Targeting the extracellular signature of metastatic colon cancers

Experimental and Molecular Therapeutics

Targeting the extracellular signature of metastatic colon cancers

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Abstract

4094

Colon cancer is a leading cause of mortality, mainly as a consequence of malignant cell spreading to liver, brain and lungs. Despite the possibility of a certain range of intervention at least for liver metastases, the success of surgery is related to the very early detection of few lesions, which is rarely achieved with our present knowledge.

Epithelial and endothelial cells in metastatic sites express peculiar proteins, to accomplish for their survival in the host environment. Investigating the complex of these characteristics (the “extracellular signature of metastasis”) is pivotal to understand the molecular mechanisms leading to metastases. This extracellular signature is dependent both on the intrinsic properties of tumor cells and on the tissue microenvironment. Consequently, the search for metastasis-specific players has to be conducted with selective processing of tumor tissues. We set up a

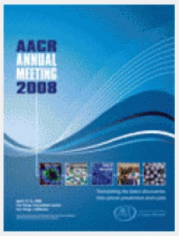

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Table of Contents
Index by Author

protocol for the isolation of heterogeneous cell populations by tissue fractionation of liver metastasis biopsies from colon cancer patients immediately after surgical removal. We screened these tissues with phage-displayed peptide libraries, obtaining more than 200 single peptides binding to liver metastasis cells, 7 of which were further validated.

We next followed two mirror approaches. From the ligand side, we investigated homologies between the 7 metastasis-validated peptides and known human extracellular proteins. This first part of the metastatic signature revealed several proteins potentially involved in tumor progression, angiogenesis and metastasis, among which angiopoietins, cadherins, heregulins, integrins and matrix proteins. From the receptor side, we set up pull-down and proteomics experiments, in which we fished potential receptors with one of the selected peptides. This second part of the metastatic signature revealed two potential players, E-cadherin and α6 integrin, possibly interacting in a molecular complex.

We propose one of more of these ligand/receptor pairs be involved in tumor angiogenesis and/or, more specifically, in the process of liver metastatization. On verification of the molecular mechanism(s), we are presently developing innovative diagnostic (imaging with nanopartilcles) and therapeutic (targeted liposomes) approaches.

Footnotes

- 99th AACR Annual Meeting-- Apr 12-16, 2008; San Diego, CA

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Previous

Back to top