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P03.16 FUNCTIONAL DEFECTS IN B-CELLS OF PATIENTS WITH VON-HIPPEL-LINDAU SYNDROME

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Von-Hippel-Lindau (VHL)-disease is an inherited cancer syndrome characterized by a variety of benign and malignant tumors, which develop upon mutation of the second allele of the VHL-tumor suppressor gene. The VHL-protein (pVHL) regulates hypoxia-induced transcription factors (Hif) and by this plays a central role for metabolic cellular adaptations to hypoxic conditions. VHL/Hif regulation plays a well-established role in the development and function of immune cells and already VHL-haploinsufficiency can alter gene expression patterns. In contrast, little is known about primary immune cell functions in VHL-patients. In this study, we analyzed the functional capacity of CD40-stimulated B-cells to act as antigen-presenting cells. We confirmed mono-allelic VHL-gene mutations in B-cells from thirteen VHL-patients and found that their response to CD40-stimulation was significantly reduced. On a functional level this translated to an impaired ability to act as antigen presenting cells leading to impaired T-cell responses *in vitro*. Taken together, we demonstrate that VHL-haploinsufficiency deregulates B-cell functions following CD40-activation as a new aspect of VHL-syndrome. (The study was registered in the German Clinical Trial Registry (www.drks.de); ID: DRKS00012413).

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P03.17 UPA-PAI-1 HETEROMERS PROMOTE ADVANCED STAGES OF BREAST CANCER BY ATTRACTING PRO-TUMORIGENIC NEUTROPHILS

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Background High tumor levels of urokinase-type plasminogen activator (uPA)-plasminogen activator inhibitor-1 (PAI-1) heteromers independently predict poor survival in early breast cancer. The pathogenetic role of this protein complex, however, remains largely obscure.

Materials and Methods Neutrophil trafficking was analyzed in orthotopic (multi-channel flow cytometry) and heterotopic (ear; multi-channel *in vivo* microscopy) mouse models of 4T1 breast cancer, in a mouse peritonitis assay (multi-channel flow cytometry), as well as in the mouse cremaster muscle (multi-channel *in vivo* microscopy). Cytokine expression in tumors was determined by multiplex ELISA. Phenotypic and functional properties of primary mouse neutrophils, microvascular endothelial cells (cell line bEnd.3), macrophages (cell line RAW 264.7), and breast cancer cells (cell line 4T1) were characterized in different *in vitro* assays. uPA/PAI-1 expression and neutrophil infiltration in human breast cancer samples were assessed by RNA sequencing, immunohistochemistry, and ELISA.

Results Here, we demonstrate that uPA-PAI-1 heteromerization multiplies the potential of the single proteins to attract pro-tumorigenic neutrophils. To this end, tumor-released uPA-PAI-1 utilizes very low density lipoprotein receptor and ERK mitogen-activated protein kinases to initiate a pro-inflammatory program in peritumoral macrophages. This promotes neutrophil trafficking to cancerous lesions and primes these immune cells towards a pro-tumorigenic phenotype, thus supporting tumor growth and metastasis. Blockade of uPA-PAI-1 heteromerization by a novel inhibitor effectively interfered with these events and prevented tumor progression.

Conclusions Our findings identify an already therapeutically targetable interplay between hemostasis and innate immunity that drives advanced stages of breast cancer. As a personalized immunotherapeutic strategy, blockade of uPA-PAI-1 heteromerization might be particularly beneficial for patients with highly aggressive uPA-PAI-1^{high} tumors.

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P03.18 ABSTRACT WITHDRAWN

P03.19 EVALUATION OF IMMUNOGENICITY DIFFERENCES IN LLC1 AND GL261 TUMOR MODELS FOR EFFECTIVE CHEMO-IMMUNOTHERAPY TREATMENT

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Background Tumor immunogenicity is a critical factor responsible for the limited success of cancer immunotherapy and determine the need for personalized treatment. Correct evaluation of effectiveness of cancer treatments and their combination is inseparable from the proper selection of the experimental tumor model. The lack of knowledge about the immunogenicity of animal tumor models makes it difficult to evaluate the efficacy of cancer immunotherapy and becomes