An extra-cellular protein signature of metastatic colon cancer

Metastasis, Invasion, and Tumor Microenvironment Targets

An extra-cellular protein signature of metastatic colon cancer

Serena Marchio, Marco Soster, Paola Bovino, Jessica Sun, Maria Monti, Piero Pucci, Renata Pasqualini, Wadih Arap, and Federico Bussolino

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Abstract

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Colon cancer is a leading cause of tumor death mainly as a consequence of malignant cell spreading and invasion of organs such as bone, brain, lung, and liver. Despite the possibility of a certain range of intervention for liver metastases, the success of surgery depends on early detection of few lesions, which is rarely achieved. Moreover, little information is available about the molecular mechanisms leading to liver metastases, making it difficult to design proper diagnostic and therapeutic approaches. Epithelial and endothelial

metastatic cells have peculiar characteristics, different from both the primary tumor and the tissues in which they localize. Particularly, modifications occur on their surfaces, where molecules are expressed or modified in order to accomplish for the best survival in the host environment.

The process of metastatization is dependent both on the intrinsic properties of tumor cells and on tissue microenvironment. Indeed, it is well established that the features of the host organ determine the phenotype and the behavior of metastatic cells. Consequently, the search for metastasis-associated genes has to be conducted with selective processing of tumor tissues.

We have set up a protocol for the isolation of heterogeneous tumor cell populations by tissue fractionation of liver metastasis biopsies from patients immediately after surgical removal. We use cells extracted from adjacent macroscopically healthy liver as a negative control.

We screened phage-displayed peptide libraries on cells from 20 human liver metastases, and isolated more than 200 tumor-targeting peptides. In our preliminary studies, we have focused on 7 of these peptides, which share homology among each other and among different patients, suggesting both specificity and wide-range applicability. We have demonstrated that these peptides specifically bind to metastatic cell lines as well as to metastatic cells and tissues from patients. A bioinformatic analysis suggested that different proteins might be the receptors for these peptides on the malignant cell surfaces. Indeed, with this approach we have identified several pairs of partners potentially involved in metastasis progression, among which Semaphorins/Plexins, HERs/ Heregulins, integrins/matrix proteins, cadherins. The analysis of this extra-cellular signature of metastatic cancers opens many intriguing possibilities for future research.

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), innovative diagnostic and therapeutic approaches might also be developed.

Footnotes

- AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics-- Oct 22-26, 2007; San Francisco, CA

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Previous

Back to top

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