
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-1inh tumors.

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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