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Abstract Submission Form

Poster Title: **Loss of Kindlin-2 Inhibits the Oncogenic Activities of Integrins and TGF-β in Triple Negative Breast Cancer Progression and Metastasis**

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Kindlins are a small gene family (3 members) of FERM domain-containing adaptor proteins that function as essential drivers of integrin activation. Aberrant Kindlin expression and activity is associated with several human pathologies, including cancer. Kindlin-2 (K2) is the most widely expressed member of the Kindlin family; its homozygous deletion in mice is embryonic lethal, while mice heterozygous at the K2 locus exhibit overtly normal phenotypes that give way to defects in angiogenesis, hemostasis, and the cytoskeletal architecture upon closer examination. K2 expression is also dysregulated in several human cancers, including those of the breast. Our published studies established K2 as a major driver of TNBC tumors progression and metastasis through the regulation of several hallmarks of cancer. A well-established pathway whereby K2 regulate TNBC oncogenic behavior is through the regulation of integrin inside-out signaling by directly binding to the cytoplasmic tail of integrin beta subunit. Interestingly, our recent studies found K2 to play a major role in activating the TGF-β-mediated regulation of the CSF1/EGF paracrine signaling through macrophage polarization to the M2 tumorigenic state and their increased tumor infiltration.

Here, we report the novel findings that K2 forms a physical bridge that links Integrins (β1-Integrin) to the TGF-β type 1 Receptor (TβRI). We found that the K2/β1-Integrin direct interaction is mediated through the C-terminal F3 domain of K2, while the K2/TβRI direct interaction is mediated through the F2 domain of K2. Disruption of this bridge, via CRISPR/Cas9-mediated knockout of K2, leads to β1-Integrin and TβRI degradation, and inhibition of the oncogenic pathways of both Integrins signaling (loss of adhesion and spreading of cancer cells on Fibronectin-coated surfaces), as well at TGF-β signaling (loss of SMDA2/3 phosphorylation). Treatment of the K2-deficent cells with the proteasome inhibitor MG-132 restored expression of both β1-Integrin and TβRI, suggesting that K2 is required for the stabilization of the β1-integrin/TβR1 complexes. In addition, our in vivo preclinical analyses found mice injected in the mammary fat pads with TNBC cells deficient in either K2, β1-Integrin or TβRI results in a significant inhibition of tumor growth in metastasis, while re-expression of K2 expression in the K2-KO cells restored tumor growth and metastasis, as well as rescued expression of both β1-Integrin and TβRI.

Our ongoing investigations focus on the molecular mechanisms whereby K2 regulates the β1-integrin/TβR1 complexes and their downstream signaling. Specifically, we will identify the oncogenic functions of K2 that are β1-Integrin-dependent versus those that are TβRI-dependent in impacting TNBC tumor progression, metastasis, and disease recurrence.