Abstract #4050: The correlation analysis between MUC16 mutation and immunotherapy predictive biomarkers in colon adenocarcinoma

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Background

- The prognosis of colon adenocarcinoma (COAD) remains unsatisfactory, but the efficacy of immune checkpoint inhibitors (ICIs) therapy was limited. Microsatellite instability (MSI), Tumor mutation burden (TMB) and Tumor immune microenvironment (TME) of ICIs have been confirmed to be promising predictive biomarkers of ICIs in pan-cancer. The function of MUC16 gene and the correlation with ICIs therapy efficacy have not been revealed.

Methods

- Whole exome sequencing (WES) data of 526 COAD patients and 66 Chinese COAD patients were obtained from the Cancer Genome Altas (TCGA) and 3DMed cohort, separately. TMB was defined as the number of somatic nonsynonymous somatic mutations per megabase in the coding region of WES. The tumor-related immune cells infiltration level difference between mutant and wildtype tumors were inferred using TIMER 2.0 (Wilcoxon test). The association between MUC16 mutation states and the efficacy of ICIs was performed in melanoma patients from Miao2018 pan-cancer ICIs treatment cohort.

Results

- In total, the alteration frequency of MUC16 gene in COAD was 28% (148/526) in TCGA cohort and 27% (18/66) in Chinese cohort (Figure 1).

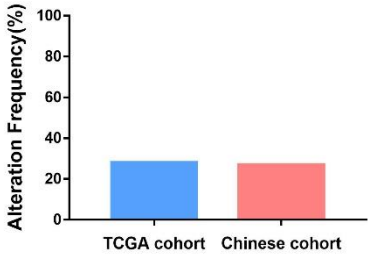

Figure 1. The comparison of the MUC16 alteration frequency in two cohorts.

Results

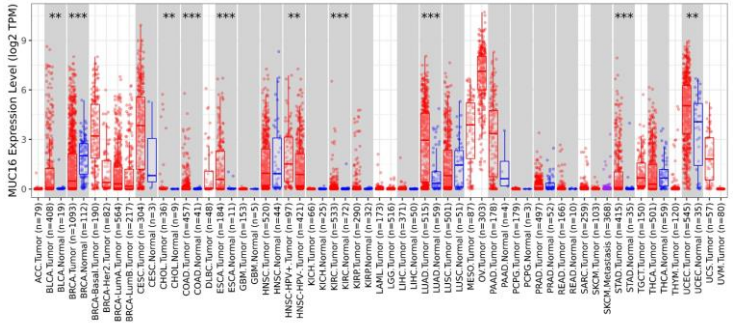

Figure 2. The expression of MUC16 between tumor tissues and normal tissues for each TCGA cancer type.

- In TCGA cohort, the expression of MUC16 of COAD tumor tissues was significantly higher than adjacent normal tissues ($p < 0.001$, Figure 2).

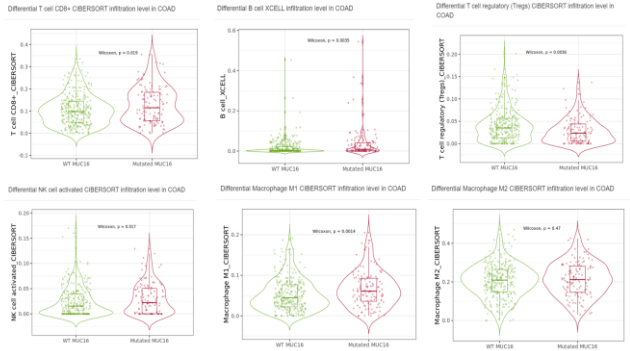

Figure 3. violin plots of immune infiltration distribution in the MUC16 mutant vs. wildtype COAD.

- The level of infiltration of CD8+ T cell, B cell, T cell regulatory (Tregs) and NK cell were all significantly increased in mutated tumors compared with wild-type tumors ($p < 0.05$). The mutant tumors with significantly higher inferred M1 macrophages than wildtype (p=0.0014), but not in M2 macrophages (Figure 3).

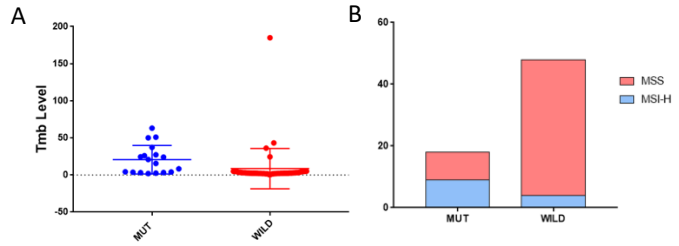

Figure 4. TMB level (A) and microsatellite statue (B) in MUC16 MUT vs. WT of Chinese cohort.

- In Chinese cohort, the TMB level was higher in mutant group compared to wild-type group (median TMB, mut vs wt = 18.26 vs 2.72 Mut/Mb, $p < 0.0001$, Figure 4A).
- The percentage of microsatellite instability-high (MSI-H) in MUC16 mutant tumors was 50.00%, while 8.33% in wild-type tumors (Fisher's exact test, p = 0.0005, Figure 4B).

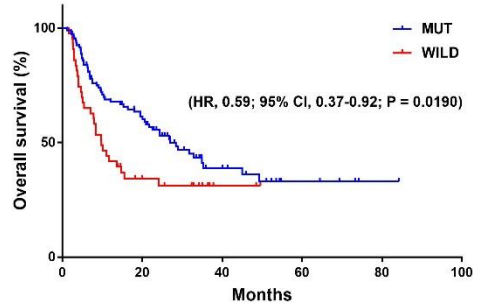

Figure 5. Association between MUC16 statue and the efficacy of ICIs in melanoma patients from pan-cancer ICIs treatment cohort.

- The overall survival (OS) of MUC16 mutation group (n=43) were significantly longer than wild-type group (n=108) (median OS, mutation vs wild-type = 20.33 vs 9.77 months; HR 0.59 [95% CI 0.37-0.92]; p = 0.019, Figure 5).

Conclusion

- The MUC16 mutation COAD tumors had highly TMB levels and infiltrating lymphocytes, which may serve as a potential biomarker to guide ICB therapy in COAD.