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Transcriptomic and Proteomic Data Integration and Two-Dimensional Molecular Maps with Regulatory and Functional Linkages: Application to Cell Proliferation and Invasion Networks in Glioblastoma

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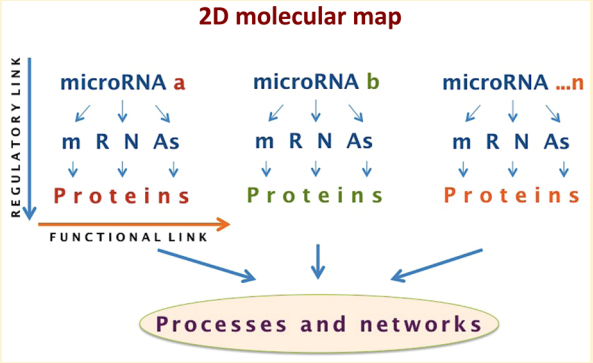
Supporting Information

ABSTRACT: Glioblastoma multiforme (GBM), the most aggressive primary brain tumor, is characterized by high rates of cell proliferation, migration, and invasion. New therapeutic strategies and targets are being continuously explored with the hope for better outcome. By overlaying transcriptomic and proteomic data from GBM clinical tissues, we identified 317 differentially expressed proteins to be concordant with the messenger RNAs (mRNAs). We used these entities to generate integrated regulatory information at the level of microRNAs (miRNAs) and their mRNA and protein targets using prediction programs or experimentally verified miRNA target mode in the miRWalk database. We observed 60% or even more of the miRNA−target pairs to be consistent with experimentally observed inverse expression of these molecules in GBM. The integrated view of these regulatory cascades in the contexts of cell proliferation and invasion networks revealed two-dimensional molecular interactions with regulatory and functional linkages (miRNAs and their mRNA−protein targets in one dimension; multiple miRNAs associated in a functional network in the second dimension). A total of 28 of the 35 differentially expressed concordant mRNA−protein entities represented in the proliferation network, and 51 of the 59 such entities represented in the invasion network, mapped to altered miRNAs from GBM and conformed to an inverse relationship in their expression. We believe the two-dimensional maps of gene expression changes enhance the strength of the discovery datasets derived from omics-based studies for their applications in GBM as well as tumors in general.



KEYWORDS: *glioblastoma, microRNA, proteomics, transcriptomics, 2D molecular maps, cell proliferation, cell invasion*

INTRODUCTION

Malignant gliomas, the most common type of brain cancer, arise from glial cells within the central nervous system. Gliomas are classified according to histopathological criteria defined by the World Health Organization as grades II, III, and IV. The grade IV tumors, also referred to as Glioblastoma multiforme (GBM),[1−3] are the most common and aggressive tumors, characterized by uncontrolled proliferation, areas of necrosis, and diffuse infiltration, with poor prognosis and a median survival rate of 12 months, even with an aggressive treatment.[1,4] The capacity of GBM cells to disperse from the primary tumor site and infiltrate the brain parenchyma severely limits the effectiveness of surgery as well as radiotherapy. Thus, targeting the invading cells to restrain their migratory capacity is likely to provide a strong alternative to GBM therapy.[5−7] There are already some efforts in this direction, and newer ways of exploring the molecular changes underlying these tumors would be useful to get better molecular insights on their pathogenesis.

The tumor has been extensively analyzed at the genomic, transcriptomic, and proteomic levels, which has resulted in a large volume of molecular data underlying tumor-associated processes and interaction networks. The repertoire of somatic genomic alterations in GBM have been extensively described by several groups using whole-genome and exome sequencing strategies to identify copy number alterations, complex rearrangements, and novel mutated genes that may drive this

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