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Discovering and Validating Enriched Signaling Pathways Associated with Organ-Specific Breast Cancer Metastasis

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Breast cancer is one of the most prevalent and devastating malignancies in the United States. Owing to its systemic nature and resistance to therapy, metastatic breast cancer is currently considered to be incurable and has a five-year survival rate of 29%. The specific pathways delegating the breast cancer metastatic cascade and tissue-specific breast cancer metastasis has much to explore and offers potential targets for therapeutic intervention. Breast cancer commonly metastasizes to four sites: brain, lung, liver and brain. Each of these sites have niche microenvironments. We hypothesize that unique adaptations and signaling pathways are required for successful metastasis at each site. We simulated spontaneous breast cancer formation and metastasis utilizing a murine model. Briefly summarized, SCP28 breast cancer cells were injected into the mammary fat pad. Primary tumors were removed after becoming well-established (~5mm). After spontaneous metastasis development at the aforementioned tumor sites, cancer cells were harvested from each organ and metastatic cell lines were generated. We then performed high-throughput RNA-sequencing of the primary tumor and metastatic cell lines. Counts data was normalized utilizing the DESeq2 package in R. Uniquely enriched, cell line specific pathways were elucidated utilizing the GAGE and pathview packages in R. Utilizing the KEGG database, we compared the enriched pathways between the primary tumor and metastatic cell lines. We discovered that the GABA pathway (KEGG entry hsa04727) was uniquely upregulated in the liver and lung metastatic cell lines. This pathway opens up several targets for intervention with drugs that are available on the market.