A meta-metastasis analysis reveals pan-cancer markers and therapeutic targets

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Introduction

Metastasis is a leading cause of cancer-related deaths across several cancer types, yet the molecular details of its development have not been fully elucidated. Transcriptomic analysis can provide insights into the expression changes in the tumor that confer metastatic potential even during early stages of tumorigenesis. Here, by leveraging RNA-seq data collected by The Cancer Genome Atlas (TCGA), we systematically identified mechanisms consistently associated with metastasis in primary tumors from 4844 patients across 13 different cancer types via comparison of primary tumors from patients with primary site, node-negative disease with no recorded distant metastasis (N0 not M1) compared to primary tumors from patients with node-positive disease (N2, N3, or N4). Differentially expressed genes were first determined within each cancer type, to reduce tissue- or disease-specific effects. Subsequently, via meta-analysis, we combine these results to identify commonly across 13 different types of cancer. Next, using a proprietary drug prediction algorithm called Drugfinder, we identified drug candidates that can target metastasis across all cancer types and within specific cancer types.

Methods

Differential expression analysis and meta-analysis. First, TCGA RNA-seq data were used to identify genes differentially expressed between N0 and N2 patients for 12 cancer types using limma (L. 2). Filter was used as a covariate to remove batch effects. The cancer gene sets were aggregated using the common variance weighting method to generate a meta-metastasis gene expression signature (Figure 1B). Differentially expressed genes were then used to analyze the significance of the signature in the context of drug responsiveness.

Survival analysis. Survival rates between top in bottom quartile patient groups were compared via log-rank test (ASS).

Results

Meta-metastasis profile captures metastasis-associated genes and drives identification of novel therapeutic candidates

To evaluate if the meta-metastasis profile captures genes that inform metastatic progression in primary tumors, we interrogated metastasis potential of patients in an independent dataset. The expression was quantified by calculating Euclidean distance between individual patient samples and the meta-metastasis gene expression profile as measured between the top and bottom quartile outpatient.

Systematic in silico screening of anti-metastasis drug candidates. A drug signature database was assembled by combining data generated from the tumor microenvironment, metagenomics, cancer screenings, drug databases, and pathways. The analysis is based on a comprehensive list of over 1000 drugs, 700 pathways, and over 100,000 genes. The analysis used the DrugFinder algorithm, which ranks drugs based on their ability to induce the expression of metastasis-associated genes.

TGFβ inhibition may suppress metastasis via downregulation of SERpine1

This gene is significantly associated with survival across a number of cancers including Colon Adenocarcinoma. It is known as an activator of keratinocytes, which is essential in metastasis (12). SERpine1 is part of the enzyme-associated gene network induced by TGFβ in human malignant keratinocytes (14). SERpine1 was reversed most clearly by Chembl410456. This gene is significantly associated with survival across a number of cancers including Colon Adenocarcinoma. It is known as an activator of keratinocytes, which is essential in metastasis (12).

Conclusions

• Metastasis-associated genes were identified by investigating 13 cancers in TCGA. This list can serve as a starting point for further understanding of metastasis biology, assess the risk of a tumor metastasizing, and identify relevant drugs and targets.
• Drugs reversing metastasis-associated genes suggest that metastasis may be suppressed by TGFβ pathway inhibition, Wnt/beta-catenin pathway inhibition, or SERpine1 downregulation (including by TGFβ pathway inhibition).
• TWIST1 inhibition

These targets warrant further consideration alone or in combination to inhibit metastasis.