Desmocollin 3 Enhances Response to Immune Checkpoint Inhibitors in Triple-Negative Breast Cancer by Remodeling the Tumor Immune Microenvironment via the CCL21-pDC-Treg Axis

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SAN ANTONIO BREAST CANCER SYMPOSIUM®

Abstract

- **Novel Biomarker Identified:** We identify Desmocollin 3 (DSC3) as a novel and robust predictive biomarker for favorable response to immune checkpoint inhibitors (ICIs) in triple-negative breast cancer (TNBC).
- **Immune-Dependent Mechanism:** DSC3 enhances ICI efficacy by profoundly remodeling the tumor immune microenvironment, increasing cytotoxic CD8+ T cells while reducing immunosuppressive plasmacytoid dendritic cells (pDCs) and regulatory T cells (Tregs).
- **DSC3-SOX2-CCL21 Axis Elucidated:** Mechanistically, DSC3 mRNA acts as a competitive endogenous RNA, sequestering the transcription factor SOX2 to suppress CCL21 transcription and secretion, thereby disrupting pDC recruitment.
- **pDC Role and Therapeutic Potential:** We elucidate the critical role of pDCs in driving ICI resistance in TNBC and demonstrate that targeting pDCs synergizes with αPD-1, offering high translational value.

Introduction

Triple-negative breast cancer (TNBC) poses significant therapeutic challenges due to its aggressiveness and lack of targeted therapies. Immune checkpoint inhibitors (ICIs) have shown promise, yet response rates remain disappointingly low (<30%), highlighting the urgent need for reliable predictive biomarkers and strategies to overcome resistance.

The tumor immune microenvironment (TIME) is a key determinant of ICI response. An immunosuppressive TIME, characterized by limited CD8+ T cell infiltration and abundance of inhibitory populations like regulatory T cells (Tregs) and plasmacytoid dendritic cells (pDCs), often underlies treatment failure. While pDCs are known for antiviral immunity, their role in fostering an immunosuppressive niche in solid tumors like TNBC is increasingly recognized but poorly understood.

Desmocollin 3 (DSC3), a cadherin family protein involved in cell adhesion, has not been explored in cancer immunology. We hypothesized that DSC3 modulates the TIME to influence ICI efficacy. This study aims to: 1) define DSC3 as a predictive biomarker for ICI response in TNBC, 2) elucidate its immunomodulatory mechanisms, and 3) validate the translational potential of targeting its associated pathway.

Methods and Materials

- **Clinical Cohorts and Biomarker Discovery:** An integrated transcriptomic analysis was performed using RNA-sequencing data from the TREND clinical trial (ChiCTR2000035262, recently published in *Signal Transduction and Targeted Therapy*[1]) and the ICI cohort of the ISPY2 trial to identify biomarkers associated with immunotherapy response. DSC3 protein expression was validated in baseline TNBC tissue specimens using immunofluorescence staining, and its levels were correlated with pathological response and progression-free survival.
- **In Vivo Modeling:** Syngeneic models (4T1, AT3) with DSC3 overexpression were established in immunocompetent and immunodeficient mice. Mice received αPD-1 alone or combined with a pDC inhibitor to assess tumor growth and survival.
- **Immune Phenotyping:** Multicolor flow cytometry profiled T cells (CD8+, Treg) and dendritic subsets (cDC1, cDC2, pDC). In vivo depletion used neutralizing antibodies. OT-1/OVA system assessed T cell cytotoxicity.
- **Molecular Mechanism Studies:** DSC3-CCL21 link was studied via transcriptome, ELISA, WB. SOX2 interaction used RIP, RNA-pull down. SOX2 binding to CCL21 promoter was tested by ChIP-qPCR. JAK2/STAT1 and STAT3/PD-L1 signaling was examined upon IFN stimulation.
- **Statistical Analysis:** Two-tailed t-test and log-rank test were used for continuous variables and survival analysis, respectively. p<0.05 was significant.

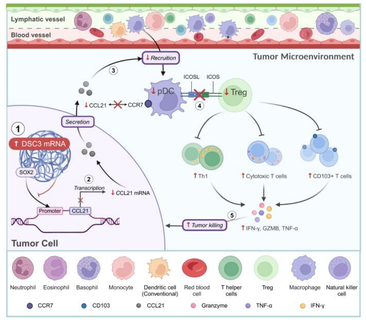


Figure 1. Graphical abstract illustrating the ,echanism of DSC3 in remodeling the tumor Immune microenvironment

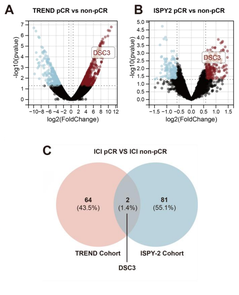


Figure 2. Identification of DSC3 as a biomarker of immunotherapy

Results

Our integrated multi-cohort transcriptomic analysis robustly identified DSC3 as a top predictor of favorable ICI response in TNBC. This clinical correlation was strongly validated at the protein level, where high DSC3 expression in baseline tumor tissues from ICI-treated patients significantly correlated with improved pathological complete response and longer progression-free survival. In immunocompetent murine models, DSC3 overexpression in TNBC cells dramatically enhanced the anti-tumor efficacy of αPD-1 therapy, leading to profound tumor regression and improved survival outcomes. Crucially, this sensitizing effect was entirely abrogated in immunodeficient mice, confirming that DSC3 enhances ICI response through an immune-dependent mechanism.

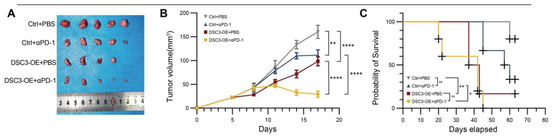


Figure 3. DSC3 overexpression inhibits tumor growth and improves immunotherapy

Comprehensive immune profiling via multicolor flow cytometry revealed that DSC3 remodels the tumor microenvironment by driving a pro-inflammatory shift. We observed a substantial increase in tumor-infiltrating, granzyme B-producing CD8+ T cells and a significant reduction in immunosuppressive regulatory T cells (Tregs). A pivotal discovery was the specific and marked reduction in plasmacytoid dendritic cell (pDC) infiltration, a cell type we found to be enriched in ICI non-responders from patient single-cell data. Using neutralizing antibodies, we demonstrated that both CD8+ T cells and pDCs are necessary for the DSC3-mediated phenotype.

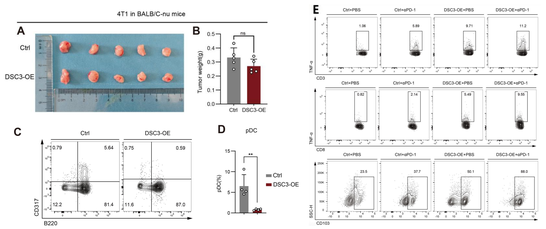


Figure 4. DSC3 enhances T cell cytotoxicity and reduces pDC infiltration

Results

Mechanistically, we uncovered a novel post-transcriptional regulatory pathway. DSC3 mRNA does not encode a signaling protein but competitively binds the transcription factor SOX2, effectively sequestering it from the CCL21 promoter. This interaction, confirmed by RIP and RNA-pull down assays, led to significant suppression of CCL21 transcription and secretion, thereby disrupting the CCL21-mediated recruitment of pDCs. The reduction in pDCs subsequently disrupted the immunosuppressive ICOS/ICOSL axis between pDCs and Tregs, breaking a key tolerance mechanism. This rewired microenvironment further established a positive feedback loop: the enhanced T cell activity sensitized tumor cells to IFN-γ-driven STAT1 activation, reinforcing antigen presentation, while simultaneously suppressing the IFN-α/STAT3/PD-L1 pathway. The translational promise of this axis was conclusively confirmed by the potent, synergistic anti-tumor effect observed when combining a pDC-targeted inhibitor with αPD-1 therapy in vivo, resulting in near-complete tumor eradication in DSC3-high models.

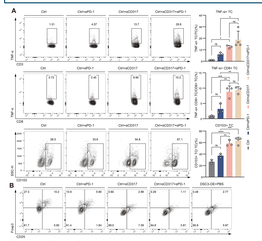


Figure 5. pDC blockade synergizes with anti-PD-1 to enhance antitumor immunity

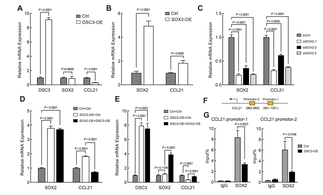


Figure 6. DSC3 regulates CCL21 expression through a competitive SOX2-binding mechanism

Discussion

This study reveals a non-canonical function of the desmosomal gene DSC3 in regulating antitumor immunity. By suppressing CCL21 through competitive SOX2 binding, DSC3 disrupts pDC recruitment and its immunosuppressive function, establishing both the role of pDCs in breast cancer immunotherapy and their therapeutic targeting value.

Conclusions

DSC3 enhances TNBC sensitivity to immunotherapy via the CCL21-pDC-Treg axis. Targeting pDCs combined with PD-1 blockade represents a promising strategy to overcome immunotherapy resistance.

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