activity. Importantly, inhibition of NFkB with Bay 11-7085 (8.5 mM) leads to loss of cell viability and is accompanied by decreased levels of HSP70 and HSP27, as well as their transcription factor, HSF-1, at the RNA and protein levels. Furthermore, overexpression of a phosphorylation-deficient mutant of IKBa in MIAPaCa-2 cells resulted in decreased NFkB activity and the loss of HSP70 expression.
Conclusion: HSP70 is known to be regulated by several mechanisms. Here we show a novel NFkB-mediated mechanism by which HSF-1 and its transcriptional targets, HSP27 and HSP70 are down-regulated in pancreatic cancer cells in response to triptolide.
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PP116—METASTATIC BREAST CARCINOMA INDUCES VASCULAR ENDOTHELIAL DYSFUNCTION IN BALB-C MICE: ROLE OF TUMOR NECROSIS FACTOR-ALPHA AND NADPH-OXIDASE

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Introduction: Although the oxidative stress and inflammation are closely related with breast cancer, there is no study directly examining the possible changes in vascular functions in the presence of breast carcinoma. The goal of the present study was to evaluate changes in vascular reactivity in tumor-bearing mice.
Patients (or Materials) and Methods: In this study, highly metastatic breast carcinoma cells which was derived from liver or brain metastasis of 4T1 murine breast carcinoma (4TLM and 4TBM, respectively), and 67NR cells which is tumorogenic but nonmetastatic cells were used. Female Balb-c mice 8 to 10 weeks old were divided into following groups: (1) control; (2) injected with 67NR; (3) injected with 4TLM; and (4) injected with 4TBM orthotopically. Thoracic aorta was removed 25 days after injection of tumor cells. Isometric tension studies were performed in response to potassium chloride (KCl), phenylephrine (Phe), acetylcholine (ACh, an endothelium-dependent vasodilator), and sodium nitroprusside (SNP, an endothelium-independent vasodilator). Endothelial nitric oxide synthase (eNOS), phosphorylated eNOS (Ser 1177) (p-eNOS), gp91phox, and tumor necrosis factor-α (TNF-α) expressions in aortic tissues were demonstrated by immunohistochemistry. The level of TNF-α in vascular tissue was evaluated by ELISA.
Results: Presence of tumor was resulted in significant inhibition of response to ACh in both 4TLM- and 4TBM-injected mice but not 67NR-injected mice. Furthermore, both KCl and Phe-induced contraction of thoracic aorta was not changed significantly in tumor-bearing animals. eNOS and p-eNOS expressions decreased while gp91phox and TNF-α expressions increased in endothelium significantly in mice with metastatic breast carcinoma compared with 67NR-injected and control mice. Moreover, TNF-α levels of thoracic aorta in 4TLM and 4TBM mice were higher than that of 67NR mice. Tumor-induced endothelial dysfunction determined by ACh-induced relaxation improved by superoxide dismutase (SOD), apocynin (a NADPH oxidase inhibitor), and infliximab (a TNF-α monoclonal antibody).
Conclusion: The findings of this study suggest that presence of metastatic breast carcinoma may cause a significant reduction in endothelium-dependent relaxation of thoracic aorta via NADPH oxidase-mediated oxidative stress and TNF-α production.
Disclosure of Interest: None declared.

PP117—THE VARYING EFFECTS OF PENTOXIFYLLINE ON CYCLIN D1 LEVELS AND G1 PHASE ARREST IN DIFFERENT RENAL CELL CARCINOMA CELL MODELS

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Introduction: Cyclin D1 is required for cells to progress from the G_1 phase of the cell cycle into the S phase. Mutation or overexpression of cyclin D1, often occurring in tumors, leads to uncontrolled cell cycle progression and proliferation. QTRRE (rodent) as well as ACHN and 786-O (human) cell models of renal cell carcinoma (RCC) display elevated cyclin D1 protein levels. Pentoxifylline (PTX), an FDA-approved competitive, nonspecific phosphodiesterase inhibitor, has found recent use as an adjunct in chemotherapy for patients to help treat cachexia and capillary leak syndrome.
Patients (or Materials) and Methods: We utilized Western blot analysis as well as propidium iodide-based cell cycle analysis to study the effects of PTX in our RCC cell models.
Results: Initially (0–8 hours), PTX induced a time- and dose-(35 μM–3.5 mM) dependent decrease in cyclin D1 levels in the RCC cell models. Cotreatment with PTX and the protein translation inhibitor, cycloheximide (5–25 μM), revealed a decrease in cyclin D1 protein half-life. Furthermore, the PTX-induced decrease of cyclin D1 was abolished in the presence of a proteasome inhibitor (MG-132, 10 μM) in all 3 RCC cell models. Subsequently (12–72 hours), PTX caused maximal cyclin D1 decreases in QTRRE and ACHN cells, whereas cyclin D1 levels in 786-O cells recovered and surpassed initial amounts seen in the control. Concomitant with cyclin D1 levels, QTRRE and ACHN cells demonstrated enhanced G1 phase cell cycle arrest at 24 hours (170% and 140%, respectively) compared with 786-O cells (107%) and the nontumorigenic human kidney cell line HK-2 (107%).
Conclusion: The data suggest that PTX decreases cyclin D1 protein levels by stimulating proteasomal degradation (and subsequent G_1 phase arrest), which is sustained in the QTRRE and ACHN but not 786-O RCC cell models. The data reveal a need to better understand the differences in PTX response between the RCC cell models. Moreover, an ability to predict a positive response to PTX may contribute to better personalized cancer therapy treatment for patients. Because our findings also reveal a novel anticancer chemotherapeutic property of PTX, the utility of PTX as an adjuvant therapy in the treatment of cancer should be further explored.
Disclosure of Interest: None declared.

PP118—IN VITRO STUDY OF SONODYNAMIC AND PHOTODYNAMIC TREATMENT ON HUMAN CANCER CELL LINES

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Introduction: Photodynamic therapy (PDT) is an anticancer treatment that uses light to activate cytotoxic compounds killing cancer cells. Sonodynamic therapy (SDT) is a new anticancer treatment where ultrasound is used to trigger the cytotoxic effect of chemical compounds known as sonosensitizers. SDT is able to focus the ultrasound energy, generated by selected continuous or pulsed ultrasound such as shock waves (SW), onto malignant sites situated deeply inside tissues overcoming the main drawback linked to the use of PDT: the poor penetration of light in biological tissues. Even if the SDT mechanism is still under debate, some researchers suggest a common basic