PS4-02-12 Combination of CDK4/6 and EZH2 Inhibitors Enhances Anti-Tumor Immunity in Triple-Negative Breast Cancer via the MAVS-TBK1-STAT1 Signaling Pathway and Synergizes with Anti-PD-1 Therapy

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Background and Purpose

- Although immune checkpoint inhibitors (ICIs) combined with chemotherapy have been established as the standard treatment regimen for triple-negative breast cancer (TNBC), the proportion of patients deriving significant clinical benefit remains limited[1-3].
- Identifying novel therapeutic targets and developing synergistic strategies to enhance the efficacy and broaden the applicability of ICIs represent critical areas of ongoing research.

Methods

A series of comprehensive experiments, including 4T1 orthotopic breast cancer mouse models, tumor-T cell co-culture systems, transcriptome sequencing, flow cytometry, immunoblotting, and qPCR, were performed to systematically elucidate the anti-tumor immune mechanisms of the drug combination.

Results

- The combination of CDK4/6 and EZH2 inhibitors significantly inhibited 4T1 orthotopic tumor growth and promoted CD8⁺ T cell infiltration.

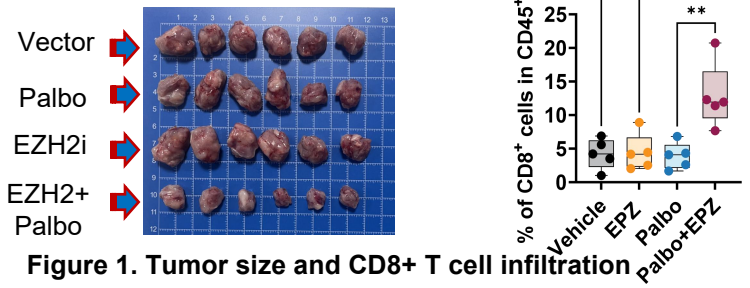


Figure 1. Tumor size and CD8+ T cell infiltration

- Transcriptomic analysis identified differential gene enrichment in pathways related to cell adhesion and migration.
- qPCR demonstrated a notable upregulation of chemokine mRNAs (e.g., CXCL9, CXCL10, CXCL11) in the combination treatment group, while in vitro migration assays confirmed enhanced recruitment of CD8+ T cells.

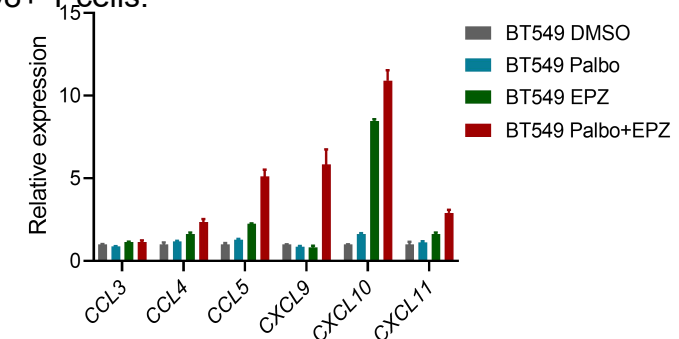


Figure 2. Chemokine mRNAs expression

- Mechanistically, the combination therapy activated the MAVS-TBK1 axis via dsRNA signaling (but not dsDNA) signaling, leading to STAT1 phosphorylation and increased IFN-β secretion, which subsequently upregulated chemokine expression.

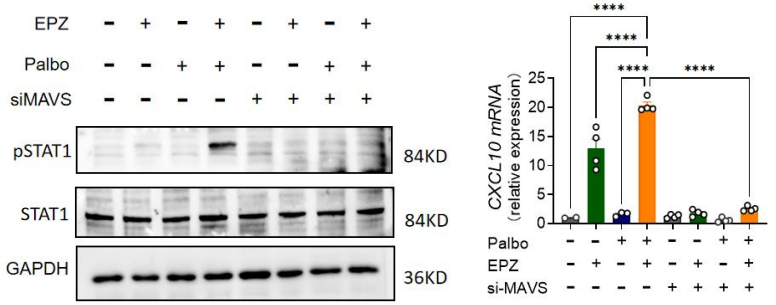


Figure 3. Blockade of the MAVS pathway

- Furthermore, the combination therapy synergistically enhanced the efficacy of anti-PD-1 monoclonal antibodies.

Conclusion

This study demonstrates that the combination of CDK4/6 and EZH2 inhibitors induces chemokine expression and facilitates CD8⁺ T cell infiltration via the MAVS-TBK1-STAT1 axis, thereby enhancing anti-tumor immunity and providing a novel synergistic approach for TNBC immunotherapy.

References

[1]Chamoto K et al. Nat Rev Immunol 2023 ; [2]Schmid P et al. Lancet Oncol 2020; [3] Mittendorf EA et al. Lancet 2020.

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