UKE Paper of the Month July 2015

Oncotarget, 2015 May 25 (PMID 26124177)

Drosophila homologue of Diaphanous 1 (DIAPH1) controls the metastatic potential of colon cancer cells by regulating micro-tubule-dependent adhesion

Yuan-Na Lin, Ridhirama Bhuwania, Kira Gromova, Antonio Virgilio Failla, Tobias Lange, Kristoffer Riecken, Stefan Linder, Matthias Kneussel, Jakob R. Izbicki, Sabine Windhorst

ABSTRACT: Drosophila homologue of Diaphanous 1 (DIAPH1) regulates actin polymerization and microtubule (MT) stabilization upon stimulation with lysophosphatidic acid (LPA). Recently, we showed strongly reduced lung metastasis of DIAPH1-depleted colon cancer cells but we found accumulations of DI-APH1-depleted cells in bone marrow. Here, we analyzed possible organ- or tissue-specific metastasis of DIAPH1-depleted HCT-116 cells. Our data confirmed that depletion of DIAPH1 strongly inhibited lung metastasis and revealed that, in contrast to control cells, DIAPH1-depleted cells did not form metastases in further organs. Detailed mechanistic analysis on cells that were not stimulated with LPA to activate the cytoskeleton-modulating activity of DIAPH1, revealed that even under basal conditions DIAPH1 was essential for cellular adhesion to collagen. In non-stimulated cells DIAPH1 did not con-trol actin dynamics but, interestingly, was essential for stabilization of microtubules (MTs). Additional-ly, DIAPH1 controlled directed vesicle trafficking and with this, local clustering of the adhesion pro-tein integrin-β1 at the plasma membrane. Therefore, we conclude that under non-stimulating condi-tions DIAPH1 controls cellular adhesion by stabilizing MTs required for local clustering of integrin-β1 at the plasma membrane. Thus, blockade of DIAPH1-tubulin interaction may be a promising approach to inhibit one of the earliest steps in the metastatic cascade of colon cancer.

STATEMENT: *Our paper represents interdisciplinary work of clinical issues combining basic molecular cancer re-search, with the goal to attain clinical application in future. In this present work, in which altogether 10 UKE researchers (clinicians and basic researchers) were involved, we aimed to reveal a new potential therapeutic approach in the treatment of metastasising colon cancers. For that purpose we started our approach at the basis of cell migration; the cytoskeleton. In summary, we were able to show the micro-tubule-modulating activity of the formin DIAPH1 (Drosophila homologue of Diaphanous 1) being essen-tially regulative in metastasis of colon cancer by controlling early cell adhesion as one of the earliest steps in the metastatic cascade. By gaining this new essential mechanistic insight of colon cancer cell dynamics, we are now able to better understand the process of DIAPH1-mediated colon cancer metas-tasis, in purpose to identify drugs specifically blocking the interaction of DIAPH1 with tubulin, which may be a promising new therapeutic approach for metastasising colon cancers.*

BACKGROUND: This work was performed by Dr. med. Yuan-Na Lin from the Department of General, Visceral and Thoracic Surgery in collaboration with PD Dr. rer. nat. Sabine Windhorst from the Institute of Biochemistry and Signal Transduction. It was supported by a “UCCH Drittelstipendium 2013” and by various UKE collaborations partners, showing the very interdisciplinary approach of this work: Prof. Dr. Tobias Lange (Department of Anatomy and Experimental Morphology), Prof. Dr. Stefan Linder (Institute for Microbiology, Virology and Hygiene), Prof. Dr. Matthias Kneussel (Department of Molecular Neurogenetics, ZMNH), Dr. Antonio Virgillio Failla (UKE Microscopy Imaging Facility) and Dr. Kristoffer Riecken (Department of Stem Cell Transplantation).