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Tumor-associated proteolytic factors uPA and PAI-1: Clinical relevance and promising targets for therapy

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There is abundant evidence that tumor-associated proteolytic factors uPA (urokinase-type plasminogen activator) and its inhibitor PAI-1 play a key role in tumor invasion and metastasis. Elevated levels of these factors in tumor tissue are associated with tumor aggressiveness and poor patient outcome in various solid tumors. In breast cancer, uPA and PAI-1 are the first novel tumor biological factors reaching the highest level of evidence (*LOE I*) for clinical application: A strong and independent prognostic impact of uPA and PAI-1 in primary breast cancer was validated by a pooled analysis performed by the EORTC Receptor and Biomarker Group (*Harbeck et al, ASCO Proc 2001, #1646).* Moreover, the utility of uPA and PAI-1 as selection criteria for therapy decisions in node-negative breast cancer was shown in a prospective randomized German multi-center trial (*Jänicke et al, JNCI 93, 2001*). Robust and quality-assured ELISA assays are available to quantify uPA and PAI-1 in primary tumor extracts, thus enabling routine uPA and PAI-1 testing for establishing risk-adapted individualized therapeutic strategies, particularly in node-negative breast cancer.
Animal models suggest that the plasminogen activator system with its key components uPA and PAI-1 is not essential for fertility or survival under physiological conditions. Therefore, it seems well suited as a therapeutic target for solid tumors. Novel therapy concepts targeting the uPA system are currently being explored *(Schmitt et al, Fibrinolysis & Proteolysis 14, 2001).* A variety of different *synthetic uPA inhibitor classes* have been developed over the last decades *(Muehlenweg et al, Expert Opin Biol Ther 2001, in press).* A few modern compounds have shown promising results in preclinical testing and are now ready for phase I clinical studies. Other therapeutic strategies such as *antagonists of uPA/uPA-R interaction* or *gene therapeutic approaches to suppress the uPA-system* are still being evaluated in *in vitro* and *in vivo* models. For clinical application, combination therapy targeting more than one of the interacting proteolytic pathways may be required for effective anti-proteolytic therapy. Anti-proteolytic agents may provide additive or synergistic treatment benefits if used in combination together with potent conventional therapeutics.

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Antivascular effect of electrochemotherapy with cisplatin

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The major determinant of antitumor effectiveness of electrochemotherapy (combination of electric pulses and chemotherapeutic drugs) is increased drug concentration in the cells due to cell membrane electroporation. However, other mechanisms were proposed to be involved, such as immune system response, tumor blood flow modifying and antivascular effects. The aim of this study was to determine the effects of electrochemotherapy with cisplatin on endothelial cells and tumor blood flow and their relation to antitumor effectiveness. Survival of SA-1 (mouse fibrosarcoma) cells after electrochemotherapy was determined by clonogenic assay and of HMEC-1 (human microvascular endothelial) cells by MTT proliferation assay. Antitumor effectiveness of electrochemotherapy *in vivo* on s.c. SA-1 tumors was determined by tumor growth delay. Tumor perfusion changes after electrochemotherapy was estimated by using Patent blue staining technique. Electrochemotherapy potentiated cytotoxicity of cisplatin for both cell lines with similar level of cell kill. Prolonged tumor growth delay was obtained in tumors treated with electrochemotherapy compared to the control groups. Electrochemotherapy with cisplatin induced a significant reduction in tumor blood flow up to 5 days after the treatment. In conclusion, our study shows that electrochemotherapy is cytotoxic for endothelial cells and reduces tumor perfusion, which provides evidents for its antivascular action.