CHARACTERIZATION AND THERAPEUTIC TARGETING OF A TUMOR-ASSOCIATED TOLERGENIC DC SUBPOPULATION DRIVEN BY SREBP2 AND THE MEVALONATE METABOLIC PATHWAY

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Background Conventional dendritic cells (DCs) are essential mediators of anti-tumor immunity and the efficacy of anti-PD-1 checkpoint immunotherapies. Recent studies suggest that tumor-mediated development of a sub-population of tolerogenic DCs plays an important role in immune evasion. Metabolic reprogramming regulates tolerogenic DCs in the tumor microenvironment (TME). Activation of DCs leads to rewiring of cDC metabolism towards glycolysis to support T cell activation while tolerogenic DCs display enhanced fatty acid oxidation. Related to DC metabolic alterations, tumor-associated DCs (TADCs) are enriched in lipids and have a reduced capacity to present antigen to T cells. Lipid homeostasis is maintained through a complex network of transcription factors including sterol regulatory element-binding protein-2 (SREBP2) which drives the expression of mevalonate pathway genes. The identification of those tumor-controlled pathways that regulate tolerogenic DCs in the TME is expected to lead to the discovery of a novel family of immunotherapeutic targets.

Methods We use transgenic mouse models of melanoma, sentinel lymph node (LN) tissue specimens derived from melanoma patients, single-cell RNA sequencing (scRNAseq), and flow cytometry-based metabolic assays to identify novel tumor-associated regulatory programs amongst different sub-populations of conventional DCs in the TME.

Results scRNAseq of DCs isolated from the tumor-draining LN (TDLN) of a BRAFV600E/PTEN-/- transgenic melanoma model revealed critical genetic differences in distinct DC sub-populations. We observed a migratory DC subset enriched in the expression of numerous immunoregulatory genes and identified CD63 as a surface marker to distinguish this DC subset from other conventional cDC1s and cDC2s. Further studies demonstrated CD63+ DCs to suppress T cell activation and promote CD4+FOXP3+ regulatory T cell (Treg) differentiation. Relative to other cDC subsets, CD63+ DCs overexpress genes of the mevalonate pathway leading to increased lipid content. Treatment of melanoma-bearing mice with a pharmacologic inhibitor of SREBP2 leads to a significant reduction in CD63+ DCs in the TDLN and reduced Tregs, resulting in suppressed tumor growth. Importantly, scRNAseq of DCs isolated from sentinel LNs of melanoma patients reveal that this population is conserved in humans.

Conclusions Lipid homeostasis in TADCs is a major determinant of their metabolic state, but despite significant advances, the molecular pathways regulating tolerogenic DCs have remained poorly understood. Collectively, this data demonstrates an important role of the mevalonate pathway in driving a tolerogenic DC program and highlights the therapeutic targeting of SREBP2 and DC lipid metabolism as a promising approach to overcoming immune tolerance in the TME and boosting immunotherapeutic responses.

REFERENCES

Ethics Approval Collection of human tissue specimens was approved by the Duke Institutional Review Board under the title Immune Markers of Sentinel Nodes in Melanoma and the protocol number Pro00090678. All patients gave informed consent prior to participating in the study. All experiments involving animals were approved by the Duke University Institutional Animal Care and Use Committee (IACUC) under protocol number A174-18-07.

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