NAMI-A controls the HCT-116 CRC invasion processes through the modulation of a5b1 integrin expression and activation

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NAMI-A, imidazolium *trans*-imidazoledimethylsulfoxidetetrachlororuthenate, is a ruthenium-based drug characterised by the selective activity against tumour metastases. With the present study we explore whether the interference of NAMI-A with a5b1 integrin may explain the mechanism of metastasis inhibition using the experimental model of HCT-116 colorectal cancer (CRC) cells *in vitro*.
This study takes advantage of the knowledge derived by the model of CRC metastases in which we have documented the influence of the liver microenvironment to direct the metastasis arrest of the CRC invading cells.
NAMI-A inhibits the adhesion and migration processes of CRC cells to ECM proteins, two important steps of the tumour metastatic progression. NAMI-A perturbs the interactions of the tumour cells with their microenvironment and its action is connected with the engagement of the cell surface integrins. In particular, a5b1 integrin resulted to be the putative specific target for the anti-adhesive effects of NAMI-A in the CRC HCT-116 cells during their interaction with the extracellular matrix. The inhibition of a5b1 integrin supports the NAMI-A induced reduction of HCT-116 cell adhesion to fibronectin, one of the main ECM components in the liver, the organ target of colorectal cancer metastases: NAMI-A reduces i) a5b1 integrin expression on the cell membrane and ii) the activation of a5b1 integrin through FAK Tyr397 auto-phosphorylation. These effects are confirmed by the use of siRNA specific for the gene encoding for the a5 integrin subunit and/or by the use of a specific blocking MoAbs against the fully assembled integrin.
These results contribute to elucidate the molecular mechanism of action of NAMI-A, and show that a5b1 integrin is the relevant target of NAMI-A for the control of CRC metastasis dissemination. This study also supports the role of NAMI-A as a reference drug to break the rule of the need of cytotoxic drugs for the control of tumour growth in favour of drugs that modulate the biological events involved in the tumour malignancy.

Acknowledgements
COST Action CM1105 is gratefully acknowledged for STSM support of Chiara Pelillo and Hilaria Mollica. Work supported by Callerio Foundation Onlus and by WG 1 'Protein targets' of COST CM1105 'Functional metal complexes that bind to macromolecules'.