Identifying and targeting novel kinase regulators for cancer metastasis

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Background: Metastasis is responsible for >90% of cancer death. However, metastasis is still poorly understood and the current approaches to prevent or treat human metastatic cancers are largely unsuccessful.

Methods and Results: Through RNAi and cDNA functional screening, genomics analysis, and functional validations, we have identified several critical but previously unknown/understudied kinase regulators for metastasis. As an example, shRNA screening revealed that GPCR-kinase 3 (GRK3) is essential preferentially for highly metastatic cancer cells as compared to lowly metastatic cancer cells. GRK3 is significantly overexpressed in metastatic prostate tumors from patients, especially in the aggressive variant of prostate cancers, so called treatment-related neuroendocrine prostate cancer (NEPC). We further found that GRK3 promotes neuroendocrine differentiation (NED) in prostate cancer cells, and it is a key missing link between two prominent phenotypes of NEPC, i.e. angiogenesis and neuroendocrine feature. Mechanistically, GRK3 phosphorylates histone deacetylase 2 (HDAC2) at S394 and enhances HDAC2's epigenetic activity. HDAC2 is the most upregulated HDAC in NEPC. We also showed that HDAC2 itself promotes NED and NEPC progression. Targeting GRK3 with our potent and specific GRK3 inhibitors blocks the GRK3-HDAC2 pathway, inhibiting NEPC progression.

Another group of metastasis regulators we identified are new EMT-regulating kinases from our kinome cDNA screening for epithelial-mesenchymal transition (EMT). For example, mixed lineage kinase ZAK positively regulates EMT phenotypes and migration of cancer cells in culture, as well as metastasis in mice. ZAK overexpression correlates with poor prognosis in cancer patients.

Conclusions: Our robust and unbiased functional screening has identified several novel kinase regulators and potential drug targets for cancer metastasis. As examples, GRK3 has emerged as a critical kinase for metastatic prostate cancer cells and a key regulator of aggressive neuroendocrine prostate cancer phenotypes, while ZAK has been identified as a potent new regulator of epithelial-to-mesenchymal transition (EMT).

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