561 TARGETING CD38-DRIVEN T CELL DYSFUNCTION RESTORES SENSITIVITY TO CANCER IMMUNOTHERAPY

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Background Terminally exhausted CD8+ T cells, resulting from chronic antigen exposure in the tumor microenvironment, are defined by loss of effector function, decreased proliferative potential, and are associated with limited response to immune checkpoint blockade (ICB).[1] CD38 is an ecto-enzyme, involved in NAD+ catabolism.[2] that was shown to be expressed in terminally exhausted CD8+ T cells in melanoma and correlate with lack of response to ICB,[3] although its specific role in T cell exhaustion and its therapeutic potential has remained poorly defined.

Methods In this study we used human CART cells, as well as, tumor infiltrating lymphocytes (TILs) from melanoma patients to study the role of CD38 in T cell exhaustion and dysfunction. Further mechanistic studies were conducted using murine cancer models. We used a set of genetic and pharmacological tools to block CD38, followed by extensive immunophenotyping and T cell effector functions analysis. Lastly, we used a cohort of patient derived biospecimens to test the efficiency of CD38 blockade to overcome clinical resistance to ICB.

Results We confirm that CD38 expression is increased in CD8 + T cells during tumor progression and following PD-1 blockade and serves as a predictive marker of ICB resistance in multiple cancers. CD38 expressing T cells have impaired effector functions and inferior metabolic potential, testes using MS-LC metabolomics and mitochondrial function analysis. CD38 blockade using genetic or pharmacological tools results in improved cytotoxic function, increased proliferation and an increase in T cell memory genes which were shown to induce durable responses to ICB.[3] Importantly, dual blockade of PD-1 (pembrolizumab) and CD38 (daratumumab) in a cohort of patient-derived organotypic tumor spheroids (PDOTS)[4 5] of patients with cutaneous melanoma and other cancers (n=35) show dramatic response to ICB (54% of the tumors), as opposed to each treatment alone (αPD-1 11%, αCD38 22.5%). Combinatorial therapy not only enhanced tumor cytotoxicity in treatment naïve tumors but was also able to overcome ICB resistance in clinically resistant refractory melanoma (10/18, 55%) and in murine mouse models in a NAD+ and CD8+ dependent manner, consistent with the role of CD38 in NAD+ catabolism.

Conclusions Taken together, these data (figure 1) confirm a role for the CD38/NAD+ axis in T cell dysfunction and its association with ICB resistance and support further pre-clinical and clinical development of CD38-directed strategy to overcome ICB resistance.

REFERENCES

1. Blank, C. U. *et al.* Defining 'T cell exhaustion'. *Nat. Rev. Immunol.* 2019;**19**, 665–674.
2. Piedra-Quintero, Z. L., Wilson, Z., Nava, P. & Guerau-de-Arellano, M. CD38: An Immunomodulatory Molecule in Inflammation and Autoimmunity. *Front. Immunol.* 2020; **11**, 597959.
3. Sade-Feldman, M. *et al.* Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma. *Cell* 2019;**176**, 404.
4. Aref, A. R. *et al.* 3D microfluidic ex vivo culture of organotypic tumor spheroids to model immune checkpoint blockade. *Lab Chip* 2018;**18**, 3129–3143.
5. Jenkins, R. W. *et al.* Profiling of PD-1 Blockade Using Organotypic Tumor Spheroids. *Cancer Discov.* 2018;**8**: 196–215.

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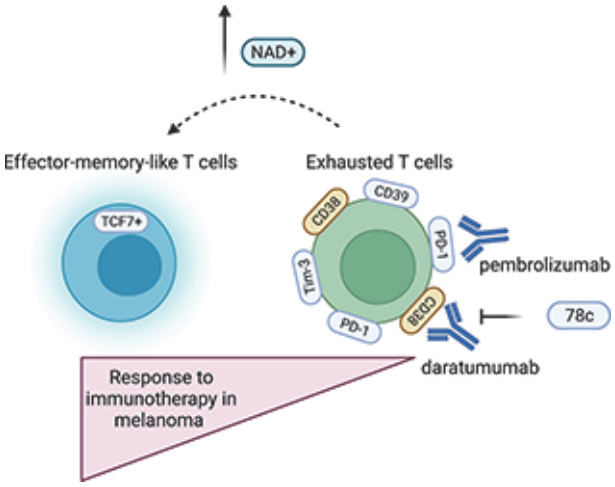

Abstract 561 Figure 1

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