

# Multiomics characterization and verification of clear cell renal cell carcinoma molecular subtypes to guide precise chemotherapy and immunotherapy

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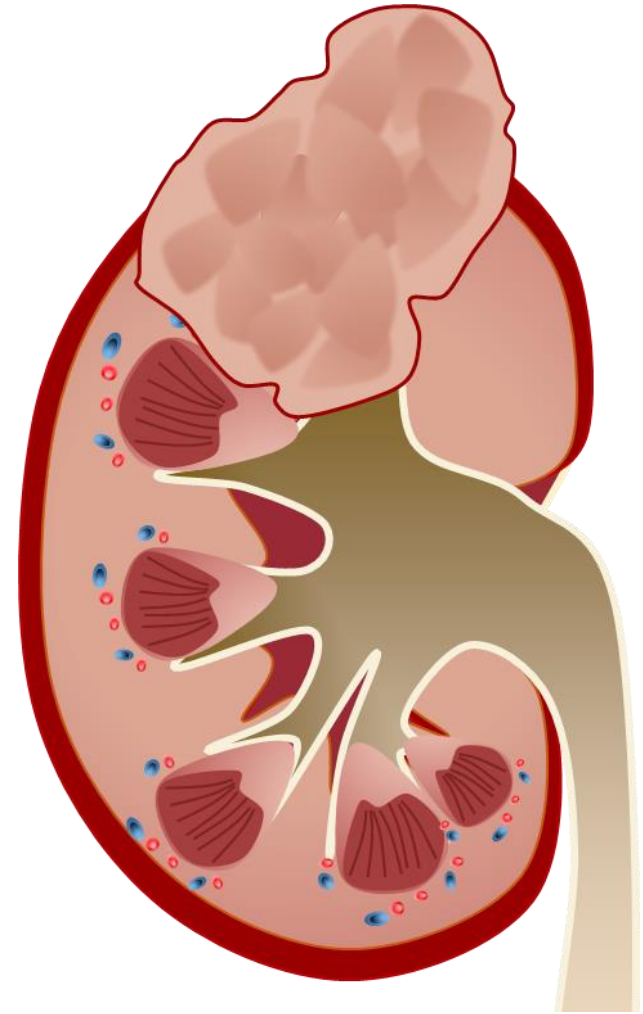


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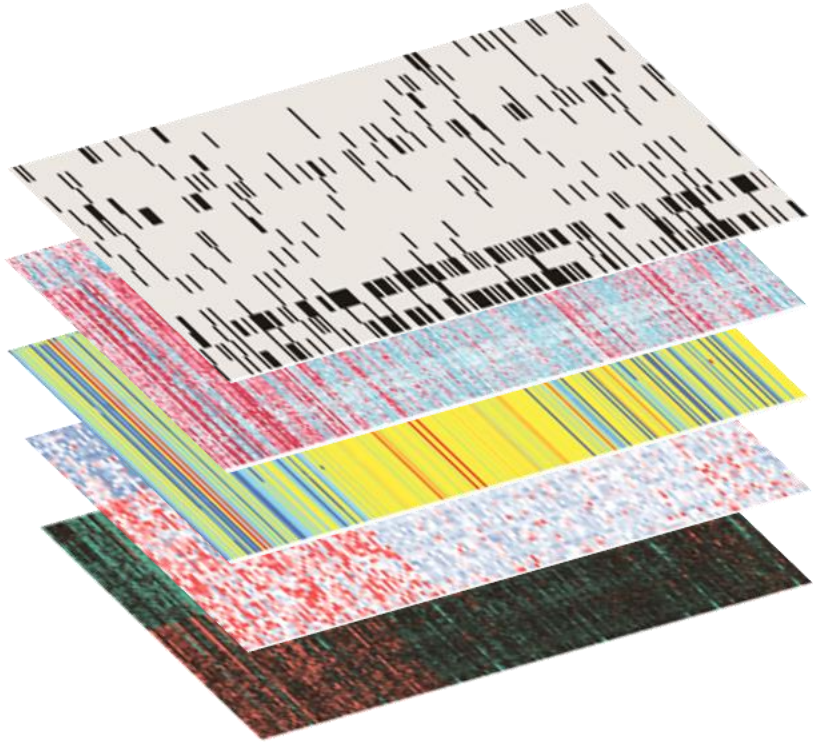
# Introduction

Kidney cancer is the ninth most common cancer among all tumor types in a global context, while renal cell carcinoma (RCC) accounts for 90% of such malignancies.

Traditional molecular typing and biomarkers only consider one type of data, ignore the interaction between molecular changes at different levels, and cannot fully reveal the molecular characteristics of ccRCC.

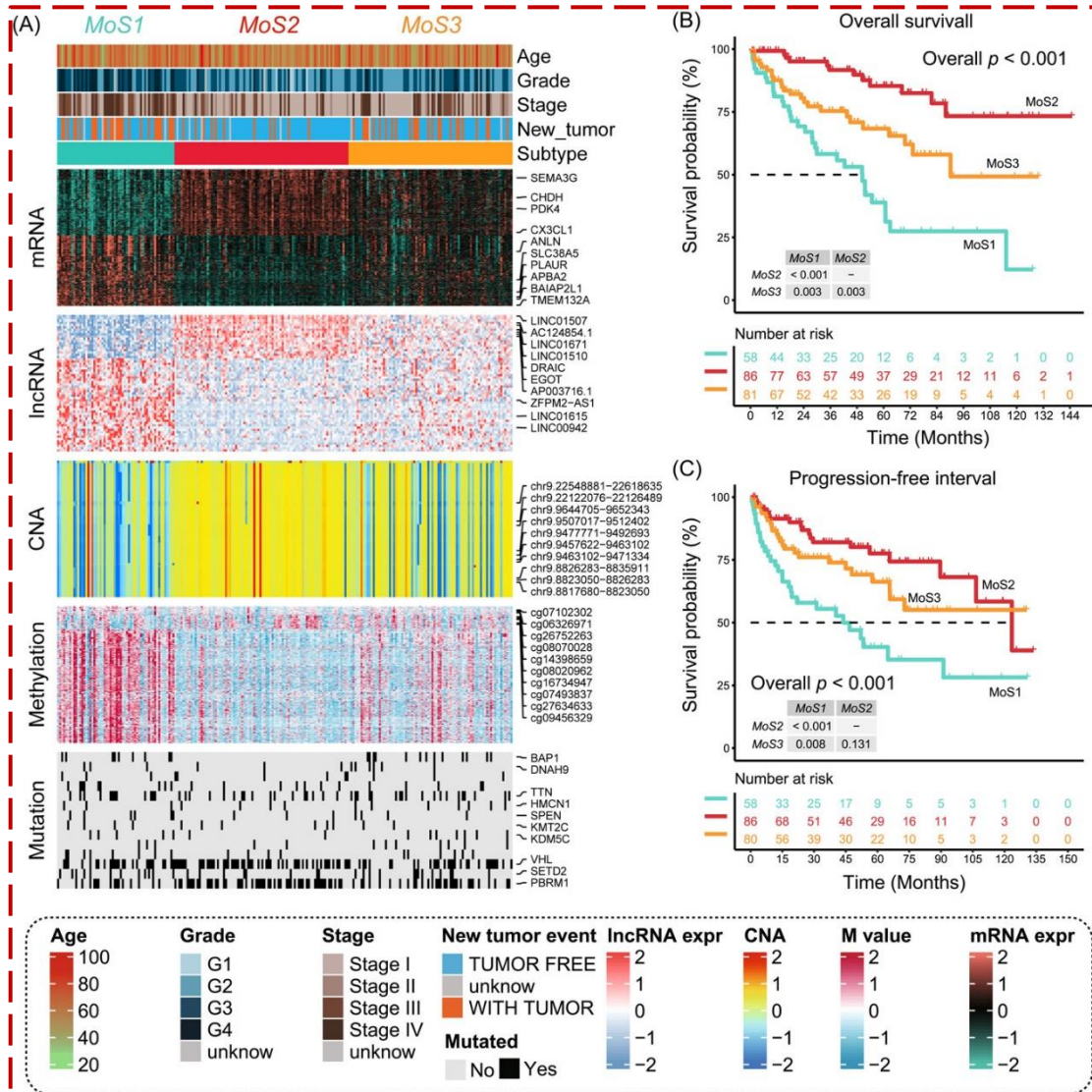


# Introduction



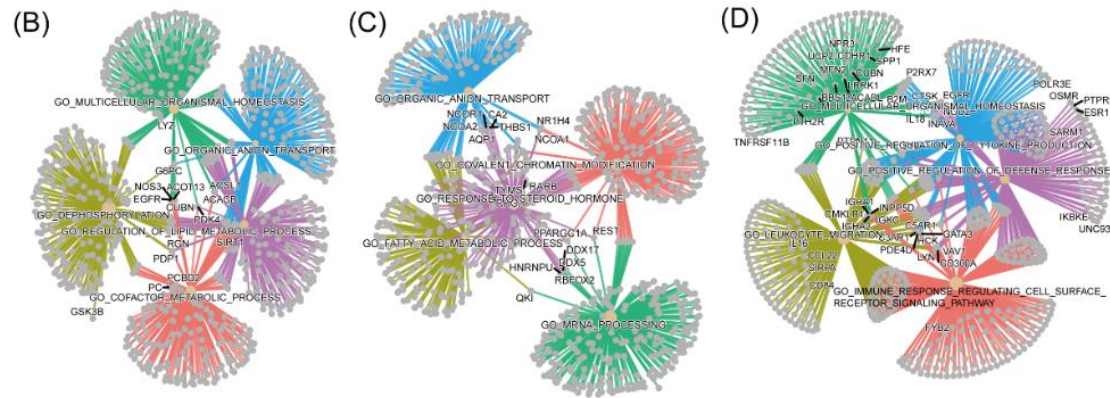
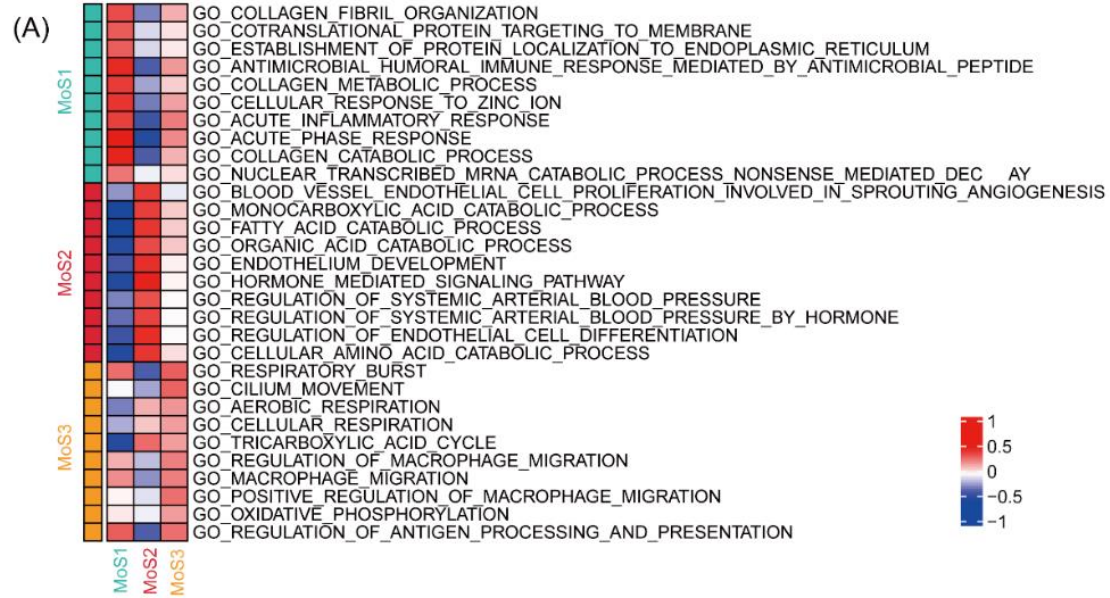
In this study, we included multi-omics data such as mRNA and lncRNA expression profiles, gene mutations, copy number alterations, and DNA methylation profiles, molecular subtypes were revealed via multiple clustering algorithms, and conducted consensus integration to establish a comprehensive consensus classification, which can provide the further understanding of the correlation between molecular characteristics and biological behavior of ccRCC, as well as the survival prediction and treatment effect assessment.

- Molecular subtypes were identified based on 225 ccRCC patients from TCGA-KIRC cohort. Ten clustering algorithms in the R package “MOVICS” were used to classify patients into 3 subtypes and perform further consensus.
- MoS2 has the best prognosis, and MoS1 has the worst prognosis. The overall survival time gradually decreases from MoS2, MoS3 to MoS1, and the progression-free survival interval also has the same trend.



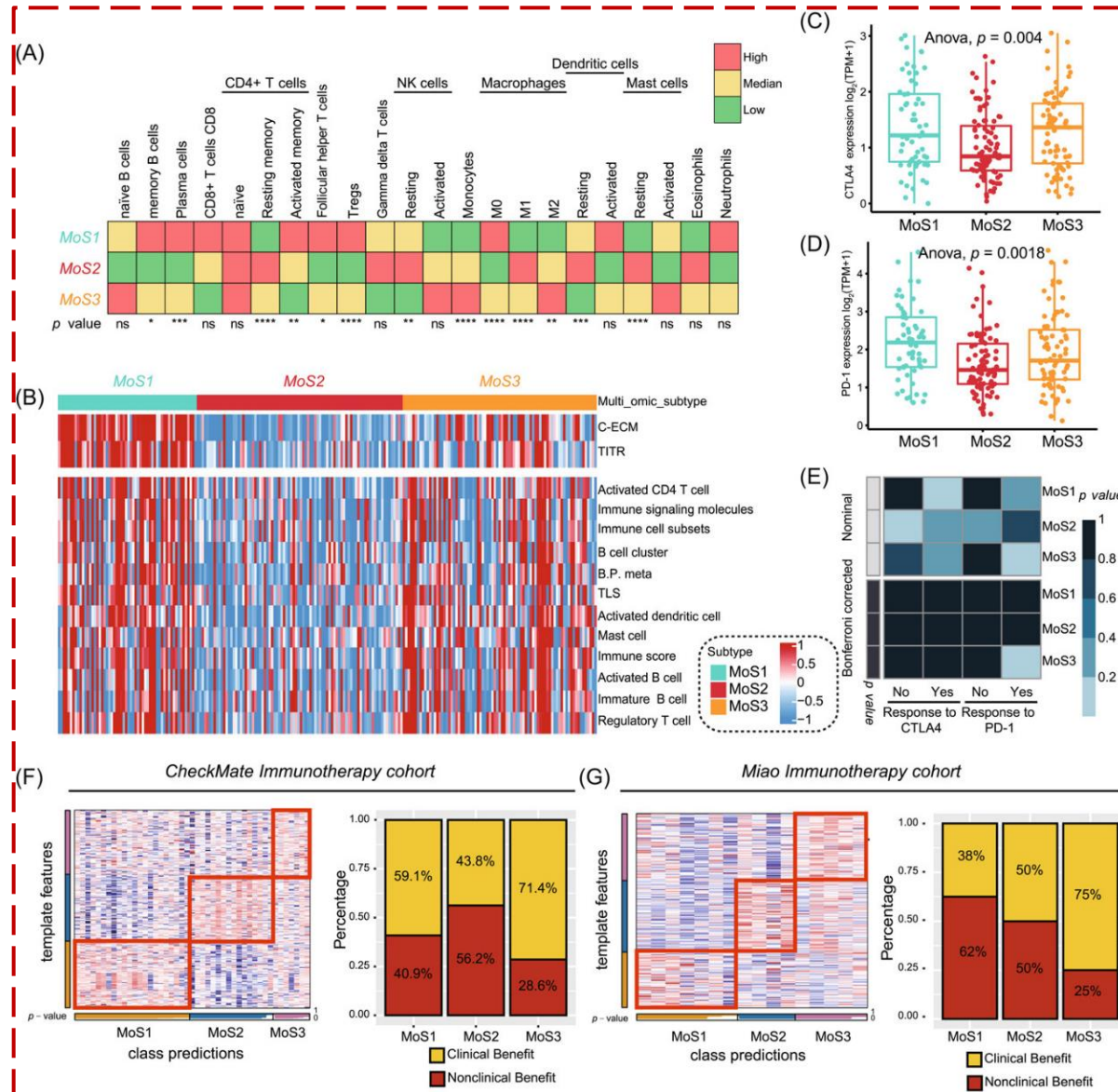


# Results



- We observed that MoS1 patients contained the activation of membrane protein targeting, collagen metabolism, and acute inflammatory.
- As for MoS2, endothelium development, fatty acid metabolic and catabolic, mRNA processing pathways were enriched
- The activation of immune-associated pathways enriched in MoS3 significantly, including macrophage migration, antigen processing and presentation, and regulation of cytokine production.

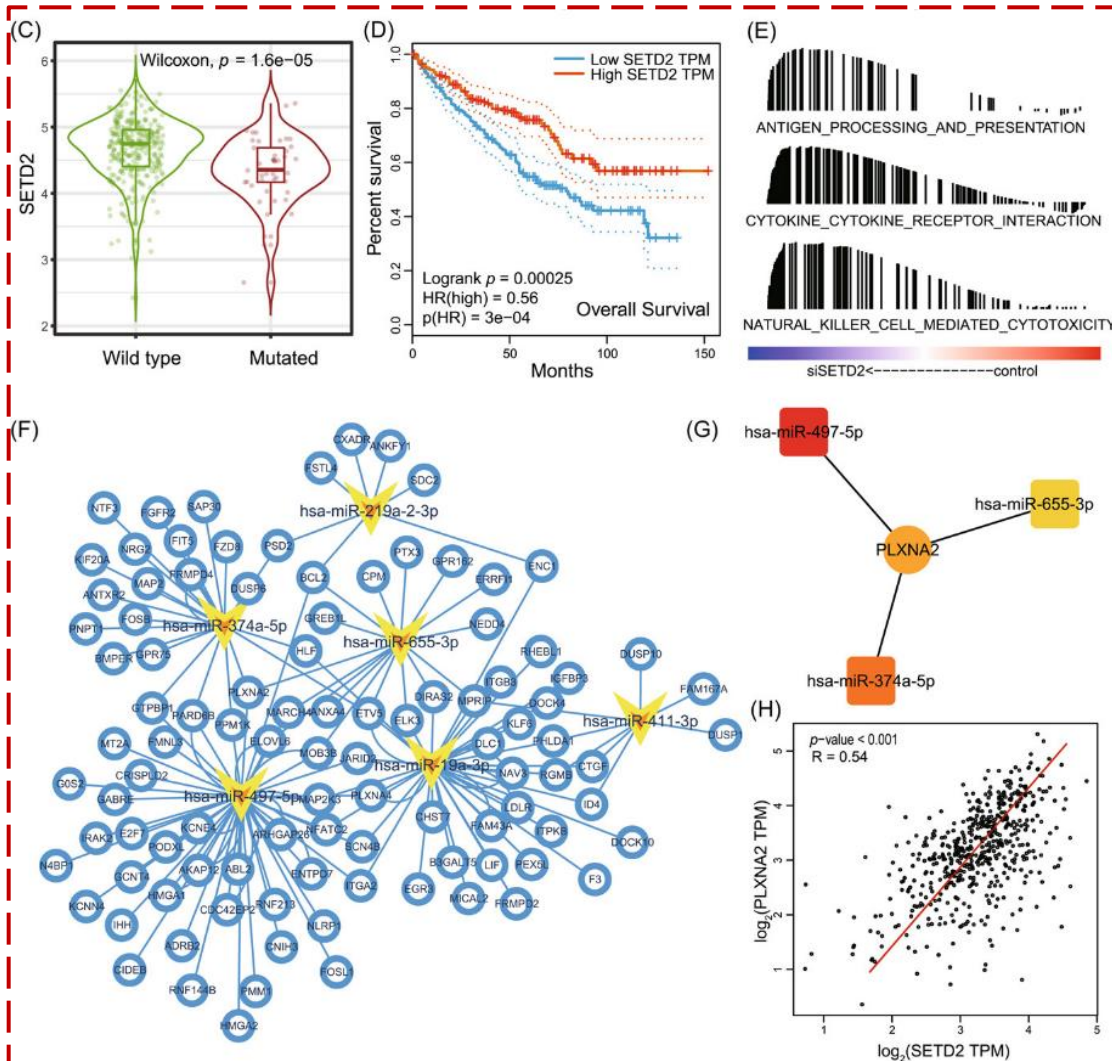
# Results



- There was a high degree of immune cell infiltration in both MoS1 and MoS3, while MoS2 also show the activation of tumor-infiltrating T regulatory cell (TITR) signature.
- Based on the Submap algorithm, we found that patients in MoS3 can benefit from anti-PD-1 immunotherapy.
- We collected two immunotherapy cohorts for validation. 71.4% of patients in MoS3 from the CheckMate cohort achieved clinical benefit, as well as 80% MoS3 patients from Miao cohort.

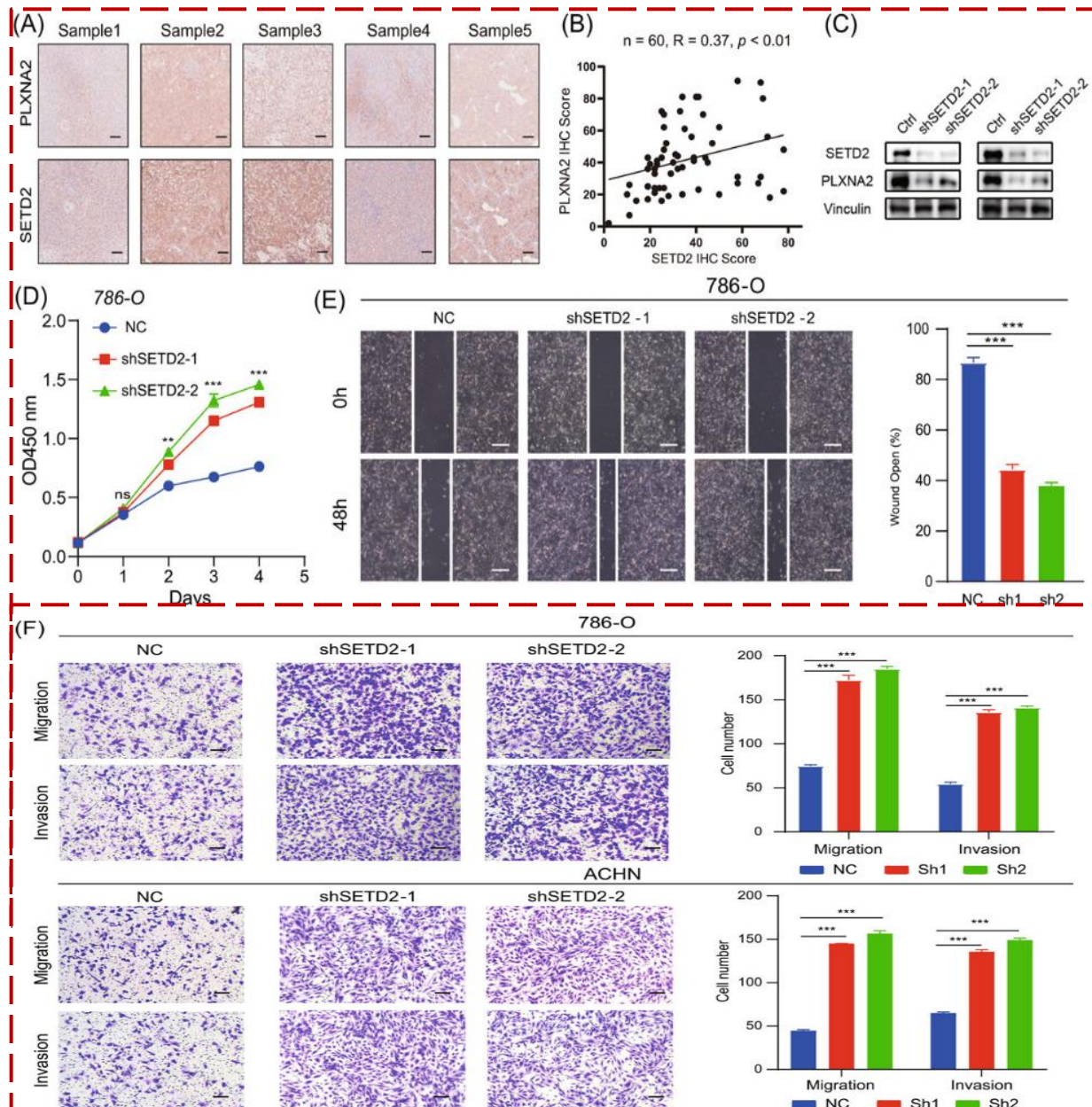


# Results



- SETD2 mutations are mainly observed in MoS1 and MoS3 and are associated with poor prognosis. SETD2 mutations result in reduced SETD2 expression.
- siSETD2 activates multiple immune-related signaling pathways, including antigen processing and presentation, cytokine cytokine-receptor interaction, and natural killer cell-mediated cytotoxicity.
- SETD2 expression is positively correlated with PLXNA2 expression, and PLXNA2 may be a potential therapeutic target for ccRCC patients with SETD2 mutations.

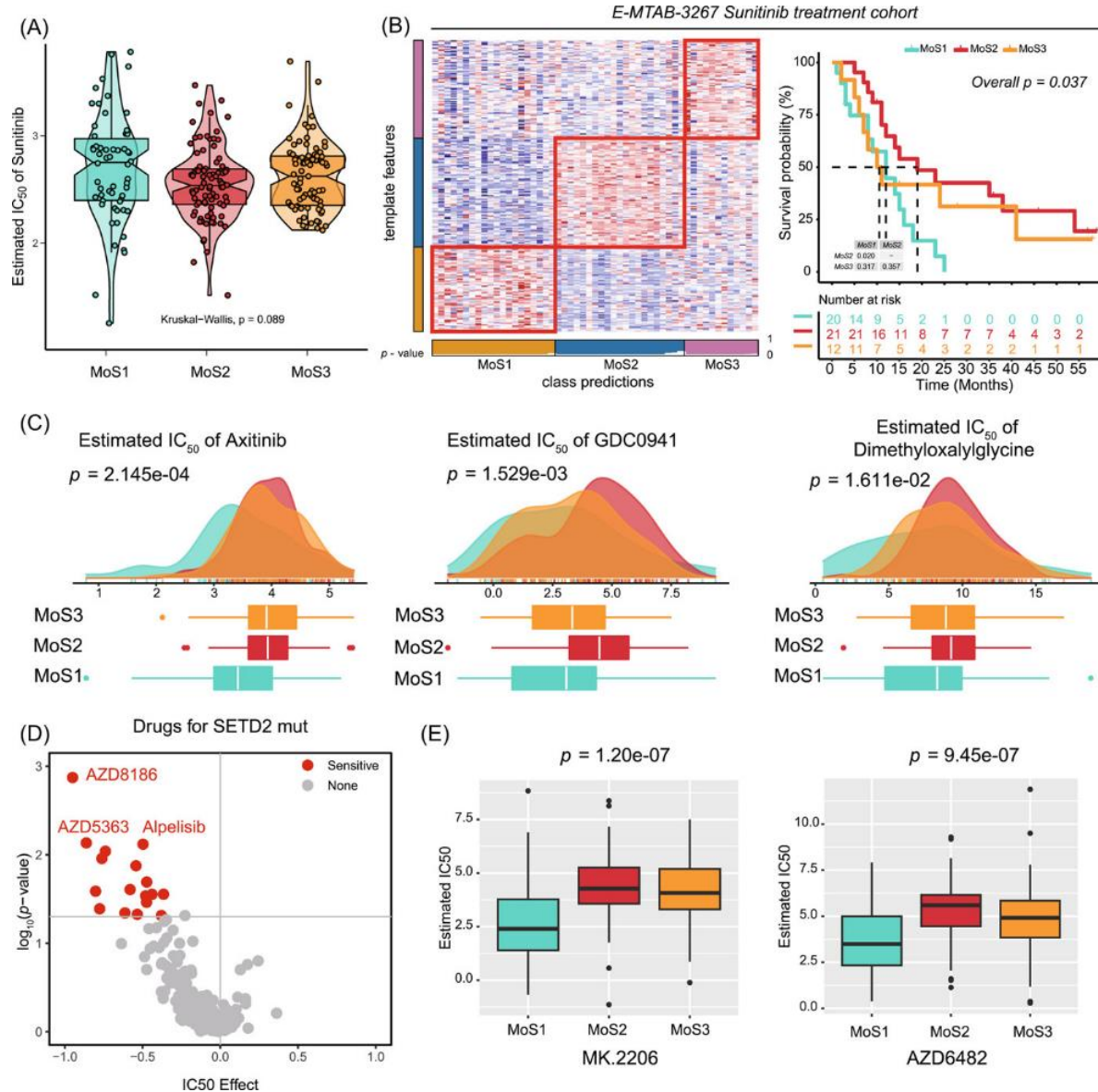
# Results



- Immunohistochemistry of clinical samples confirmed that the expression of SETD2 and PLXNA2 was significantly positively correlated. When SETD2 was knocked down, the expression of PLXNA2 decreased.
- Knockdown of SETD2 promoted the proliferation, migration and invasion abilities of ccRCC cells. Taken together, these results suggest that SETD2 may function as a tumor suppressor in ccRCC.

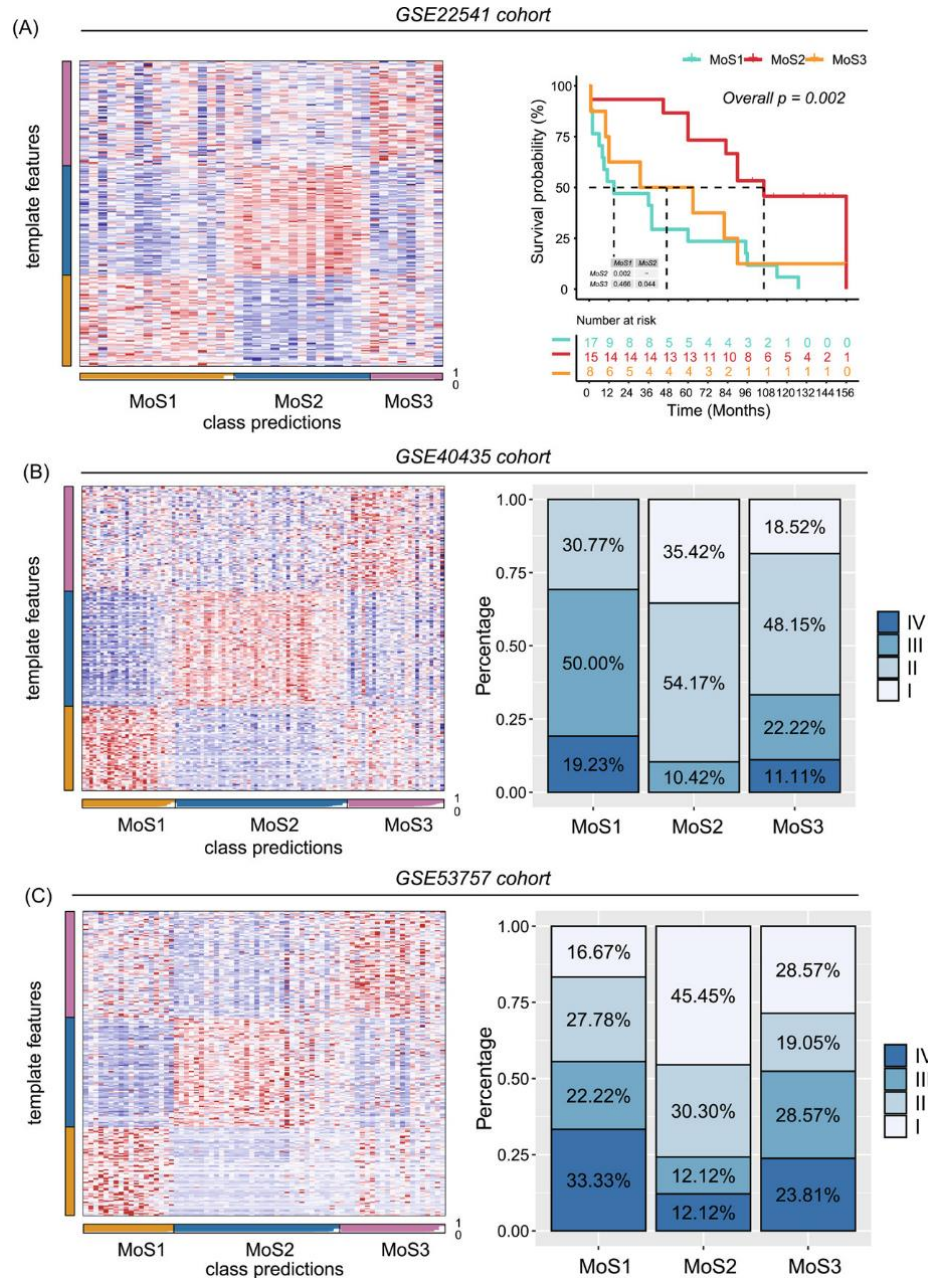


# Results



- The MoS2 subtype is more sensitive to sunitinib treatment. Results from the E-MTAB-3267 cohort of 53 patients treated with sunitinib showed that MoS2 patients had the best overall survival.
- Axitinib, GDC0941 and DMOG, which are more suitable for the treatment of MoS1 patients.
- SETD2 mutant cells are sensitive to PI3K/AKT inhibitors, so patients belongs to MoS1 subtype are also suitable for PI3K/AKT inhibitor treatment.

# Results



- We screened 100 specific markers for each subtype and to reproduce MoS classification in external cohorts.
- In GSE22541, patients with MoS2 had the best prognosis, while patients with MoS1 had the worst clinical outcome. After adjusting for the effect of gender, MoS classification was still an independent prognostic predictor of ccRCC.
- In GSE40435 and GSE53757, patients in MoS2 were mostly in early tumor stages, while MoS1 contained the majority of stage IV patients.

# Summary

- Three molecular subtypes of ccRCC based on multiomics data were identified, with diverse overall survival time, and validated in external cohorts.
- MoS1 is an immune exhausted subtype, which can benefit from PI3K/AKT inhibitors; MoS2 is an immune “cold” subtype, but is more suitable for sunitinib therapy; MoS3 is an immune “hot” subtype, which can benefit from anti-PD-1 immunotherapy.
- SETD2 is a tumor suppressor in ccRCC, and knock-down of SETD2 leads to the promotion of cell proliferation, migration, and invasion.





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