PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Mechanisms of melanoma metastasis

ArticleInfo		
ArticleID	:	3649
ArticleDOI	:	10.1186/gb-2000-1-3-reports0067
ArticleCitationID	:	reports0067
ArticleSequenceNumber	:	18
ArticleCategory	:	Paper report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2000–8–23 Received : 2000–8–23 OnlineDate : 2000–9–18
ArticleCopyright	:	BioMed Central Ltd2000
ArticleGrants	:	

ArticleContext	:	130591133

Jonathan B Weitzman

Abstract

Analysis of highly metastatic melanoma cells using oligonucleotide arrays has identified genes regulating tumor invasiveness.

Significance and context

Metastasis, the ability of cancer cells to leave the primary tumor site and spread throughout the body, presents the greatest clinical threat to the survival of cancer patients. Metastasis is a complex process, and little is known about the genetic events that regulate the switch to a metastatic phenotype. It is expected that the genes involved include those that regulate cell adhesion, cell migration and invasiveness. A useful experimental system for selecting metastatic variant cells lines involves *in vivo* selection in nude mouse tumorigenesis models. Poorly metastatic tumor cell populations are injected into the tail vein and relatively rare cells that are capable of metastasizing to the lungs are dissected several weeks later. Repeated rounds of selection can generate cell lines with a spectrum of metastatic capacities. Differential analysis of these variants allows the identification of proteins involved in the metastatic switch. This is the first example of the application of DNA microarray technology to the identification of metastasis-related genes.

Key results

The authors began their study by using repeated rounds of *in vivo* selection to generate metastatic variants of melanoma cells: amelanotic A375P human cells and the B16F0 mouse cell line. To search for metastasis-specific genes the authors used oligonucleotide arrays (containing 7,070 human genes and 6,347 mouse genes, of which 50% overlap). They report data on 32 genes that were upregulated in either human or mouse metastases. Notably, three genes were upregulated (more than 2.5 fold) in both species in all metastatic variants. These genes (for fibronectin, thymosinα4 and RhoC) encode proteins with functions that might be predicted for metastasis-associated genes. Fibronectin is a key component of the extracellular matrix and a ligand for integrin cell-adhesion receptors. Thymosinα4 is an actin-sequestering protein and regulates actin polymerization. RhoC is a member of the Rho family of small GTPases and has been linked to cytoskeleton reorganization. The authors chose to focus on RhoC for subsequent experiments. They showed that overexpression of RhoC in the parental A375P cells dramatically increased metastasis *in vivo* and cell migration *in vitro*. Conversely, expression of a

dominant-negative Rho mutant (N17RhoA) suppressed metastasis and motility of the highly metastatic A375M selected variant.

Methodological innovations

The generation of metastatic variants by selection *in vivo* offers an attractive experimental model, as any differences relative to parental lines may be related to metastatic capacity. Previous studies have used this approach combined with hybridoma technology or differential cloning techniques. The strength of the current paper is its thoroughness - the authors used two different human and mouse melanoma models and an extensive functional genomics screen to focus on a relatively small number of metastasis-associated genes.

Links

Further information about analysis of large-scale datasets generated by microarray experiments can be found at the Molecular pattern recognition website at the Whitehead/MIT Genome Center and at the Hynes lab.

Conclusions

The authors conclude that RhoC is essential and sufficient for metastasis. They state that RhoC differs from the well-studied RhoA protein by just six non-conservative amino-acid substitutions in the carboxyl terminus, suggesting that there may be functional differences between these related proteins.

Reporter's comments

This study identifies a surprisingly small number of genes involved in the complex process of metastasis. It fails to identify several genes that have previously been implicated in metastasis, such as metalloproteinases and integrins; perhaps the levels of expression of those in parental lines is already sufficient. It will be important to determine which of the identified genes are relevant in a clinical context and which may be prognostic for metastasis and patient survival.

Table of links

Nature

Molecular pattern recognition

Hynes lab

References

1. Clark EA, Golub TR, Lander ES, Hynes RO: Genomic analysis of metastasis reveals an essential role for RhoC. Nature. 2000, 406: 532-535. 0028-0836