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Restriction of cancer metastasis - Translating gene discovery into clinical application

Cancer metastasis is the most lethal attribute of cancer, is responsible for >90% of cancer deaths and critically limits successful therapy in many tumor entities, directly linked to patient survival. We identified the novel, previously undescribed gene Metastasis-Associated in Colon Cancer 1 (MACC1). MACC1 induces fundamental processes like cell proliferation, migration, invasiveness and metastasis in xenografted and transgenic mice. Meanwhile, MACC1 has been established as key player, important prognostic and predictive biomarker for tumor progression and metastasis in >20 solid cancers. By pan-omics, we discovered MACC1-regulating and regulated networks, and their functional impact in cell culture, organoids, animal models, patient tumor tissue and blood. We unveiled transcriptional targets, protein-protein interactors, and post-translational effectors, serving as new diagnostic, prognostic and predictive key players for tumor progression and metastasis. BRET revealed MACC1 as homodimers in living cells, with mutations of the predicted dimer interface hindering metastasis formation in vivo. We identified repositioned drugs and novel compounds as transcriptional and post-translational small molecule inhibitors, restricting MACC1-induced metastasis in mice. Together with the metastasis inducer S100A4, which we first identified as Wnt-signaling target and metastasis predictor, but also as a MACC1 transcriptional target, we demonstrated their beneficial combinatorial impact for early identification of high-risk cancer patients, for improved prognosis and response prediction using tumors and blood of solid cancer patients. A phase II clinical trial to investigate the safety and efficacy of niclosamide tablets in patients with metastases of a CRC progressing after therapy: NIKOLO, registered under ClinicalTrials.gov NCT02519582, demonstrated a significant reduction of S100A4 by niclosamide in patient blood. In conclusion, our ultimate goal are signaling-based new sussessful therapeutic concepts for metastasis prevention and restriction.

Keywords

cancer metastasis, MACC1, S100A4, signaling network, clinical impact, intervention

Biography

ULRIKE STEIN graduated in biochemistry at the Martin-Luther-University Halle, received her PhD in Biochemistry at the Humboldt-University Berlin and post-graduated in Biochemical Medicine, Germany. She was Post-Doc as Feodor-Lynen-fellow, Alexander von Humboldt-foundation at the National Cancer Institute (NCI), Frederick, MD, USA, and was invited there as visiting scientist from 1996-2011. She received her Habilitation (Assistant Professorship) in Biochemistry in 2003 and was appointed to a professorship in 2009 at the Charité, Universitätsmedizin Berlin. Currently, she is head of the research group “Translational oncology of solid tumors” at the Experimental and Clinical Research Center, Charité and Max-Delbrück-Center for Molecular Medicine Berlin, Germany

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