A Mechanistic and Proteomic Analysis of Tumor MK2's Promotion of Tumor Metastasis and Cell Migration-Invasion in Head and Neck Cancer

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Introduction. Metastasis is a major contributor to the high mortality rates observed in head and neck cancer (HNC), necessitating a deeper understanding of the mechanisms involved to identify potential treatment targets for improved patient outcomes. This study focuses on investigating the role and mechanism of MAPK-activated protein kinase 2 (MK2) in HNC progression.

Methods. Using lentiviral and CRISPR-Cas9 systems, we modified MK2 expression in human and murine HNC cell lines, conducting *in vivo* experiments using syngeneic orthotopic mouse models. *In vitro*, we evaluated cell migration and invasion in both 2D and 3D culture systems, supported by mass tag proteomic and phospho-proteomic analyses for an unbiased assessment of protein expression/phosphorylation changes regulated by MK2.

Results. The results showed that knocking out (KO) MK2 in the metastatic murine cell line Ly2 abrogates tumor growth and metastases in orthotopic *in vivo* models. *In vitro* experiments demonstrated that MK2 KO significantly decreased their migratory and invasive capacity in 2D & 3D models. Proteomic/phospho-proteomic analysis of Ly2 WT vs MK2 KO cells revealed significant variations in proteins involved in integrin-β4 signaling, cMET receptor pathway, and focal adhesion/actin remodeling dynamics.

Conclusions. These results implicate MK2 in promoting metastasis in HNC *in vivo*, and the regulation of migration and invasion likely contributes to this phenotype. This study uncovers several pathways not previously associated with MK2 signaling that may regulate the progression of these tumors. Further deconstructing these novel signaling cascades will expand our understanding of HNC spread and validate MK2 and its related proteins as therapeutic targets for metastatic HNC patients.