Molecular landscape of gastric cancer (GC) harboring mutations of histone methyltransferases.


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Background

- Alteration of histone modifications participating in transcription, DNA repair and genomic instability, has been recognized as an important step in tumorigenesis. Members of the histone-lysine N-methyltransferase (KMT) family methylate histone H3 on lysine 4 (H3K4) play important roles in these processes, promoting genome accessibility and transcription in cancer cells [1, 2].
- Recurrent somatic mutations of KMT2 family were identified in gastric cancer (GC) [3, 4], and aberrant expression of them were also significantly correlated with poor survival in GC [4]. Understanding how gene mutations of KMT2 family interplay to affect cancer progression could lead to new treatment strategies.
- Herein we aim to highlight the molecular differences between GC harboring pathological mutations of KMT2 vs wild-type tumors.

Methods

- NGS was performed on genomic DNA isolated from FFPE tumor samples using the NexSeq (92-pes) MiSeq platform (44-pes) (Illumina, San Diego, CA). All variants were detected with greater than 99% confidence based on allele frequency and coverage, with an average sequencing depth of coverage of greater than 500 and an analytic sensitivity of 5%.
- Microsatellite instability (MSI) was examined by counting number of microsatellite loci that were altered by somatic insertion or deletion counted for each sample. The threshold to determine MSI by NGS was determined to be 46 or more loci with insertions or deletions to generate a sensitivity of >95% and specificity of >99%.
- Tumor mutational burden (TMB) was estimated from 92 genes (14 megabases (Mb) sequenced per tumor) by counting non-synonymous missense mutations found per tumor that had not been previously described as genuine alterations.
- IHC was performed on FFPE sections of glass slides. PD-L1 testing was performed using the SP142 (Ventana, Tucson, AZ) anti-PD-L1 clone.
- Gene fusion was evaluated using Archer or Whole Transcriptome Sequencing.
- Chi-square and Wilcoxon Rank was used for comparative analyses using R version 3.5.0.

Results

1. Study Population.

2. Molecular Profiles (top 40 significantly different mutated genes) of KMT2 MT vs WT in all GC cohort.

3. Pathways of significantly different mutated genes.

4. Molecular Profiles of KMT2 MT vs WT in MSS GC cohort.

5. Amplification of KMT2 MT vs WT

6. RELA fusion of KMT2 MT vs WT

7. Immune checkpoint related markers

Conclusions

This is the largest study to investigate the distinct genomic landscape between KMT2-MT and WT GC to date. Our data indicates that GC patients with KMT2 mutations could potentially benefit from agents targeting DNA damage repair, as well as immunotherapy. Efficiency of these therapeutic targets in KMT2-MT GC warrant further in vitro and in vivo investigation.

References