Genomic alterations in SPEN predict outcome of immune checkpoint therapy in gastrointestinal cancer

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BACKGROUND

- Application of Immune Checkpoint Inhibitors (ICIs) has become important therapy for gastrointestinal cancer (GC).
- SPEN gene encodes Msx2-interacting protein which can block the differentiation of precursor B-cells into marginal zone B-cells and represses transcription.
- However, the correlation between SPEN mutation and immune efficacy is unclear.

METHODS

- We retrospectively analyzed the genomic and survival data from 236 patients with gastrointestinal cancer derived from MSKCC 1661 (Nat Genet 2019) immunotherapy cohort to evaluate the relationship between SPEN mutation status and efficacy of immunotherapy.
- Then we explored the prognostic value of SPEN mutation in 914 GC patients from The Cancer Genome Atlas (TCGA) database. Survival was estimated by Kaplan-Meier curves, with the p value determined by a log-rank test. TMB was calculated as the total count of nonsynonymous mutations in coding sequence.
- The CIBERSORT analysis relied on RNA-seq data in TCGA database to evaluate the 22 types immune cell infiltration status.

RESULTS

- The TMB level of SPEN-mutant patients was higher than SPEN-wildtype patients in both MSKCC (Median [IQR]: 64.94[2.63-203.64] vs 6.14[0.00-153.47], P < 0.001) and TCGA (Median [IQR]: 31.20[0.96-296.91] vs 2.70[0.05-194.70], P < 0.001) cohort.

- In MSKCC cohort, compared to SPEN-wildtype patients, the SPEN-mutant patients achieved prolonged OS (median OS: 34 vs 13 months, HR= 0.30 [95%CI, 0.11-0.82], P = 0.009). In TCGA cohort, there was no significant difference in OS between SPEN-wildtype group and the SPEN-mutant group (median OS: 67.3 vs 60.8 months, P = 0.33).

CONCLUSION

- The CIBERSORT analysis revealed that CD8+ T cell infiltration and activated CD4 memory T cell were significantly higher in SPEN-mutant group than SPEN-wildtype group (p<0.05).

- SPEN mutation is associated with higher TMB in ICI-treated gastrointestinal cancer patients. Survival analysis suggests that the SPEN mutation may serve as a novel predictive biomarker in GC patients with ICIs, but not a prognostic factor. The significantly higher CD8+ T cell infiltration and activated CD4 memory T cell in SPEN-mutant group may be the potential mechanism.