Inhibition of Lysine Demethylase 4A Rescues 3p Haploinsufficiency

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Chromosome 3p loss is a truncal event in von Hippel Lindau (VHL) disease and renal cell carcinoma (RCC) with >95% of patients showing loss of heterozygosity (LOH) of the *VHL* tumor suppressor. In addition to inactivation of *VHL*, 3p loss results in deletion of several chromatin remodeler genes including *Set-domain containing 2* (*SETD2*). SETD2 was recently discovered to function as a dual chromatin and cytoskeletal methyltransferase. Mono-allelic loss of *SETD2* occurs concomitant with loss of chromosome 3p in VHL disease and results in the inability of SETD2 to methylate microtubules of the cytoskeleton, while fully retaining its ability to methylate histones on chromatin. The haploinsufficiency of SETD2 results in decreased methylation of microtubules during mitosis, contributing to the genomic instability associated with these tumors. We have now discovered lysine demethylase 4A (KDM4A) as a centrosome associated protein that opposes the function of SETD2 on microtubules. KDM4A via its demethylase activity modulates microtubule methylation leading us to hypothesize that inhibition of KDM4A could be leveraged as a strategy to elevate methylation on microtubules in the setting of *SETD2* haploinsufficiency. A genetic knockdown of KDM4A resulted in increased microtubule methylation and a concurrent decrease in genomic instability (assessed as a reduction in micronuclei formation) in the setting of mono-allelic loss of *SETD2*. Our data provide a novel target, with potential for therapeutic intervention, within an alternate paradigm wherein loss of 3p tumor suppressors directly alter the cytoskeleton and drive disease progression via cytoskeletal defects.