218P - DSG2+ cancer stem cells co-located with POSTN+ myofibroblasts in the tumor boundary that determines the efficacy of immunotherapy in non-small cell lung cancer

Guangyu Fan[1], Tongji Xie[1], Le Tang[1], Xiaohong Han[2], Yuankai Shi[1]

1Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College,Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs; No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China.2Clinical Pharmacology Research Center, Peking Union Medical College Hospital, State Key Laboratory of Complex Severe and Rare Diseases, NMPA Key Laboratory for Clinical Research and Evaluation of Drug, Beijing Key Laboratory of Clinical PK & PD Investigation for Innovative Drugs, Chinese Academy of Medical Sciences & Peking Union Medical College; No.1, Shuaifuyuan, Dongcheng District, Beijing 100730, China

Background

The recent phenotype plasticity model proposes that cancer stem cells (CSCs) constitute a dynamic subpopulation of cancer cells, capable of reversible transition from non-CSC states. Prior studies lacked a nuanced examination of gene expression patterns in this continuum, and the spatial structure of CSCs remained unclear.

Method

Addressing these limitations, we conducted a comprehensive study that integrated single-cell data (92,820 cells from 40 samples) and spatial data (34,661 spots from 14 samples) to establish a CSC signature and unveil its spatial structure.

Conclusion

This study successfully constructed a CSC signature and demonstrated the co-location of DSG2+ CSCs and POSTN+ myCAF at the tumor boundary, contributing to immunotherapy resistance.

Result

A CSC signature comprising 127 genes was developed using Weighted Gene Co-expression Network Analysis (WGCNA). Notably, DSG2 within the CSC signature correlated with chemotherapy resistance in the ORIENT-3 clinical trial. Furthermore, DSG2 emerged as a serum marker for predicting the response to EGFR-TKI-targeted therapy, based on serum proteomics data from 186 patients in the BPI-7711 clinical trial. Spatial analysis revealed the presence of DSG2+ CSCs at the tumor boundary, co-located with POSTN+ myofibroblasts (myCAF), validated by multiplex immunofluorescence. POSTN+ myCAFs expressed metalloproteinases (MMP9 and MMP12) associated with epithelial-mesenchymal transition, constructing an invasive front supporting DSG2+ CSC maintenance.

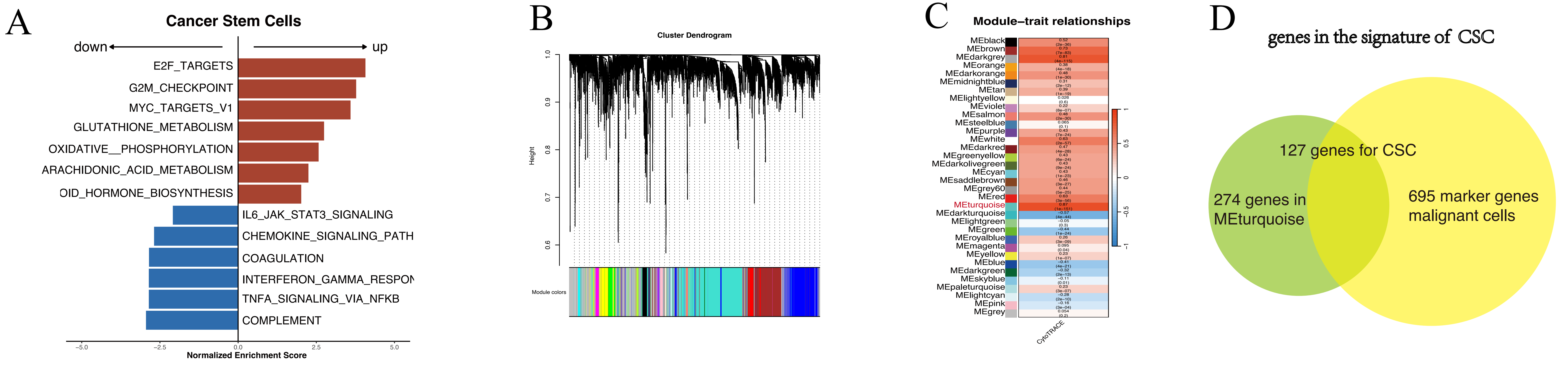

Figure 1. (A) The pathways upregulated and downregulated in CSCs. (B) The modules identified in WGCNA analysis. (C) The correlations between each module and CytoTRACE score. (D) The genes in the signature of CSCs.

Both DSG2+ CSCs and POSTN+ myCAF were correlated with unfavorable immunotherapy responses in ORIENT-3 clinical trial. Within the co-location area, the MDK signaling pathway exhibited the highest activity in cell-cell communication, identifying MDK-NCL as the main ligand-receptor pair.

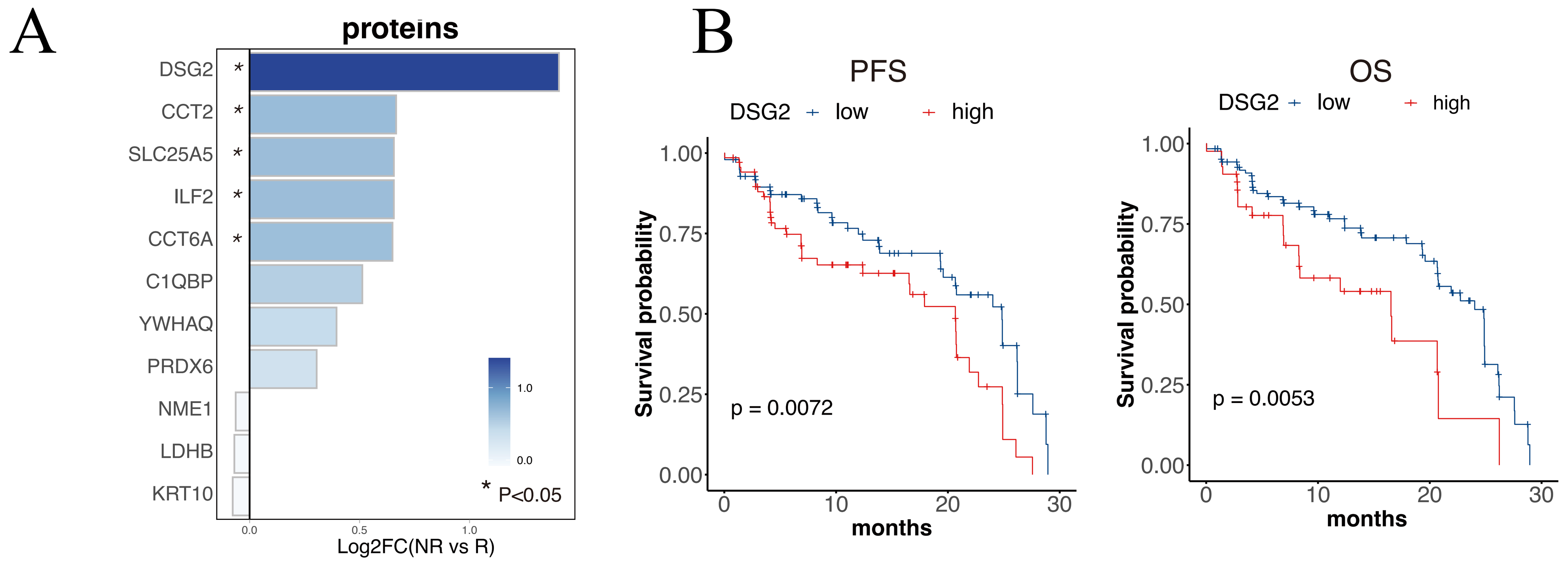

Figure 2. (A) Among all 521 proteins in the proteomic data, 11 proteins were present in the CSC signature, and their expression in NR and R is shown. (B) Serum DSG2 demonstrated an adverse association with a worse clinical outcome in patients treated with EGFR-TKI therapy in the BPI-7711 clinical trial..