Selective inhibition of metastasis in vivo, partly through disruption of nucleoli


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Identification and development of effective anti-cancer drugs using PNC as a phenotypic marker for metastatic potential of cancer cells.

Methods: To identify compounds selectively targeting the metastatic state, we used the perinuclear compartment (PNC), a complex nuclear structure associated with metastatic behaviors of cancer cells, as a phenotypic marker for a high-content screen of over 140,000 structurally diverse compounds. Extensive medicinal chemical optimization of a screening hit yielded metarrestin, which has been evaluated for in vitro and in vivo efficacy against xenograft tumor growth and metastasis from three type’s human cancers in animal models. Biochemical and cellular characterizations have identified some of the modes of action for metarrestin. Results: Metarrestin disassembles PNCs in multiple cancer cell lines, inhibits invasion in vivo, blocks metastatic development in three mouse models of human cancer, and extends survival of mice in a metastatic pancreatic cancer xenograft model even when macrometastasis have developed. Metarrestin induces little toxicity or discernable adverse effects in animals when treated daily up to 4 months. Metarrestin selectively disrupts the nucleolar structure and inhibits RNA polymerase (Pol) I transcription in cancer cells, at least in part by interacting with the translation elongation factor eEF1A2. Thus, metarrestin represents a potential therapeutic approach for the treatment of metastatic cancer.

Conclusion: PNC and nucleoli may play roles in metastatic cancer development.

The systematic study on the epigenomics of mei-Cohesins in the norm and as Cancer-Testis proteins

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