# CYTOKINESIS DEFECTS DUE TO HIPK2 DEFICIENCY PROMOTE CHROMOSOMAL INSTABILITY AND INCREASE TUMORIGENICITY

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Homeodomain-Interacting Protein Kinase 2 (HIPK2) is a S/T kinase involved in cell fate decision in development and in response to stress. In the DNA damage response HIPK2 modulates the activity of several proteins in a p53-dependent and independent manner. Reduction of HIPK2 expression was shown to impair apoptosis, and a few mechanisms of HIPK2 inactivation have been identified in human cancers. We have recently demonstrated a novel HIPK2 function in the control of cytokinesis. HIPK2-depleted cells fail abscission and accumulate tetraploid and multinucleated cells.

To analyze HIPK2 deficiency effects on the predisposition to chromosomal instability (CIN) and tumorigenicity, we induce transformation in *Hipk2* +/+ and -/- MEFs by expressing E1A and Ras oncogenes. We found that HIPK2 depletion facilitates transformation induced by these oncogenes. *Hipk2* -/- E1A/Ras MEFs became aneuploid more readily than *Hipk2* +/+ E1A/Ras MEFs, suggesting that oncogene induced CIN is exacerbated in the absence of HIPK2. Importantly, *Hipk2* -/- E1A/Ras MEFs formed more aggressive and aneuploid tumors in nude mice. In addition, we will present data suggesting an inverse correlation among HIPK2 protein level, aneuploidy and high grade of malignancy in pancreas tumors.

Overall, our data show that loss of HIPK2 induces aneuploidy and results in an increased ability of cells to become malignant and aggressive, indicating that HIPK2 oncosupressor activity is not only linked to its pro-apoptotic function, but also to its role in cytokinesis and ploidy maintenance.