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Novel key players in cancer metastasis and signaling-based inventions for metastasis restriction

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Metastatic dissemination of primary tumors is directly linked to patient survival in many tumor entities and critically limits successful therapy. In human colorectal cancer (CRC), we identified the novel gene Metastasis Associated in Colon Cancer 1, MACC1. MACC1 regulates fundamental processes like proliferation, motility, and dissemination in cell culture and metastasis in mouse models. MACC1 regulates the transcription of genes able to induce metastasis by themselves; e.g., it was identified as a master regulator of c-Met. In CRC patient tumors and blood, MACC1 is a tumor stage-independent predictor for metastasis and survival, allowing early identification of high-risk patients. MACC1 is confirmed as prognostic and predictive biomarker and decisive driver for tumorigenesis and metastasis in a broad variety of solid cancers, correlating to patient survival. MACC1 inhibitors are not available so far. Thus, we developed MACC1-signaling based interventions for metastasis restriction. First, we identified the gene promoter of MACC1, unveiled its transcriptional regulation, and employed the MACC1 promoter for high throughput screenings. We identified the first transcriptional small molecule MACC1 inhibitors. These drugs restrict MACC1-induced metastasis in mice. Furthermore, we addressed the impact of MACC1 post-translational modifications for developing intervention strategies. Using mass spectrometry, we identified kinases phosphorylating MACC1. Targeting the kinase for MACC1 tyrosine phosphorylation with inhibitors employed in clinical trials restricts MACC1-induced tumor growth and metastasis in mice. In summary, transcriptional and post-translational regulations of MACC1 are druggable by small molecules inhibitors. We present first MACC1-signaling based interventions for restriction of tumor progression and metastasis of CRC.

Biography

Ulrike Stein has completed his PhD from the Humboldt University Berlin, Post-doctoral studies from the National Cancer Institute/NIH Frederick MD, her habilitation from the Charité Universitätsmedizin Berlin and was 2009 appointed as Professor. She heads the research group of Translational Oncology of Solid Tumors at the Experimental and Clinical Research Center, Charité and Max-Delbrück-Center for Molecular Medicine in Berlin. She has published more than 130 papers in reputed journals, reveiced national and international scientific awards, is contributing to scientific consortia, is serving as Editorial Board Member of several journals, and acts as reviewer for journals and funding organizations.

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