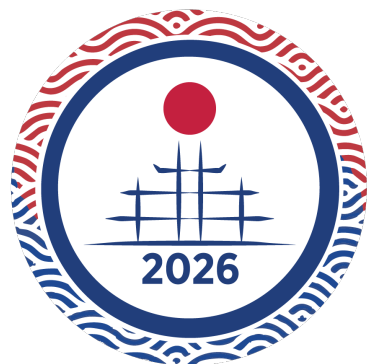




P2.100: Integrative analysis reveals immune heterogeneity and immune regulatory genes in KRAS-mutant lung adenocarcinoma

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INTRODUCTION

1.Non-small-cell lung cancer(NSCLC), a heterogeneous group of tumors, accounts for approximately 85% of all lung cancer cases. Lung adenocarcinoma (LUAD) is the most common subtype of NSCLC, with approximately 30% of cases driven by KRAS mutations.

2.Recently, the development and FDA approval of KRAS (G12C) inhibitors have marked a breakthrough. However, therapeutic resistance and limited response rates highlight the continued need for alternative approaches in KRAS-mutant lung cancers.

3.Oncogenic KRAS actively reshape the TIME by modulating cytokine and chemokine secretion, promoting immunosuppressive signaling, and driving immune evasion.

METHODS

Design:

Bulk RNA-seq data from TCGA
Single-cell RNA-seq data and processing
TIME comparison of KRAS-mutant and wild-Type LUAD patients

Immune subtype classification of KRAS-mutant LUAD
Somatic mutation association analysis
Immunotherapy response prediction

Survival analysis.
Differential expression analysis
Integration of bulk and single-cell transcriptomic analyses to define KCIR genes

Functional enrichment analysis
KRAS perturbation in cell lines and RNA sequencing
Immunohistochemical analysis

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Upregulated PDE4D decreases immune-stimulatory cytokines including IL23, IFNB1 and IL36G, which further impairs the recruitment and activation of immune cells.
- Elevated PDE4D inhibits the JAK-STAT pathway and reduces STAT1 activity, leading to downregulation of IRF1; meanwhile, CREB1 expression is also decreased. The combined reduction of IRF1 and CREB1 suppresses HLA class I expression, ultimately attenuating MHC class I-mediated antigen presentation and dampening anti-tumor immunity.

Future Direction for Research

- PDE4D may affect HLA-I expression via the CREB1 or JAK-STAT1-IRF1 pathways, thereby influencing CD8+ T cell-mediated tumor cell killing.

REFERENCES & ACKNOWLEDGEMENTS

List the most critical references and recognize any support or contributions from others.

- Use QR code to save space and to link to more extensive lists or related works.



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RESULTS

- CD8⁺ T cell and $\gamma\delta$ T cell—were significantly lower infiltration in the KRAS-mutant group (adjusted $p < 0.01$; Fig. 2b), suggesting impaired antitumor immunity due to the depletion of these key effector cells.
- KRAS-mutant LUAD, compared to KRAS wild-type, tends to exhibit “cold” tumor characteristics, potentially contributing to limited response to immunotherapy.
- immune-suppressive genes, including CGA, GRIN1, HCAR2, HCAR3, NPY, and PDE4D, were significantly enriched in the cAMP signaling pathway, suggesting a potential role of cAMP signaling in mediating immune evasion. Among these genes, PDE4D encodes a cAMP-specific phosphodiesterase that hydrolyzes cAMP, thereby lowering its intracellular levels.
- PDE4D may contribute to immune heterogeneity in KRAS-mutant LUAD, potentially by suppressing CD8+ T cell infiltration and promoting an immunosuppressive tumor microenvironment.

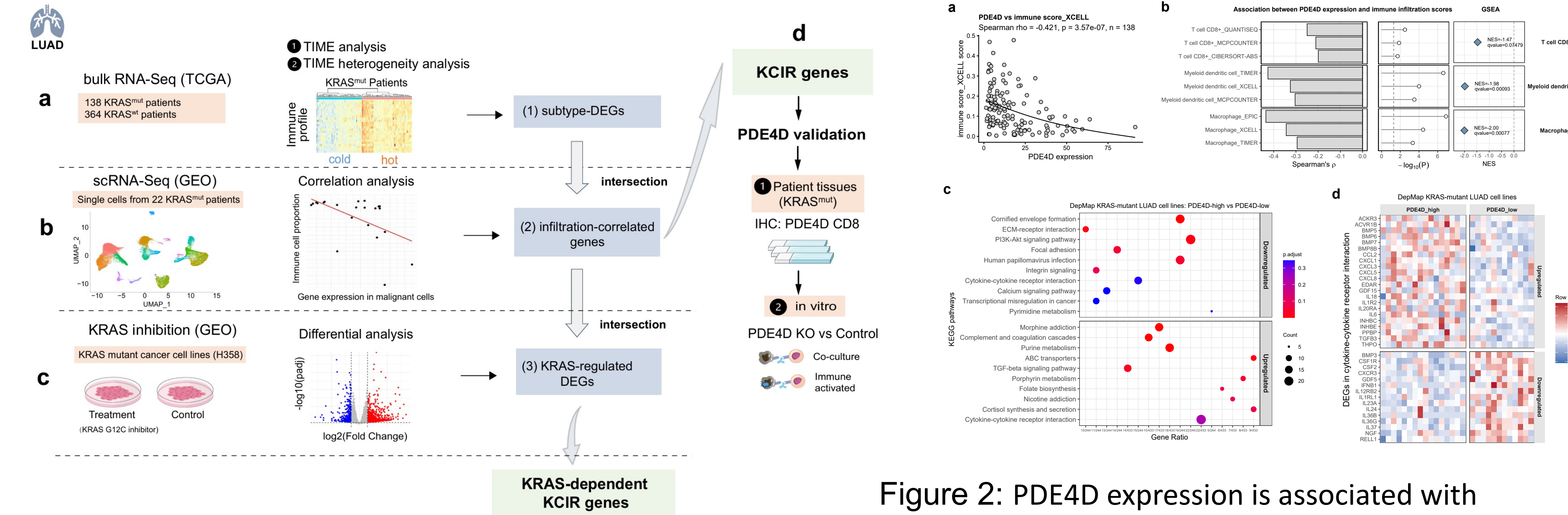


Figure 1: Overview of the analysis pipeline for identifying and validating immune regulatory genes in KRAS-mutant LUAD.

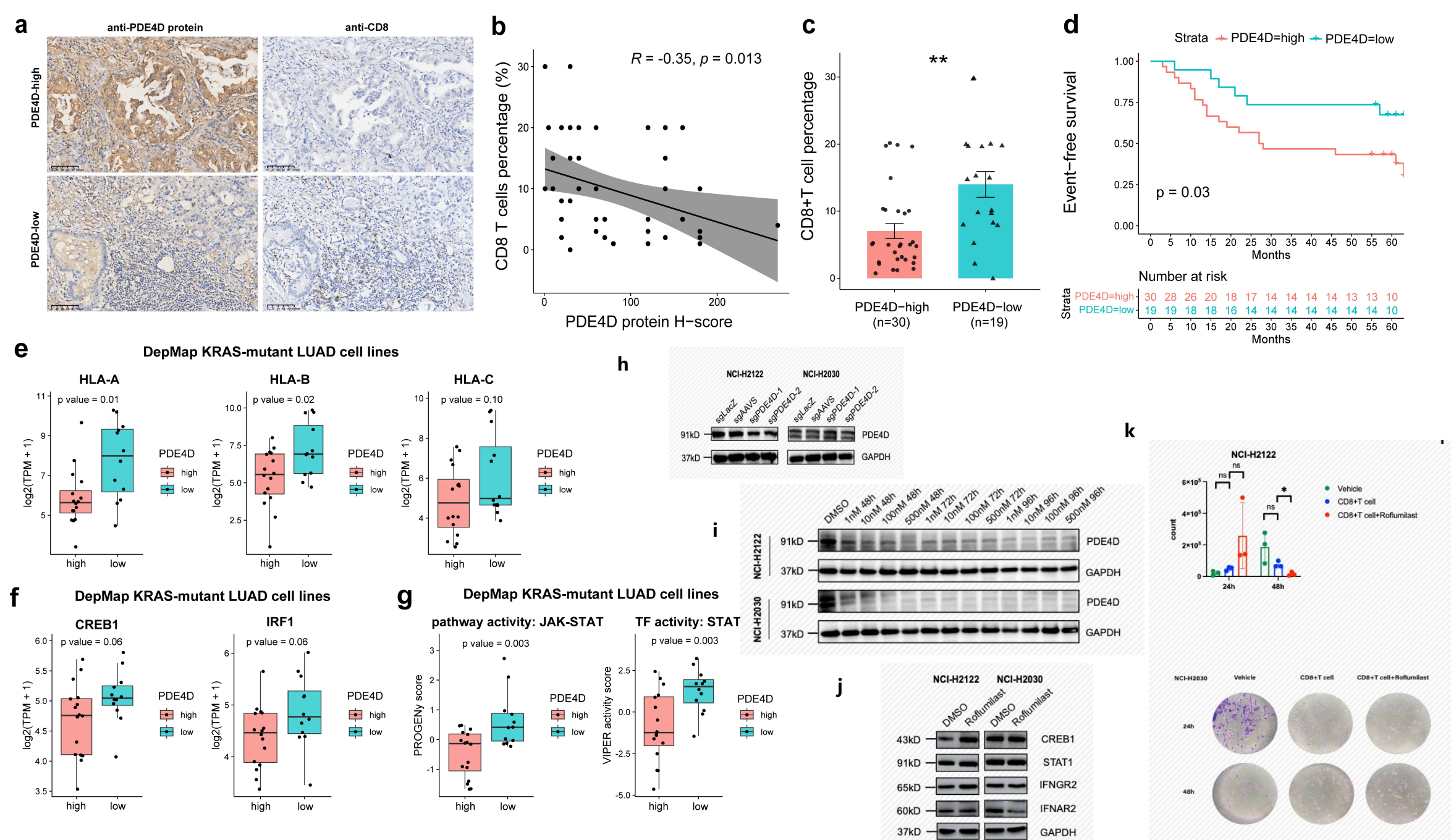


Figure 3: PDE4D reduces the cytotoxicity of CD8+T cells against LUAD cells by downregulating HLA, CREB1, SATAT1 and IFNGR2 expression.

Figure 2: PDE4D expression is associated with reduced immune infiltration and altered cytokine-related transcriptional program in KRAS-mutant lung adenocarcinoma..

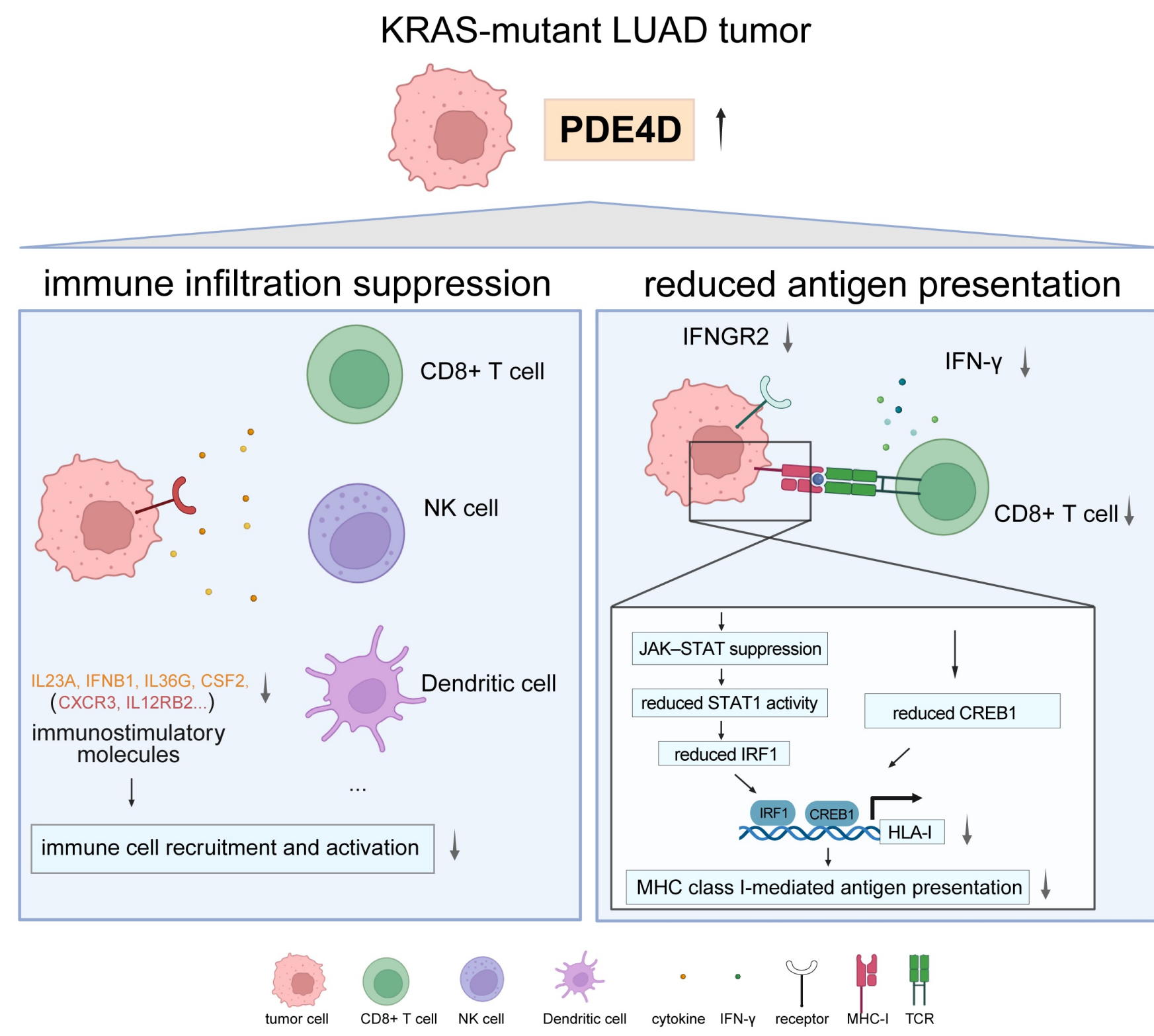


Figure 4: Schematic diagram of immunosuppression mediated by upregulated PDE4D in KRAS-Mutant LUAD tumors.