



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

203.LYMPHOCYTES AND ACQUIRED OR CONGENITAL IMMUNODEFICIENCY DISORDERS

Primary Immune Regulatory Disorders (PIRDs) That Amplify mTOR Signaling Share a T Cell Exhaustion-like Process

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Background: Primary Immune Regulatory Disorders (PIRDs) are a complex and challenging-to-treat subset of Inborn Errors of Immunity (IEI), which are characterized by immune dysregulation leading to recurrent infections, lymphoproliferation, and autoimmunity including refractory cytopenias. Since many ultra-rare monogenic PIRDs exist, it is not feasible to design targeted therapies for each. An alternate strategy is to identify shared aspects of T cell dysfunction and strategies targeting them. We have focused our studies on PIRDs that chronically amplify T cell receptor (TCR) signaling, mimicking chronic infection. Under conditions of chronic inflammation and antigen presentation, seen during chronic infections, CD8 T cell exhaustion (Tex) can result and is characterized by increased inhibitory receptor expression, altered transcriptional networks, epigenetic poise, and impaired T cell functions including cytokine production. Here, we have evaluated CD8 T cell dysfunction in PIRDs, including the potential for Tex.

Methods: Deep immune phenotyping and T cell functional analyses were performed using CyTOF and spectral flow cytometry, in addition to single cell RNA-sequencing and CITE-seq from untreated PIRD and healthy control PBMCs. Finally, CRISPR/Cas9 editing in healthy control CD8 T cells was used to create a cellular disease model.

Results: We identified a Tex-like process in activated PI3 kinase delta syndrome (APDS), CTLA-4 haploinsufficiency, and Ras-associated Autoimmune Leukoproliferative Disease (RALD), which share increased mTOR activation. We identified increased PD-1, CD39, TIGIT and TOX expression on CD8 T cells consistent with a Tex-like phenotype. We also found impaired CD8 T cell cytokine and proliferation consistent with Tex. Lastly, a cellular model of CTLA-4 haploinsufficiency was created for perturbation studies to evaluate best available therapies and target novel therapeutics in these rare disorders.

Conclusion: By identifying shared patterns of CD8 T cell dysfunction in these ultra-rare disorders, we may both identify novel therapeutic strategies and increase our understanding of CD8 T cell function, including cytokine production.

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