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Cancer metastasis biomarkers: Discover, develop and intervene

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Statement of the Problem: Metastasis is directly linked to colorectal cancer (CRC) patient survival and accounts for about 90% of patient deaths. It represents the most lethal event during the disease course and critically limits successful therapy.

Aim: Our translational concepts aim at the identification of key molecules such as S100A4 in tumor progression and metastasis for improved prognosis and therapy of solid cancers.

Methodology: We discovered key players of metastasis, their transcriptional targets, protein binding partners and signaling pathways thereof as new diagnostic, prognostic and predictive biomarkers for tumor progression and metastasis. Biomarker development was done in established and patient-derived 3D cultures, cell line-derived and patient-derived xenografts (PDX) and newly generated genetically engineered mouse models. We exploited this knowledge for improved disease prognosis and treatment response prediction in tissue and blood of cancer patients of several tumor entities. We established intervention strategies targeting biomarkers such as S100A4 for metastasis inhibition in mice.

Results: Small hairpin RNA (shRNA) acting on the biomarkers, on their transcriptional or post-translational targets decreased *in vivo* metastasis, also when applied systemically. In particular, small molecule transcriptional inhibitors were identified by high throughput screening, restricted biomarker-induced metastasis in mice. This repositioning of already FDA-approved drugs for the new indication of metastasis restriction paved the way for clinical trials.

Conclusion & Significance: We currently translate our findings on restricting S100A4-driven colorectal cancer metastasis into clinical practice. Novel therapeutic approaches targeting S100A4 are currently tested in phase II clinical trials to treat patients with metastatic disease. Our assay for detecting and quantifying circulating biomarker transcripts in patient blood is used to monitor treatment success.

Biography

Ulrike Stein completed her Diploma degree at Martin-Luther University Halle, Germany and PhD at Humboldt University Berlin. For her Post-doctoral studies, she joined the laboratory of Dr. R H Shoemaker at National Cancer Institute/NIH Frederick as Feodor-Lynen-Fellow of Alexander von Humboldt foundation. She received her Habilitation at Charité Universitätsmedizin Berlin and appointed as Professor. She heads the research group of Translational Oncology of Solid Tumors at Experimental and Clinical Research Center, Charité Universitätsmedizin and Max Delbrück Center for Molecular Medicine in Berlin. Her research is focused on "Understanding and intervening in tumor progression and cancer metastasis formation". She has published more than 130 papers in reputed journals. She is an Editorial Board Member and Reviewer of several journals. She received various national and international scientific awards.

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