Overexpression of KMT2A is associated with worse prognosis and specific immune signatures in patients with TP53-mutated hepatocellular carcinomas

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Introduction

Aberrant expression of epigenetic regulators is often associated with pathogenesis. Histone H3K4 methyltransferase, known as KMT2A, has been implicated in transcription and cell cycle regulation in pediatric leukemia and myeloma. However, the role of KMT2A expression in solid tumors is under-investigated. Here we examine the implications of KMT2A overexpression in prognosis, gene pathway enrichment, aneuploidy and immune infiltration patterns using a large, real-world clinical HCC dataset.

Methods

- A total of 403 HCC samples underwent comprehensive molecular profiling at Caris Life Sciences, including DNA-(592 Gene Panel, NextSeq, or whole exome sequencing, NovaSeq) and RNA- (NovaSeq, whole transcriptome sequencing, WTS) sequencing.
- Wilcoxon, Fisher's exact test were used to determine statistical significance (p value without and q value with multi comparison correction). Aneuploidy scores were generated from CNVkit. Apoptotic index (AI), GSEA were assessed using mRNA levels (FDR<0.25 as cutoff).
- Overall survival was calculated from date of tissue collection to date of last contact from insurance claims data and used for Kaplan-Meier method.

Results

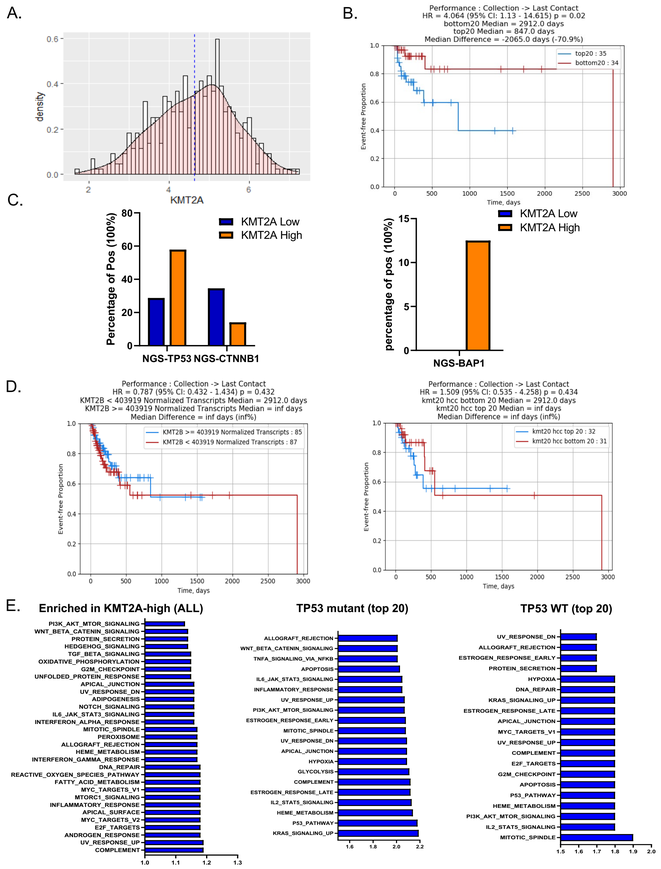

Figure 1. A, Histogram of mRNA levels of KMT2A (TPM). B, Overexpression of KMT2A is associated with worse prognosis (top 20 percentile, blue vs. bottom 20 percentile, red). C, KMT2A-high tumors had less TP53 mutation but more CTNNB1 mutation, when stratifying by TP53 mutational status, KMT2A-high tumors had more BAP1 mutation. D, KMT2B was not prognostic in HCC. E, Pathway enrichment in KMT2A-high tumors (left, all; middle, TP53 mutants; right, TP53 WT tumors).

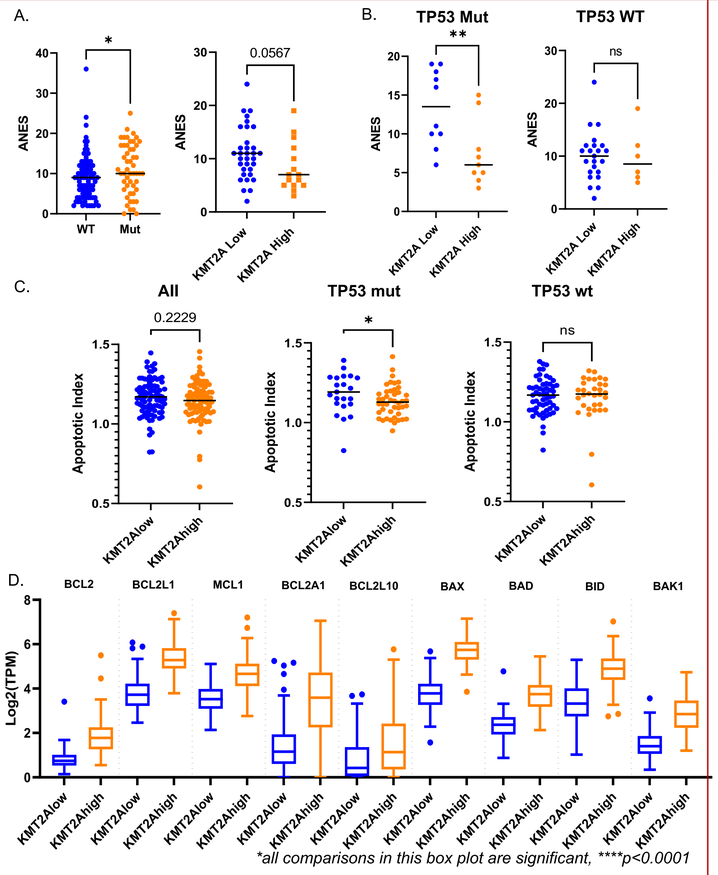

Figure 2. A, Aneuploidy scores in TP53 mutants vs TP53 WT tumors (left) and association between KMT2A expression with aneuploidy scores (right). B, Association with KMT2A expression levels with aneuploidy scores in TP53 mutants (left) and TP53 WT tumors (right). C, Differential levels of apoptotic index in KMT2A-high vs KMT2A-low tumors. D, Differentially expressed apoptotic gene set in KMT2A-high vs KMT2A-low tumors.

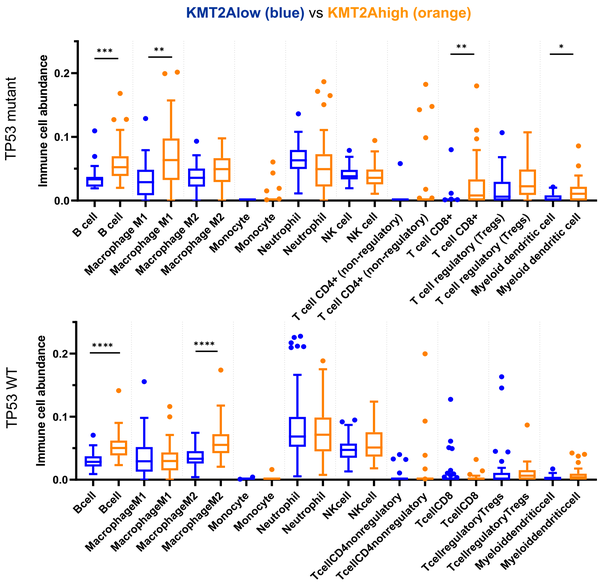

Figure 3. Different tumor immune infiltrates in KMT2A-high vs KMT2A-low tumors when stratifying by TP53 mutational status (top, TP53 mutants; bottom, TP53 WT tumors).

Conclusions

- KMT2A could act as an independent prognostic marker in HCC.
- The negative correlation between KMT2A expression and aneuploidy scores in TP53 mt indicates potential roles of KMT2A in maintaining genome stability.
- Furthermore, our results suggest TP53 status is an important stratification factor for HCC with KMT2A overexpression.
- Our results warrant further investigation on the impact of KMT2A level on immune modulation and may define a subset of HCC that responds most effectively to immune checkpoint inhibition.