Disturbing the STAT1-AhR Interaction by Fludarabine Ameliorates Type 1 Diabetes via Facilitating Ahr Nuclear Translocation-Mediated Tolerogenic Dendritic Cell Polarization

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Abstract

Background: Type 1 diabetes imposes a substantial burden on patients yet effective therapies to halt disease progression are lacking. Among the various immune cell types implicated in T1D, dendritic cells act as the most potent antigen-presenting cells for insulitis initiation. Tolerogenic dendritic cells act as key regulators that induce immune tolerance, thereby attenuating the progression of Type 1 Diabetes. However, the current tolDC-based strategies face the challenge of suboptimal efficacy and high cost, which limit their broad clinical applications.

Methods: Based on single-cell RNA sequencing analysis, we observed a significant upregulation of STAT1 expression across DC subsets in T1D patients, along with an upward trend in pathways related to antigen phagocytosis and presentation. Herein, we repurposed fludarabine, a clinically available drug and a known STAT1 inhibitor, for the type 1 diabetes setting.

Results: we confirmed that fludarabine induces tolerogenic dendritic cells using Bulk RNA-seq, Nanobead phagocytosis, DC-T cell co-culture, RT-PCR, and flow cytometry. Mechanistic studies employing molecular docking, molecular dynamics simulations, Cellular Thermal Shift Assay, co-immunoprecipitation with mass spectrometry, confocal microscopy, and immunofluorescence revealed that fludarabine disrupts STAT1-AhR interaction, promotes AhR nuclear translocation, and consequently drives tolerogenic DC polarization. Finally, we validated the critical role of the STAT1/AhR axis using DC-specific Ahr-knockout mice (Itgax-Ahr).

Conclusions: Collectively, our findings identify fludarabine as a promising immunometabolic therapeutic candidate that restores immune tolerance and enhances β cell resilience, which could be a viable approach against T1D in clinical settings.