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

Jingyuan Wang[1], Joanne Xiu[2], Yasmine Baca[2], Richard M. Goldberg[3], Philip A. Philip[4], Andreas Seeber[5], Francesca Battaglin[1], Hiroyuki Arai[1], Shivani Soni[1], Ryuma Tokunaga[1], Wu Zhang[1], Jimmy J. Hwang[6], Anthony F. Shields[4], John L. Marshall[7], Igor Astaturov[8], A. Craig Lockhart[9], Zoran Gatalica[2], W. Michael Korn[2], and Heinz-Josef Lenz[1].

[1] Division of Medical Oncology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, USA. [2] Caris Life Sciences, Arizona, USA. [3] West Virginia University Cancer Institute, West Virginia, USA. [4] Department of Oncology, Karmanos Cancer Institute, Michigan, USA. [5] Department of Haematology and Oncology, Innsbruck Medical University, Austria. [6] Levine Cancer Institute, North Carolina, USA. [7] Lombardi Comprehensive Cancer Center, Washington, D.C., USA. [8] Fox Chase Cancer Center, Philadelphia, USA.[9] University of Miami/Sylvester Comprehensive Cancer Center, Miami, Florida, USA.

Abstract ID: 418

wangjingyuan@bjmu.edu.cn

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 2 (*KMT2*) family methylate histone H3 on lysine 4 (H3K4) play important roles in these process, promoting genome accessibility and transcription in multi-cancers(1, 2).
- Recurrent somatic mutations of *KMT2* family were identified in gastric cancer (GC)(3), and aberrant expression of them were also significantly correlated with poor survival in GC(4). Understanding how gene mutations of *KMT2* family interact 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* versus wild-type tumors.

Methods

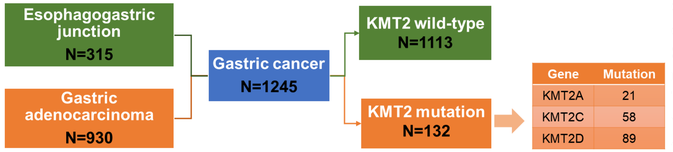
- NGS was performed on genomic DNA isolated from FFPE tumor samples using the NextSeq (592-genes)/MiSeq platform (44-gene) (Illumina, Inc., San Diego, CA). All variants were detected with greater than 99% confidence based on allele frequency and amplicon coverage, with an average sequencing depth of 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 592 genes (1.4 megabases [MB] sequenced per tumor) by counting all non-synonymous missense mutations found per tumor that had not been previously described as germline 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 were used for comparative analyses using R version 3.5.0.

References

[1] Shilatifard A. *Annu Rev Biochem*. 2006;
[2] Milne T. A., et al. *Mol Cell*, 2002.
[3] Zang Z., et al. *Nature Genetics*, 2012;
[4] Cho Soo-Jeong, et al. *Clin Cancer Res*, 2018;

Results

1. Study Population.



Gene	Mutation
KMT2A	21
KMT2C	58
KMT2D	89

Fig.1 A cohort of 1,245 GC cases, including 315 GEJ cancer and 930 GAC samples with comprehensive genomic profiling by Caris Life Sciences (Phoenix, AZ) was identified from a retrospective database and included in this analysis. The overall mutation rate of genes in *KMT2* family was 10.6% (132/1,245; *KMT2A*: 1.7 %, *KMT2C*: 4.7%, *KMT2D*: 7.1%).

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

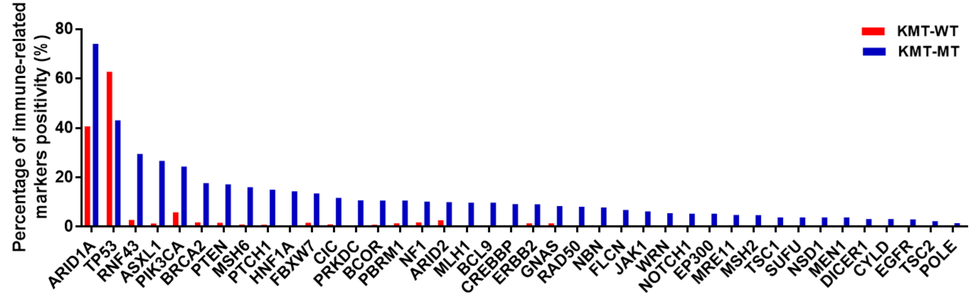


Fig.2 Overall, the mutation rates of most genes were significantly higher in *KMT2*-mutated (MT) GC than *KMT2*-wild type (WT) GC, except for TP53 (43.1% vs. 62.8%, *p<.0001*). Interestingly, **BRCA1, BRCA2, RAD50, ATM, ATRX, MSH6** et al, related to DNA damage repair, and **ARID1A/2, SMARCA4/B1/E1, CREBBP/EP300,** et al, related to epigenetic modification, had significantly higher mutation rates in *KMT2-MT* GC (*p<.05*).

3. Pathways of significantly different mutated genes.

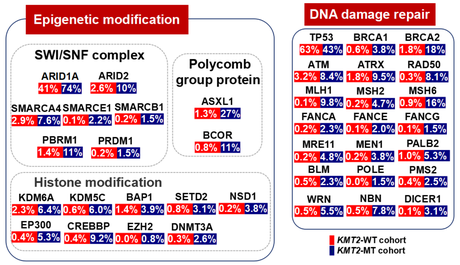


Fig.3 The details of gene mutations in epigenetic modification and DNA damage repair in *KMT2*-MT vs. WT in GC.

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

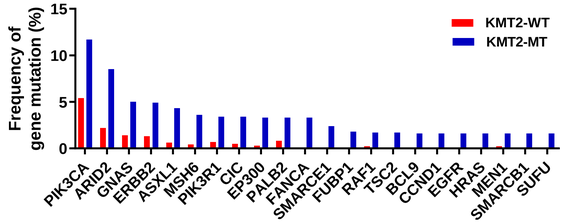


Fig.4 Several genes remained significantly more mutated in *KMT2*-MT MSS tumors compared to *KMT2*-WT, including **PIK3CA, ARID2, GNAS, ERBB2, ASXL1, MSH6, PIK3R1 et al.**

5. Amplification of *KMT2* MT vs WT

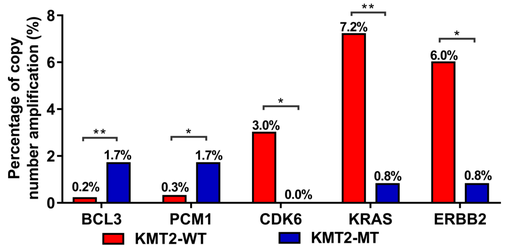


Fig.5 Amplification rates of *KRAS*, *CDK6* and *ERBB2* were significant lower, while *PCM1* and *BCL3* amplification rates were significant higher in *KMT2*-MT GC, compared to KMT2-WT (*, *p<.05;* **, *p<.01*).

6. RELA fusion of *KMT2* MT vs WT

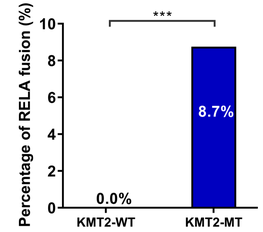


Fig.6 The fusion rate of RELA was significantly higher in *KMT2*-MT GC compared to *KMT2*-WT (***, *p<.001*).

7. Immune checkpoint related markers

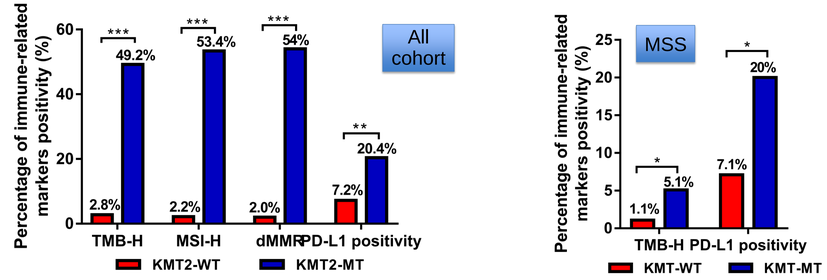


Fig7. Significantly higher rates of TMB-high (>17mut/MB) (49.2% vs 2.8%), MSI-H (53.4% vs 2.2%), dMMR (54.0% vs. 2.0%) and PD-L1 (SP142) overexpression (20.4% vs 7.2%) were seen in *KMT2*-MT GC, compared to *KMT2*-WT GC. TMB and PD-L1 positivity remained higher in *KMT2*-MT GC, compared to *KMT2*-WT GC. (*, *p<.05;* **, *p<.01;* ***, *p<.001*)

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 and immunotherapy. Efficiency of these therapeutic targets in *KMT2-MT* GC warrant further *in vitro* and *in vivo* investigation.