Discovering Novel Candidate Oncogenic Drivers for Metastasis in Synovial Sarcoma

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INTRODUCTION:

Synovial sarcoma (SS) is an aggressive soft-tissue malignancy. Unlike non-metastatic patients who benefit from rigid surgery and systemic treatment, patients with metastasis have very limited treatment options and dismal survival. However, only a few patients who develop distant metastasis have detectable metastases at presentation. In particularly aggressive cases, metastasis developed after years of primary tumor resectioning. Identifying oncogenic drivers for SS metastasis will facilitate exploring the mechanism and stratifying patients of high risks for adaptive treatment and survival prediction, which has been neglected in most previous studies.

METHODS:

The differentially expressed genes (DEGs) method was applied in a public genetic sequencing dataset of synovial sarcoma patients (GSE40021) from the Gene Expression Omnibus database to screen for discrepancies between primary tumors with and without subsequent metastasis. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Set Enrichment Analysis (GSEA) analyses were performed to identify the functional roles of DEGs, and those related to metastasis were focused. A weighted gene co-expression network (WGCNA) analysis was carried out to investigate gene modules and hub genes that highly correlated with metastatic features of SS. The co-expressed genes were identified by taking the intersection of DEGs and hub genes of WGCNA. Subsequently, characteristic genes associated with metastasis and prognosis were identified by the LASSO regression analysis. Further, the prognostic and diagnostic potency of these characteristic genes were further validated and confirmed in an independent public dataset (GSE40018). Finally, immunohistochemistry of characteristic makers was applied in another independent cohort containing 69 cases of primary SS samples with metastatic outcomes to validate the expression with the prognosis.

RESULTS:

A total of 186 DEGs were identified (Figure A). The biological functions and signaling pathways closely associated with SS metastasis were extracellular matrix (ECM) organization and ECM-receptor interaction (Figure B, C). The GSEA analysis showed enrichment of the gene sets involved in cell cycle, DNA replication, homologous recombination and mismatch repair in the primary tumors that develop metastasis subsequently (Figure D). Further, WGCNA analysis identified the most relevant module with 133 hub genes (Figure E, F). By taking intersection, 31 crossover genes were obtained by combining DEGs and WGCNA (Figure G). Subsequently, four characteristic genes, namely EXO1, NCAPG, POLQ, and UHRF1 were finally identified as the potential biomarkers associated with SS metastasis using LASSO algorithm. Their prognostic value was further validated in an outside independent dataset (Figure H, I, J). Finally, the immunohistochemistry results from a separate cohort also support the oncogenic role of characteristic genes in the metastasis group versus the non-metastasis group (Figure K).

DISCUSSION AND CONCLUSION:

In this study, we carried out *bioinformatic analyses* leveraging publicly available genetic sequencing results to identify molecular drivers and investigate the mechanism of SS metastasis. Our data revealed that primary tumors that developed subsequent metastasis expressed activated homologous recombination and mismatch repair compared with tumors that did not develop metastasis. We further identified four characteristic pro-metastatic drivers with consistent potency in multiple SS patient cohorts. Although further studies are needed to explore the detailed mechanism, they were first reported as potential novel biomarkers that can be applied for SS metastasis prediction.