer (Roche Diagnostics) to quantify lactate in media; transwell migration assays were used to measure lactate-induced *in vitro* migration; RT-PCR was used to determine expression of genes involved in lactate transport; ^{13}C NMR spectroscopy was used to track the metabolic fate of lactate; luciferase assays were used to monitor growth of tumour cells.
Results: We find that MDA-MB-231 breast cancer cells (MDAs) secrete significantly higher levels of lactate under hypoxia, and that lactate recruits mesenchymal stem cells (MSCs), the precursors of CAFs. Lactate is transported by monocarboxylate transporters (MCTs); cells take up lactate via MCT1 and efflux it via MCT4. Expectedly, MDAs display low expression of MCT1 while exhibiting high expression of MCT4. However, CAFs show high expression of MCT1 while displaying low expression of MCT4, indicating that lactate extruded by the tumour cells is taken up by stromal cells, in a source-sink manner. NMR analyses indicate that ^{13}C-lactate is metabolized via the Krebs cycle in stromal cells. Finally, pyruvate-mediated tumour cell growth assays indicate that CAFs may serve to evacuate lactate from the TME, thereby reducing lactate-mediated inhibition of stroma-derived pyruvate influx into tumour cells.
Conclusions: Thus, stromal cells in the TME (1) have the capacity to take up tumour-secreted lactate and use it as an energy source, and (2) may provide subsequent/surplus metabolites, such as pyruvate, to tumour cells as a secondary source of energetic and biosynthetic precursors. To our knowledge this is the first *in vitro* model system demonstrating tumour/stroma metabolic coupling by which tumour cells exploit stromal cells. A better understanding of the molecular mechanisms governing metabolic cooperation within the tumour milieu will potentially identify new targets for therapeutic intervention.

1065 POSTER

An in Vitro Comparative Study of Fulvestrant and Tamoxifen in Breast Cancer Cells

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Aim: In the current study, two selective antagonists of the estrogen receptor (ER), fulvestrant which suppresses and degrades the ER (SERD, selective estrogen receptor down regulator) and tamoxifen which modifies the function of the ER (SERM, selective estrogen receptor modulator) were