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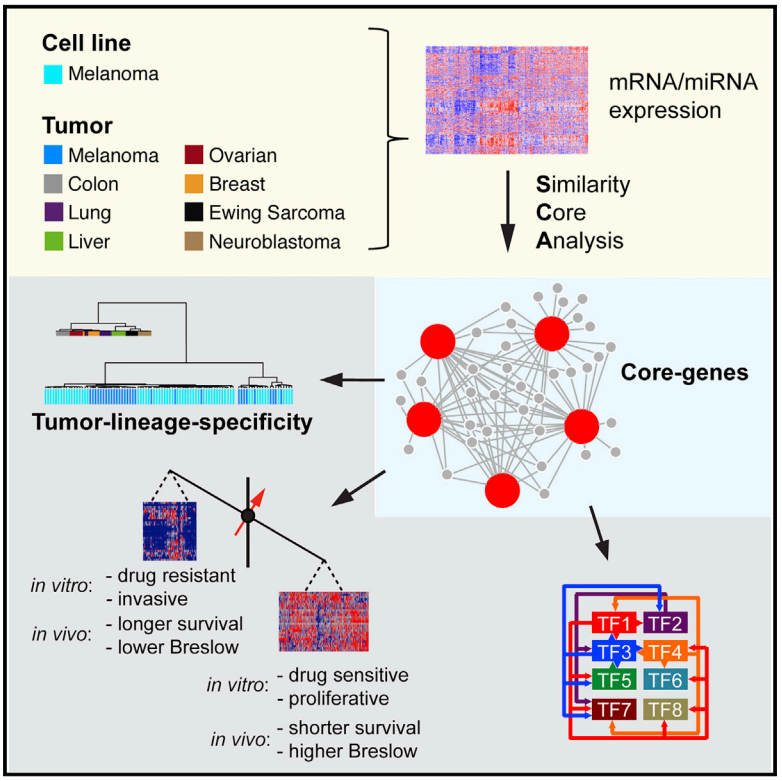
New Functional Signatures for Understanding Melanoma Biology from Tumor Cell Lineage-Specific Analysis

Graphical Abstract



Highlights

- Similarity core analysis (SCA) is a bioinformatics tool for analyzing expression data
- SCA generates specific transcriptome-miRnome signatures for any tumor type
- SCA clusters aggressive and non-aggressive tumors and cell lines
- Molecular signatures reveal a lineage-specific regulatory network for melanoma

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In Brief

Cancer cell lines are at the forefront of drug discovery but are often limited in representing the tumor of origin due to the artificial culture conditions. Rambow et al. develop a computational approach for identifying tumor cell lineage expression cores. These core genes reveal relevant molecular dependencies linking aggressiveness, patient survival, and drug sensitivity.

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New Functional Signatures for Understanding Melanoma Biology from Tumor Cell Lineage-Specific Analysis

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SUMMARY

Molecular signatures specific to particular tumor types are required to design treatments for resistant tumors. However, it remains unclear whether tumors and corresponding cell lines used for drug development share such signatures. We developed similarity core analysis (SCA), a universal and unsupervised computational framework for extracting core molecular features common to tumors and cell lines. We applied SCA to mRNA/miRNA expression data from various sources, comparing melanoma cell lines and metastases. The signature obtained was associated with phenotypic characteristics in vitro, and the core genes *CAPN3* and *TRIM63* were implicated in melanoma cell migration/invasion. About 90% of the melanoma signature genes belong to an intrinsic network of transcription factors governing neural development (*TFAP2A*, *DLX2*, *ALX1*, *MITF*, *PAX3*, *SOX10*, *LEF1*, and *GAS7*) and miRNAs (*211-5p*, *221-3p*, and *10a-5p*). The SCA signature effectively discriminated between two subpopulations of melanoma patients differing in overall survival, and classified MEKi/BRAFi-resistant and -sensitive melanoma cell lines.

INTRODUCTION

Genome-wide profiling approaches have provided molecular insight into cancer initiation and progression, promoting the development of targeted drugs for personalized treatment (Gonzalez-Angulo et al., 2010). However, cancer treatments targeting driver mutations are prone to resistance development, due to genetic and epigenetic tumor heterogeneity. Tumor cell-type- or lineage-specific expression characteristics were identified as key predictors of responses to several compounds in a screen of 479 cancer cell lines of 36 different tumor types (Barretina et al., 2012). Cancer-derived cell lines also are used in drug discovery, but may differ from the tumor of origin (Ertel et al., 2006; Gillet et al., 2013; Masters, 2000). In tumors, different cell types interact with each other and the tumor microenvironment, whereas cell lines are essentially clonal. Culture conditions and long-term passaging select the most adapted (potentially artificial) patterns of gene expression, resulting in differences in gene expression and epigenetic status between cell lines and tumors (van Staveren et al., 2009). The unsupervised clustering of whole-transcriptome expression data clearly separates cell lines from tumor samples, even if they contain the same mutations (Domcke et al., 2013). We therefore need to identify significant similarities in gene expression between cancer-derived cell lines and tumors that might be masked by differences due to biological growth conditions.

Differential gene expression analyses have identified differences, but not core similarities, between cell lines and tumors for particular cancers. Comparisons of cell lines and tumors on this basis are uninformative, as they simply separate in vivo and in vitro samples (Domcke et al., 2013). Supervised gene lists can be used to identify suitable tumor models from cancer cell lines (Dancik et al., 2011; Gillet et al., 2011; Uva et al., 2010), or similarities between cancer cell lines and their tumors of origin can be scored with a tissue similarity index (TSI). This method uses expression data, without identifying the features underlying the similarity (Sandberg and Ernberg, 2005).

We designed a computational framework for the unsupervised extraction of core (= signature) molecular features common to tumors and cell lines. Characterization of this core should provide information about phenotypic in vitro and clinical in vivo